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Prognosis and endocrine therapy selection for patients with low hormone receptor-positive breast cancer following neoadjuvant chemotherapy: A retrospective study of 570 patients in China

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Abstract. The 2010 American Society of Clinical Oncology guidelines have reduced the immunohistochemistry cut-off value for determining estrogen receptor b positivity from 10 to 1% of stained cells in breast cancer. In clinical practice, low-hormone receptor positive (low HR+) tumors are classified in the luminal subtype, although they exhibit aggressive features and poor prognosis. Information regarding the prognosis of patients with breast cancer following treatment with optimal endocrine therapy and neoadjuvant chemotherapy (NAC) is currently lacking. In the present study, the differences in clinical characteristics and survival of patients with breast cancer were compared among those with low and high HR+ breast cancer who received NAC. Furthermore, the effects of different types of endocrine therapies on the prognosis of patients with breast cancer were compared. The study population comprised patients with primary breast cancer who were treated at the Zhejiang Cancer Hospital between January, 2007 and December, 2017. Patients were divided into three groups based on the results of immunohistochemistry: HR+ (positive staining >10%), HR- (positive staining <1%) and low HR+ (positive staining 1-10%). The low HR+ group was further divided into three subgroups according to the different endocrine therapies administered: Tamoxifen, aromatase inhibitor or no treatment. Among the 570 patients included in the present study, 60 (10.53%) patients had low HR+ tumors. With a median follow-up of 48.98 months, patients with low HR+ tumors had reduced survival rates compared with those with HR+ tumors. Furthermore, the pathologic complete response rate (pCR) of patients with low HR+ was comprised between pCR from patients with HR+ and pCR from patients with HR- following NAC treatment. In addition, no significant difference in the overall prognosis was observed among patients with low HR+ following treatment with different endocrine therapies. Subsequently, patients in the low HR+ group were more likely to benefit from NAC compared with patients in the HR+ group. Intensive endocrine therapy may therefore improve the prognosis of patients with breast cancer and low HR+; however, further investigation is required.

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Abbreviations: AJCC, American Joint Committee on Cancer; DFS, disease-free survival; ER, estrogen receptor; HER-2, human epidermal growth factor receptor 2; HR, hormone receptor; NAC, neoadjuvant chemotherapy; NG, nuclear grade; pCR, pathological complete response; PR, progesterone receptor; OS, overall survival; TNBC, triple negative breast cancer

Key words: breast cancer, estrogen receptor, progesterone receptor, neoadjuvant chemotherapy, pathologic complete response

Introduction

The status of hormone receptors (HRs), including estrogen receptor (ER) and progesterone receptor (PR), in breast cancer is crucial for predicting patient responsiveness to endocrine therapy (1,2). The majority of breast tumors (~70%) highly express hormone receptor (HR+). Patients with HR+ tumors have better disease-specific survival and overall survival (OS) compared with those with HR-negative (HR-) tumors (1,2).

Previously, HR positivity was assessed using immunohistochemistry (IHC) scoring with a ≥10% cutoff value for nuclear staining of tumor epithelial cells (3). However, the 2010 guidelines from the College of American Pathologists and American Society of Clinical Oncology changed the IHC cut-off value for determining HR positivity from 10% to 1% of stained cells (4). This has led to the creation of a subclass of low HR+ (1-10%) tumors in breast cancer. This new subclass has been reported to have beneficial impact on patients' response to antiestrogen therapy (2,5,6).

It has been demonstrated that, although triple-negative breast cancer (TNBC) is more sensitive to chemotherapy than

HR+ breast cancer, its prognosis remains poor (7). Previous studies reported that low HR-positive tumors (low HR+) have more aggressive features and poorer prognosis compared with high HR+ tumors (6,8). Numerous studies have reported that tumors with ER expression <10% are likely to exhibit biological behaviors similar to those from ER negative (ER-) tumors (5,6,9). However, to the best of our knowledge, studies comparing the neoadjuvant chemotherapy (NAC) response between low ER+ breast cancer tumors and other types of breast cancer remain limited (10,11). In addition, there is no consistency in the choice of endocrine therapy for the treatment of low HR^+ breast cancer.

The present study compared low HR+ tumors with HR+ and HR- tumors in order to understand the clinical characteristics and prognosis of patients with breast cancer following NAC treatment. To do so, the pathological response to NAC in these three types of tumors was determined. The effect of various endocrine treatment regimens on the prognosis of patients with breast cancer and low HR^+ expression was subsequently investigated.

Materials and methods

Patient selection. The present study was approved by the Ethics Committee of Zhejiang Cancer Hospital. The medical records of 1,194 patients with stages IIA-IIIC primary breast cancer who received NAC at the Zhejiang Cancer Hospital in China between January, 2007 and December, 2017 were examined retrospectively. All patients enrolled had undergone a core needle biopsy and subsequent surgery prior to and following NAC treatment. Patients with incomplete or inconsistent IHC data were excluded. Other exclusion criteria were: i) Patients with stage IV breast cancer, bilateral breast cancer, inflammatory breast cancer or diagnosed with another primary cancer; ii) patients who did not complete the standard NAC regimen; and iii) patients who received radiation therapy prior to surgery. The pathological stage of tumors was assessed according to the American Joint Committee on Cancer (AJCC) 8th Staging System (12). The intensity of HR nuclear staining was divided into three groups and defined as negative, low positive and positive for <1%, 1-10% and >10% of nuclear staining, respectively. The following conditions were defined as low HR+: Low ER+/low PR+, low ER+/PR-, and ER-/low PR+. The therapeutic response of patients was investigated according to alterations in tumor size that was determined by radiographic assessment or clinical examination, as documented in the patient medical records. The pathologic complete response (pCR) was defined as the absence of invasive tumor in the breast resection specimen and regional lymph nodes following surgery.

Patients had received NAC under various regimens. The most common were anthracycline and cyclophosphamide followed by paclitaxel (EC-T, daily injection, 21 days per cycle, 8 cycles total) (13) or a combination of three drugs (Paclitaxel/anthracycline/cyclophosphamide, TEC, daily injection, 21 days per cycle, 6 cycles total) (14). Trastuzumab was routinely administered to patients with human epidermal growth factor receptor-2 (HER-2) positivity as an anti-HER therapy. Tamoxifen or aromatase inhibitors were used as postoperative adjuvant endocrine therapeutic agents for patients with HR+ tumors.

Statistical analysis. The expression data of HR staining from IHC analysis were divided into three groups (HR+, low HR+ and HR-) and analyzed as categorical variables. χ^2 test was used to examine the association between HR expression and the clinicopathological factors of patients. Kaplan-Meier analysis was performed to investigate the disease-free survival (DFS) and overall survival (OS) of patients and a log-rank test was conducted to determine significant differences. Patient features with P<0.1 in univariate analysis were used for multivariate analysis, which was used to determine differences in prognosis between the HR+, low HR+ and HR- groups. Forward conditional logistic regression was also performed. P<0.05 was considered to indicate a statistically significant difference. All statistical analyses were performed using SPSS software version 24 (IBM Corp.).

Results

Clinical and pathological characteristics of tumors. The median age of the enrolled patients was 50 years (range, 21-75 years), and 9.1% of patients were ≤35 years old. In the present study, 301 (52.8%) patients had HR+ tumors, 209 (36.7%) patients had HR- tumors and 60 (10.5%) patients had low HR+ tumors (Table I). The median follow-up duration for the 570 patients included in this analysis was 48.98 months (range, 22.37-93.73 months). The rate of patients who successfully completed the follow up was 92% (n=525); 45 patients discontinued contact during follow-up.

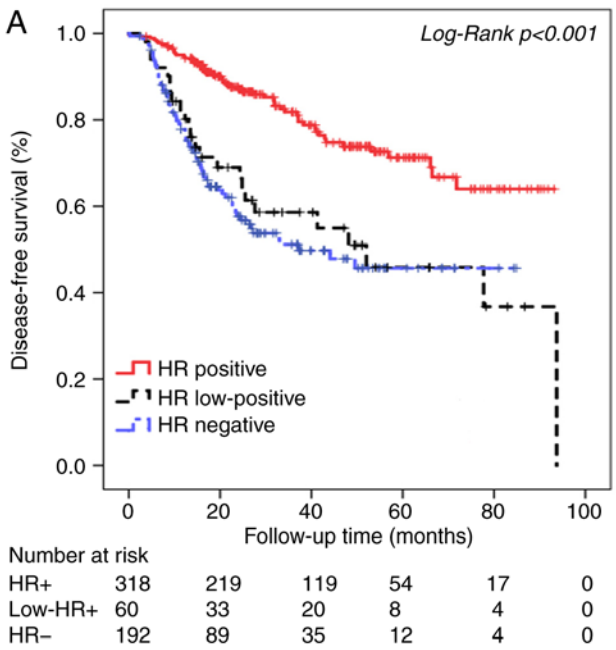
Overall, HR+ tumors were detected more frequently in premenopausal women (60.13%) compared with other subtypes (low HR+, 45.0% and HR-, 47.4%; P=0.006). A total of 537 (94.2%) patients had invasive ductal carcinoma, and among the other patients, 14 (2.5%) had invasive lobular carcinoma, 11 (1.9%) had invasive micropapillary carcinoma, four (0.7%) had mucinous breast carcinoma and four (0.7%) had metaplastic breast carcinoma. The majority of patients had stage II (59.8%) or III (40.2%) disease. In addition, there were 374 (65.6%) T2 tumors and 331 (58.1%) N1 tumors based on the National Comprehensive Cancer Network (NCCN) guidelines (15). Furthermore, the 11 (3.7%) patients who had nuclear grade (NG) I tumors were included in the HR+ group. Compared with HR+ tumors, low HR+ tumors were not significantly different with regards to the histopathological type, AJCC stage and T stage. In addition, compared with HR+ tumors, HR- and low HR+ tumors exhibited higher NG (NG III of 20 and 25.4%, respectively vs. 15.6%; P<0.001), upregulated Ki-67 expression (83.3 and 89.0%, respectively vs. 67.4%; P<0.001), increased HER-2 expression (40.0 and 46.9%, respectively vs. 20.6%; P<0.001) and higher N stage (N2/N3 stages of 33.3 and 24.4%, respectively vs. 21.3%; P=0.046). However, there was no difference between the clinicopathological characteristics of HR- tumors and low HR+ tumors (P>0.05).

A total of 424 (74.4%) patients presented a positive clinical response (complete response and partial response) to NAC based on the Response Evaluation Criteria In Solid Tumors (Table I). The rates of CR for HR+, low HR+ and HR- tumors were 10.6, 15.0 and 22.5%, respectively; however, no statistically significant difference between the three groups was observed (P=0.219).

Table I. Comparison of clinicopathological characteristics according to HR expression level in patients with primary breast cancer.

Patient characteristics	HR positive		Low HR positive		HR negative		P-value
	Number	%	Number	%	Number	%	
Total	301	52.81	60	10.53	209	36.67	
Age, years							
Median	48		51		50		
≤35	30	10.0	8	3.3	14	6.7	0.22
>35	271	90.0	52	86.7	195	93.3	
Menopausal status							
Premenopausal	181	60.1	27	45.0	99	47.4	0.01
Postmenopausal	120	39.9	33	55.0	110	52.6	
Histology							
IDC	279	92.7	58	96.7	200	95.7	0.23
Others	21	7.0	2	3.3	8	3.8	
Missing	1	0.3	-	-	1	0.5	
Nuclear grade							
I	11	3.7	-	-	-	-	<0.001
II	97	32.2	9	15.0	36	17.2	
III	47	15.6	12	20.0	53	25.4	
Missing	146	48.5	39	65.0	120	57.4	
AJCC stage							
IIA	69	22.9	9	15.0	33	15.8	0.09
IIB/IIA	174	57.8	34	56.7	132	63.2	
IIIB/IIIC	58	19.3	17	28.3	44	21.1	
Ki-67 expression							
≤14%	80	26.6	6	10.0	17	8.1	<0.001
>14%	203	67.4	50	83.3	186	89.0	
Missing	18	6.0	4	6.7	6	2.9	
Her-2 expression							
Negative	200	66.4	32	53.3	97	46.4	<0.001
Equivocal	37	12.3	4	6.7	14	6.7	
Positive	62	20.6	24	40.0	98	46.9	
Missing	2	0.7	-	-	-	-	
Therapeutic evaluation							
cCR	32	10.6	9	15.0	47	22.5	0.22
cPR	192	63.8	41	68.3	103	49.3	
cSD	75	24.9	9	15.0	53	25.4	
cPD	2	0.7	1	1.7	6	2.9	
T stage							
T0/1	26	8.6	8	13.3	16	7.7	0.10
T2	211	70.1	37	61.7	126	60.3	
T3	26	8.6	7	11.7	44	21.1	
T4	37	12.3	8	13.3	23	11.0	
Missing	1	0.3	-	-	-	-	
N stage							
N0	60	19.9	6	10.0	38	18.2	0.05
N1	177	58.8	34	56.7	120	57.4	
N2	37	12.3	10	16.7	28	13.4	
N3	27	9.0	10	16.7	23	11.0	

IDC, invasive ductal carcinoma; AJCC, American Joint Committee on Cancer; HER-2, human epidermal growth factor receptor-2; HR, hormone receptor; cCR, clinical complete response, disappearance of all target lesions; cPR, clinical partial response, ≥30% decrease in the sum of diameters of target lesions; cPD, clinical progression of disease, ≥20% increase in the sum of diameters of target lesions; cSD, clinical stable disease, neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.



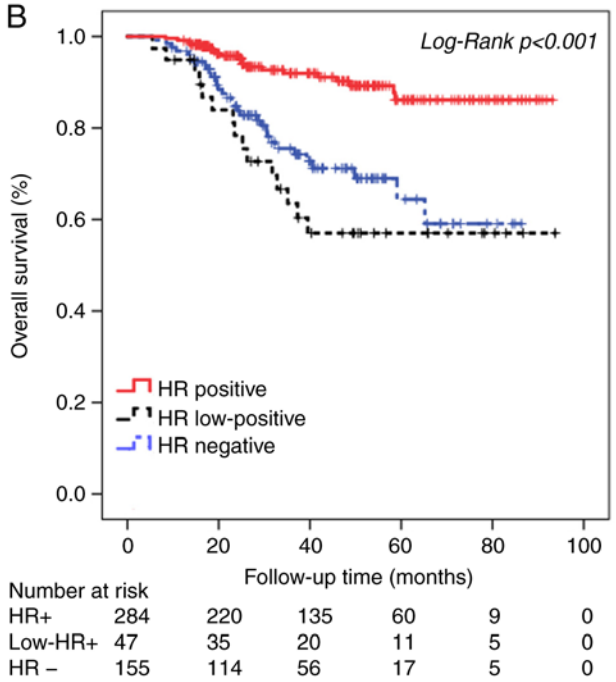
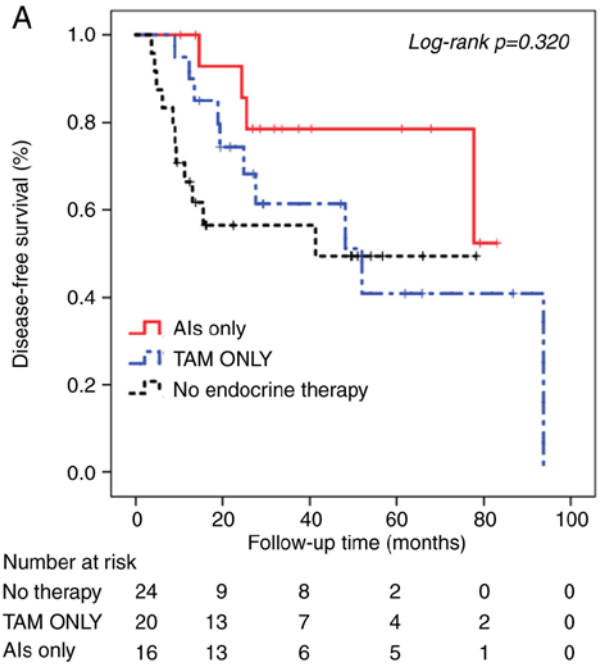


Figure 1. Kaplan-Meier curves of survival outcomes among patients with three different levels of HR expression in the primary tumor. (A) Distant recurrence-free survival. (B) Overall survival. HR, hormone receptor.



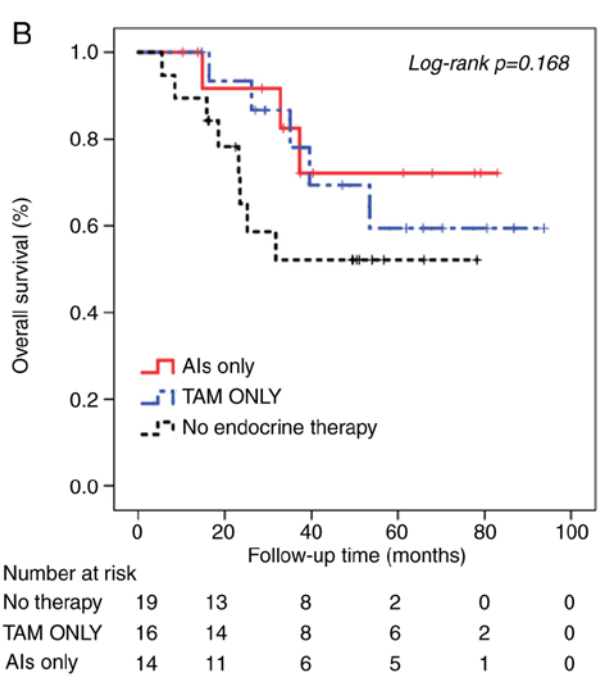


Figure 2. Kaplan-Meier curves of survival outcomes among patients treated with different endocrine therapies. (A) Distant recurrence-free survival. (B) Overall survival.

Survival analysis outcomes. Univariate analysis for DFS and OS in the HR+, HR- and low HR+ tumors groups was performed using Kaplan-Meier survival analysis. The survival curve for low HR+ tumors was located between that of HR^+ and HR^- tumors. Patients with low HR+ tumors had worse DFS and OS (Fig. 1) compared with patients with HR+ tumors, which was similar to that of HR- patients. The median DFS was 72.71±2.42, 53.57±5.97 and 48.18±3.16 months for the HR+, low HR+ and HR- groups, respectively (χ^2=43.59; P<0.001). The median OS was 85.11±1.73, 63.92±5.92 and 65.24±3.17 months for the HR+, low HR+ and HR- groups, respectively (χ^2=28.31; P<0.001). The 5-year DFS for patients with HR+, low HR+ and HR- tumors was 71.3, 45.9 and 45.7%, respectively, and the 5-year OS for patients with HR+, low HR+ and HR- tumors was 86.2, 57.0 and 64.4%, respectively.

The multivariate Cox proportional hazards model was used to determine differences in prognosis between the HR+, low HR+ and HR- tumors groups, excluding potential survival confounding factors, including age, menopausal status, histological type, NG, AJCC staging, and tumor and lymph node staging. As presented in Table II, patients with HR+ tumors had significantly better DFS and OS compared with patients

Table II. Cox regression analysis of patient survival outcomes according to HR expression level in patients with primary breast cancer.

A, Disease-free survival

	Univariate Analysis			Multivariate Analysis		
HR status	Hazard Ratio	95% CI	P-value	Hazard Ratio	95% CI	P-value
Positive	1		<0.001	1		<0.001
Low-positive	2.60	1.60-4.24	0.006	2.82	2.10-3.86	0.018
Negative	3.04	2.13-4.35	<0.001	2.94	1.75-5.00	<0.001

B, Overall survival

	Univariate Analysis			Multivariate Analysis		
HR status	Hazard Ratio	95% CI	P-value	Hazard Ratio	95% CI	P-value
Positive	1		<0.001	1		0.001
Low-positive	4.57	2.34-8.92	<0.001	4.76	4.11-5.56	0.019
Negative	3.28	1.87-5.74	<0.001	4.76	2.08-11.11	<0.001

HR, hormone receptor; CI, confidence interval.

with low HR+ tumors (DFS, P=0.018; OS, P=0.019). In addition, patients with HR- tumors had similar DFS and OS to patients with low HR+ tumors (data not shown).

Among the 60 patients with low HR+ tumors, 24 (40.0%) patients did not receive postoperative adjuvant endocrine therapy. The remaining 36 patients underwent different regimens of endocrine therapy: 20 patients (33.3%) received tamoxifen and 16 patients (26.7%) were administered an aromatase inhibitor. Univariate Kaplan-Meier analysis was performed of the low HR+ tumors group stratified according to the different endocrine therapies administered. The results demonstrated that patients who did not receive endocrine therapy had poorer DFS (45.44±7.20 months, Fig. 2A) and OS (50.21±7.31 months, Fig. 2B) compared with patients who received endocrine therapy. Among patients who received endocrine therapy, patients who received treatment with the aromatase inhibitor exhibited better DFS (68.42±6.68 months) compared with patients treated with tamoxifen (55.79±9.21 months). However, there were no significant differences in the DFS and OS between the three groups (DFS, χ^2=2.28, P=0.320; OS, χ^2=3.56, P=0.168).

Discussion

The present study evaluated the clinicopathological characteristics and prognosis of patients with low HR+ tumors compared with patients with HR+ and HR- tumors. The results demonstrated that 10.5, 52.8 and 36.7% of patients had low HR+, HR+ and HR- tumors. As demonstrated in previous studies, the clinical and biological features of low HR+ tumors were similar to those of HR- tumors, which presented aggressive biological behaviors (5,6). In addition, patients with low HR+ tumors of advanced stages presented an increased incidence of aggressive phenotype. With regards to NG and the expression of Ki-67 and HER-2, low HR+ tumors exhibited moderate characteristics compared with the other two cohorts. The survival curve of patients with low HR+ tumors was located between that of patients with HR+ and HR- tumors, which indicated poorer DFS and OS compared with patients with HR+ tumors. It has been reported that increased activity of the growth factor signaling pathways and upregulated Ki-67 expression could be associated with the aggressiveness of low HR+ tumors (16-19).

Numerous studies have investigated the concept of low HR+ tumors (9,10,17); however, the efficacy of NAC against low HR+ tumors remains to be determined. In the majority of cases, this subtype are often not considered in the clinical treatment of tumors, as patients are divided into two categories: HR+ and HR-. The present study identified a group of low HR+ tumors with a distinct phenotype that were sensitive to NAC. Guarneri *et al* (20) demonstrated that, although the overall prognosis of TNBC is poor compared with that of breast cancer luminal subtype, TNBC has a higher pCR rate following NAC treatment. Furthermore, Carey *et al* (21) reported that there was no difference in prognosis between patients with TNBC subtype and non-TNBC subtypes who achieved pCR after NAC treatment. However, the prognosis of TNBC subtype is significantly worse compared with non-TNBC subtypes following non-pCR after NAC. compared with non-triple-negative ones. The CREATE-X studies also reported that in certain subgroups of breast cancer, including HER-2 positive and TNBC types, increased pCR rate following NAC treatment could benefit patient survival (7). The present study evaluated the efficacy of chemotherapy in low HR+, HR+ and HR- tumors following NAC treatment. The results demonstrated that the pCR rates

of the three groups following NAC treatment were 10.63 (HR+), 15.00 (low HR+) and 22.49% (HR-). In addition, the pCR rate of the low HR+ group was slightly increased compared with the HR+ group. Regarding the response to NAC, the low HR^+ cohort appeared to have potentially benefited from postoperative enhanced adjuvant chemotherapy regimens, including 6-8 cycles of capecitabine.

To the best of our knowledge, only a few studies have determined whether different endocrine therapy regimens: Tamoxifen, aromatase inhibitor or combined treatment with ovarian function suppression, affect the prognosis of patients with low HR+ tumors. The findings from the present study were consistent with results from Yi *et al* (11) that demonstrated that tumors with an ER-positivity rate of 1-9% do not significantly benefit from endocrine therapy. However, the DFS and OS of patients who received endocrine therapy had notably improved compared with non treated patients (11). The St Gallen 2005 guidelines for the primary therapy of early breast cancer (3) suggested the three following categories for scoring ER status: i) Endocrine responsive, with strong ER expression; ii) endocrine response uncertain, with low ER expression; and iii) endocrine nonresponsive, with no ER expression. These guidelines suggested that the endocrine responsive group should receive endocrine therapy and adjuvant chemotherapy; however, the distinction between 'endocrine responsive' and 'endocrine response uncertain' was not determined in the guidelines. It has been suggested that the loss of PR could be considered as a marker of aberrant growth factor signaling and was proposed as being associated with endocrine resistance (22).

A recent meta-analysis reported that the recurrence rate of breast cancer continued to rise over 5-20 years following treatment and after 5 years of endocrine therapy, whereas the cumulative risk may vary between 10 and 41% (23). The BIG19-8 (24) and ATAC (25) clinical studies have confirmed that enhanced or prolonged endocrine therapy might be beneficial for the survival of patients with a recurrence high risk. Furthermore, the NCCN guidelines (version 3.2018) (26) recommended that some genomic assays could have a prognostic value for screening patients with a high risk of recurrence 0-10 years after surgery, including the 21-gene Oncotype Dx assay (27), 70-gene MammaPrint assay (28), PAM50 (Prosigna) (29), EPclin (12 gene, EndoPredict) (30,31) and the Breast Cancer Index (32). Dowsett *et al* (33) reported a simpler predictive tool called CTS5 for investigating endocrine therapy-enhancing strategies that is based on the analysis of the clinicopathological characteristics of patients with breast cancer. The results from the present study suggested that the prognostic benefits of postoperative adjuvant endocrine therapy may be restricted for low HR^+ patients; however, with the rational use of the aforementioned effective tools to predict the risk of recurrence following standard treatments in patients with high risk and poor prognosis, including patients with low HR+ tumors, enhanced endocrine therapy may be beneficial to patient survival.

This study presented certain limitations. This study was a retrospective analysis, and the type of adjuvant treatment was not administered on a randomized basis. Furthermore, patient classification was not made according to treatment with trastuzumab, since only 49.49% (98/198) of patients overexpressing HER-2- received trastuzumab due to drug availability and unfavorable health care policies.

In conclusion, the present study demonstrated that patients with breast cancer and low HR+ tumors presented similar clinicopathological characteristics to patients with HR- tumors. Furthermore, patients with low HR+ tumors exhibited poorer survival compared with patients with HR+ tumors. In addition, no significant difference in the survival between patients with low HR+ tumors and those with HR- tumors was reported. These findings suggested that patients with low HR+ tumors may benefit from postoperative intensive adjuvant chemotherapy and endocrine therapy. Further investigation is required to determine the underlying mechanism of low HR+ breast cancer. In addition, prospective clinical studies are urgently needed to validate the importance of enhanced adjuvant therapy for the prognosis of patients with low HR+ breast cancer.

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Availability of data and material

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

YD designed the study, analyzed and interpreted the data, prepared figures, wrote the manuscript and supervised the study. KD analyzed and interpreted the data. XD and DZ developed the methodology and revised the manuscript. HY provided technical support, assisted in developing the methodology and revised the manuscript. XH and WM prepared tables and figures, performed database research and analyzed and interpreted the data. KY and XY provided and prepared histological sections from patients with breast cancer. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Administration Ethics Committee of Zhejiang Cancer Hospital and conducted in accordance with the Principles of Helsinki Declaration. Patient consent was not required because of the retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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