Clinical characteristics and survival outcome of patients with estrogen receptor low positive breast cancer

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ARTICLE INFO

ABSTRACT

Background: The benefit of endocrine therapy for patients with estrogen receptor (ER)-low (1%–10%) positive breast cancer is a matter for debate. We aimed to compare the clinical characteristics and survival outcome of ER-low patients with ER-high (> 10%) positive patients and ER-negative patients.

Methods: From the breast cancer database of our institution, we identified 5466 patients with known ER status who were diagnosed with early-stage breast cancer between January 2008 and December 2016. Variables associated with initiation of endocrine therapy were identified using multivariate logistic regression model. According to ER status, all patients were classified into ER-low (1%–10%), ER-high (>10%) and ER-negative subgroups. Fine and Gray competing risks regression was performed to compare the survival outcome of three subgroups.

Results: Age at diagnosis, ER status and progesterone receptor (PR) status were identified as correlates of initiation of endocrine therapy. ER-low patients were more likely to have advanced, PR-negative, human epidermal growth factor receptor 2 (HER2)-positive or grade III disease compared to ER-high patients. Similar to ER-negative patients, ER-low patients presented increased rate of locoregional recurrence (LRR), distant recurrence (DR) and breast cancer mortality (BCM) than ER-high patients. Endocrine therapy showed nonsignificant trends toward lower LRR, DR and BCM in ER-low patients.

Conclusion: Similar to ER-negative patients, ER-low patients had more aggressive clinical characteristics and worse survival outcome than ER-high patients. ER-low patients appeared to benefit less from endocrine therapy. Randomized studies are needed to further explore the endocrine responsiveness of ER-low patients.

1. Introduction

Breast cancer consists of distinct molecular subtypes categorized by the expression of hormone receptors (HR) and human epidermal growth factor receptor 2 (HER2). Estrogen receptor (ER)-positive tumors represent two thirds of breast cancer diagnoses and this proportion raises up to 79%–84% in contemporary studies [1–7]. As an important predictive marker for endocrine therapy, ER expression also represents a prognostic marker in eighth edition of American Joint Committee on Cancer (AJCC) staging system in breast cancer [8].

In 2020, the ASCO/CAP guideline recommended that 1% or more nuclear ER staining by immunohistochemistry demonstrated a positive

ER result and the indication for endocrine therapy [9]. However, the benefit of endocrine therapy for tumors staining ER positive 1%–10% (ER-low) remains controversial. Recent studies suggested ER-low patients as a heterogeneous category, whose clinical behaviors and molecular profiles appears more similar to those of ER-negative breast cancers [10–13]. Due to the low frequency of this subgroup, there is limited evidence on endocrine responsiveness of ER-low patients. In this prospective cohort study, we compared the clinical characteristics and survival outcomes of ER-low patients with ER-high (>10%) and ER-negative patients.

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2. Materials and methods

2.1. Patient cohort

From the Breast Cancer Information Management System (BCIMS) of our institution [14], we identified 6688 consecutive patients with invasive breast cancer diagnosed between January 2008 and December 2016 with known ER status. The BCIMS prospectively collected demographic, clinical and outcome information of patients who received diagnoses of breast cancer in our institution since January 2008. All patients were actively followed by telephone contact and medical visits until death or June 19, 2020, whichever came first. Patients who did not receive surgery and those with synchronous distant metastases, unknown tumor size or unknown number of positive lymph nodes were excluded. Since early clinical events after diagnosis might induce potential selection bias regarding receipt of endocrine therapy, we further excluded patients who survived less than 6 months and those who experienced LRR (locoregional recurrence), DR (distant recurrence) and all-cause mortality within 6 months after diagnosis (Fig. 1). In total, 5466 patients were included into this study. Institutional review board approval was acquired from the Clinical Test and Biomedical Ethics Committee of our institution.

Paraffin-embedding of tissues were mostly performed in our institution, with only 267 sample slides obtained from other clinical centers. According to the same standard operating procedures, all immunohistochemical (IHC) staining of ER on paraffin-embedded slides were conducted with selected antibody in our institution, after deparaffinization, rehydration, and antigen retrieval. Reports of ER status included both the percentage and intensity of nuclear staining in tumor cells. Progesterone receptor (PR) or ER positive was defined as 1% or more nuclear PR or ER staining by IHC, respectively.

2.2. Statistical analysis

Patients were classified into three groups: ER-low patients, ER-high and ER-negative patients. Comparisons of patient clinical characteristics were performed between groups using Chi-square test. Correlates of initiation of endocrine therapy were identified using multivariate logistic regression model, with odds ratio (OR) adjusted by age at diagnosis, year of diagnosis, TNM stage, ER status, PR status, HER2 status and histologic grade.
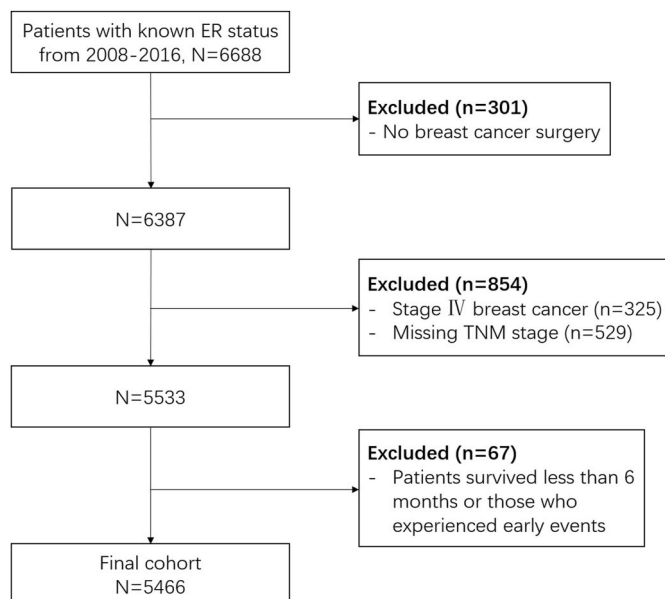
LRR, DR and BCM (breast cancer mortality) were defined as tumor recurrence in the ipsilateral chest wall or regional lymph nodes, disease recurrence at distant organs and death from breast cancer, respectively. Time interval for clinical endpoints were calculated from date of diagnosis. The rates of LRR, DR, and BCM were estimated by cumulative incidence function, with Gray's test assessing the differences between groups. Death was deemed as a competing risk event for LRR and DR. Other-cause mortality was treated as competing risk event for BCM. Correlates of survival outcome were identified using Fine and Gray competing risks proportional hazards regression model, with hazard ratio (HR) adjusted by age at diagnosis, year of diagnosis, TNM stage, PR status, HER2 status, histologic grade, receipt of radiotherapy and endocrine therapy. R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis. A 2-tailed P value less than 0.05 was deemed statistically significant.

3. Results

Of the 5466 patients identified in this study, 277 (5.1%) patients were ER-low, 3457 (62.2%) patients were ER-high, and 1732 (32.7%) patients were ER-negative. Table 1 summarized the baseline characteristics of patients stratified by three groups. Compared with ER-high patients, ER-low patients were more likely to have advanced, PR-negative, HER2-positive or grade III disease. Compared with ER-negative patients, ER-low patients were more likely to have grade II or PR-positive disease.

The median value of ER ranged from 0.75 to 0.85 during the study period (Supplementary Fig. S1). All patients received chemotherapy and surgery (mastectomy or lumpectomy). ER-low patients were less likely to receive endocrine therapy than ER-high patients. Compared with ER-negative patients, ER-low patients were more likely to receive endocrine therapy and radiotherapy (Table 1). For the entire cohort, the rates of patients receiving endocrine therapy ranged from 59.1% to 75.3% (Supplementary Fig. S1). For ER-low patients, the rates of endocrine therapy use ranged from 57.7% to 77.3%. For ER-negative patients, the rates of endocrine therapy use ranged from 9.7% to 22.2% (Supplementary Fig. S1).

For the entire cohort, age at diagnosis, ER status and PR status were identified as correlates of initiation of endocrine therapy (all $P < 0.001$; Supplementary Table S1). Among patients with ER $\geq 1\%$ tumor (n = 3726), the information on endocrine therapy initiation and duration is available for 2679 (71.6%) patients in our study. The median period between diagnosis and endocrine therapy initiation was 147 days. The median endocrine therapy duration was 3.0 year.

At a median follow-up of 74.0 months, 130 patients experienced LRR as the first event. A total of 553 patients developed DR and 247 patients died from breast cancer. Compared with ER-low patients, ER-high patients presented decreased LRR (5-year cumulative incidence 1.2% vs 5.5%; HR 0.266; 95%CI, 0.144–0.492; $P < 0.001$; Fig. 2; Table 2), DR (5-year cumulative incidence 6.8% vs 17.0%; HR 0.452; 95%CI, 0.323–0.633; $P < 0.001$; Fig. 2; Table 2) and BCM (5-year cumulative incidence 1.6% vs 9.0%; HR 0.197; 95%CI, 0.118–0.329; $P < 0.001$; Fig. 2; Table 2). ER-low patients presented similar rates of LRR (5-year cumulative incidence 4.0% vs 5.5%; $P = 0.110$; Fig. 2; Table 2), DR (5-year cumulative incidence 14.3% vs 17.0%; $P = 0.700$; Fig. 2; Table 2) and BCM (5-year cumulative incidence 8.5% vs 9.0%; $P = 0.810$; Fig. 2; Table 2) to ER-negative patients.

Fig. 2 also displays survival outcomes between ER-low and ER-high patients with endocrine therapy. In patients receiving endocrine therapy, compared with ER-low patients, ER-high patients had reduced rates of LRR (5-year cumulative incidence 1.2% vs 4.2%; HR 0.409; 95%CI, 0.192–0.869; $P = 0.020$; Fig. 2; Table 2), DR (5-year cumulative incidence 6.4% vs 16.0%; HR 0.535; 95%CI, 0.359–0.797; $P = 0.002$; Fig. 2; Table 2), and BCM (5-year cumulative incidence 1.3% vs 8.2%; HR 0.216; 95%CI, 0.114–0.410; $P < 0.001$; Fig. 2; Table 2). In contrast, ER-low patients with endocrine therapy exhibited similar rates of LRR (5-

Fig. 1. Flow diagram of patient selection.

Patients with known ER status from 2008-2016, N=6688

Excluded (n=301)
- No breast cancer surgery

N=6387

Excluded (n=854)
- Stage IV breast cancer (n=325)
- Missing TNM stage (n=529)

N=5533

Excluded (n=67)
- Patients survived less than 6 months or those who experienced early events

Final cohort N=5466

Table 1
Characteristics of patients with ER-low, ER-high or ER-negative breast cancer.

		ER-low	ER-high	P^a	ER-negative	P^b
		n = 277	n = 3457		n = 1732	
Age (mean, SD)		48.41 (9.13)	47.85 (9.49)	0.349	49.27 (9.85)	0.171
Year of diagnosis				0.877		0.018
	2008–2012	114 (41.2)	1446 (41.8)		849 (49.0)	
	2013–2016	163 (58.8)	2011 (58.2)		883 (51.0)	
TNM stage				0.036		0.219
	I	48 (17.3)	733 (21.2)		376 (21.7)	
	II	148 (53.4)	1935 (56.0)		852 (49.2)	
	III	81 (29.2)	789 (22.8)		504 (29.1)	
PR status				<0.001		<0.001
	Negative	138 (49.8)	410 (11.9)		1502 (86.7)	
	Positive	139 (50.2)	3047 (88.1)		230 (13.3)	
HER2 status				<0.001		0.073
	Negative	115 (41.5)	2313 (66.9)		829 (47.9)	
	Unknown	26 (9.4)	554 (16.0)		179 (10.3)	
	Positive	136 (49.1)	590 (17.1)		724 (41.8)	
Histologic grade				<0.001		<0.001
	I	1 (0.4)	111 (3.2)		3 (0.2)	
	II	60 (21.7)	1539 (44.5)		223 (12.9)	
	III	180 (65.0)	1296 (37.5)		1141 (65.9)	
	Unknown	36 (13.0)	511 (14.8)		365 (21.1)	
Surgery				0.182		0.999
	Mastectomy	263 (94.9)	3201 (92.6)		1643 (94.9)	
	Lumpectomy	14 (5.1)	256 (7.4)		89 (5.1)	
Radiotherapy				0.114		0.048
	No	167 (60.3)	2254 (65.2)		1153 (66.6)	
	Yes	110 (39.7)	1203 (34.8)		579 (33.4)	
Endocrine therapy				<0.001		<0.001
	No	85 (30.7)	242 (7.0)		1491 (86.1)	
	Yes	192 (69.3)	3215 (93.0)		241 (13.9)	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.
^a Comparisons between ER-low and ER-high.
 ^a Comparisons between ER-low and ER-high.
 ^b Comparisons between ER-low and ER-negative.

year cumulative incidence 4.2% vs 2.5%; $P = 0.210$; Table 2), DR (5-year cumulative incidence 16.0% vs 20.7%; $P = 0.130$; Table 2) and BCM (5-year cumulative incidence 8.2% vs 10.8%; $P = 0.160$; Table 2) to ER-negative patients with endocrine therapy.

In patients not receiving endocrine therapy, compared with ER-low patients, ER-high patients had decreased rates of LRR (5-year cumulative incidence 1.6% vs 8.3%; HR 0.068; 95%CI, 0.017–0.275; $P < 0.001$; Fig. 2; Table 2), DR (5-year cumulative incidence 12.6% vs 19.2%; HR 0.479; 95%CI, 0.231–0.992; $P = 0.047$; Fig. 2; Table 2), and BCM (5-year cumulative incidence 5.8% vs 10.9%; HR 0.258; 95%CI, 0.100–0.667; $P = 0.005$; Fig. 2; Table 2). On the contrary, compared with ER-low patients not receiving endocrine therapy, ER-negative patients not receiving endocrine therapy had comparable LRR (5-year cumulative incidence 4.2% vs 8.3%; $P = 0.550$; Table 2), DR (5-year cumulative incidence 13.3% vs 19.2%; $P = 0.230$; Table 2) and BCM (5-year cumulative incidence 8.1% vs 10.9%; $P = 0.650$; Table 2).

To explore potential effect modification, we performed stratified analyses in ER-low and ER-high patients. In stratified analyses, greater benefit from endocrine therapy was found in ER-high patients, in terms of DR (P-for-interaction = 0.488) and BCM (P-for-interaction = 0.030; Supplementary Table S2). In ER-low patients, the receipt of endocrine therapy showed nonsignificant trends toward lower LRR (HR 0.541; 95%CI, 0.191–1.531; $P = 0.247$), DR (HR 0.859; 95%CI, 0.452–1.632; $P = 0.643$) and BCM (HR 0.722; 95%CI, 0.308–1.693; $P = 0.454$; Supplementary Table S2; Fig. 2).

4. Discussion

Since the benefits of endocrine therapy might be lower or absent in patients with tumors that have 1%–10% ER staining, ER-low patients were recommended to be reported as a new category [9]. In this large sample sized prospective cohort study, ER-low patients demonstrated more aggressive clinical characteristics than ER-high patients.

Moreover, ER-low patients appeared to benefit less from endocrine therapy.

Increasing evidence suggested the difference of clinicopathological characteristics between ER-low and ER-high patients. In a retrospective study including 9639 patients with breast cancer [10], compared with patients whose tumors were ER-positive ≥ 10%, those with ER-positive 1%–9% were younger, more likely to have advanced, HER2-positive and grade III disease. In a retrospective cohort of 1823 patients with breast cancer, Poon et al. [12] found that ER-low (1%–10%) patients revealed more similar clinicopathologic and biomarker profiles (including younger age, larger tumor, high proliferation, HER2 and basal markers expression) to ER-negative than ER-high (>10%) patients. Consistently, in the present study, ER-low patients were more likely to have advanced, PR-negative, HER2-positive or grade III disease when compared with ER-high patients, suggesting more aggressive clinicopathological characteristics.

There is limited evidence on the endocrine responsiveness and clinical prognosis for patients with low level (1%–10%) ER expression. In a retrospective study including patients with stage II or III HER2-negative primary breast cancer, patients with 1% ≤ ER < 10% tumors had worse recurrence-free survival and overall survival than patients with ER > 10% tumors. Moreover, adjuvant hormonal therapy was not associated with better recurrence-free survival or overall survival in patients with 1%≤ ER < 10% tumors [15]. Yi et al. who analyzed 9639 patients with breast cancer, documented that patients with ER-positive 1%–9% breast cancer who received endocrine therapy had worse survival rates than the counterparts with ER-positive ≥ 10% breast cancer [10]. Poon et al. [12] demonstrated that patients with ER-low (1%–10%) cancers who received hormonal therapy showed a significantly worse survival outcome than the ER-high (>10%) cancer patients. In the present study, ER-low patients had poorer survival outcome than ER-high patients, independent of receipt of endocrine therapy. Moreover, ER-low patients appeared to benefit less from endocrine therapy.
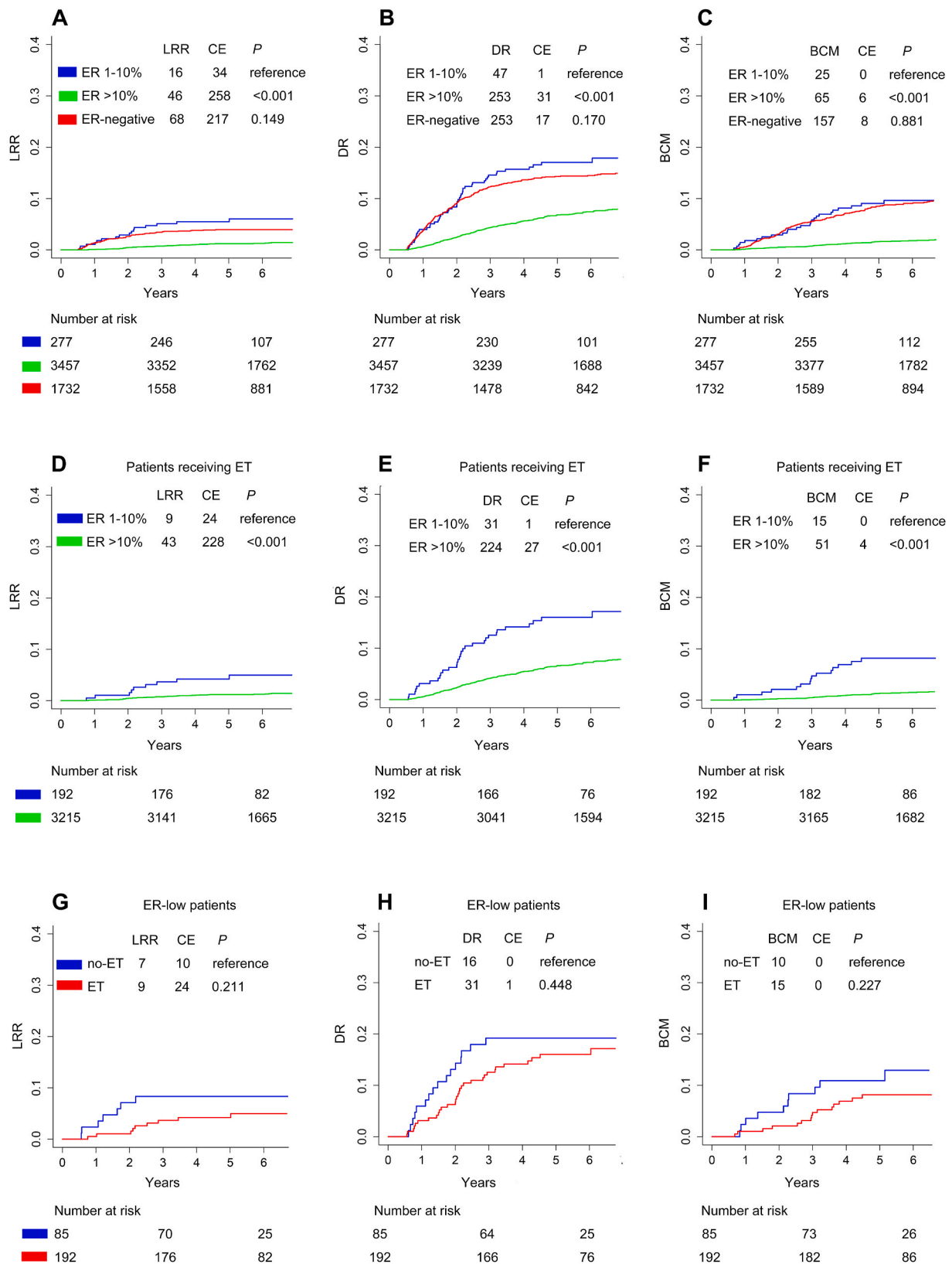
Fig. 2. Cumulative incidence of LRR, DR and BCM in ER-low, ER-high and ER-negative subgroups (A–C); in ER-low and ER-high subgroups who received ET (D–F); in ER-low patients, stratified by receipt of ET (G–I).

Table 2

Adjusted Fine and Gray models for survival outcomes among three subgroups, stratified by receipt of endocrine therapy[a].

	LRR		DR		BCM	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
All patients						
ER-low	Reference		Reference		Reference	
ER-negative	0.603 (0.323–1.128)	0.110	0.929 (0.640–1.349)	0.700	0.940 (0.564–1.568)	0.810
ER-high	0.266 (0.144–0.492)	<0.001	0.452 (0.323–0.633)	<0.001	0.197 (0.118–0.329)	<0.001
Patients receiving endocrine therapy						
ER-low	Reference		Reference		Reference	
ER-negative	0.505 (0.172–1.476)	0.210	1.428 (0.901–2.262)	0.130	1.598 (0.830–3.079)	0.160
ER- high	0.409 (0.192–0.869)	0.020	0.535 (0.359–0.797)	0.002	0.216 (0.114–0.410)	<0.001
Patients not receiving endocrine therapy						
ER-low	Reference		Reference		Reference	
ER-negative	0.756 (0.301–1.900)	0.550	0.724 (0.428–1.227)	0.230	0.853 (0.425–1.711)	0.650
ER- high	0.068 (0.017–0.275)	<0.001	0.479 (0.231–0.992)	0.047	0.258 (0.100–0.667)	0.005

Abbreviations: LRR, locoregional recurrence; DR distant recurrence; BCM, breast cancer mortality; HR, hazard ratio; CI, confidence interval.

[a] The Fine and Gray model was adjusted by age at diagnosis, year of diagnosis, TNM stage, progesterone receptor (PR) status, HER2 status, histologic grade, receipt of radiotherapy and endocrine therapy.

However, none of these nonrandomized studies can address the endocrine responsiveness for ER-low patients.

Genomic assays were conducted to explain the biological basis of clinical inconsistency between ER-low and ER-high breast tumors. Iwamoto et al. who performed gene-expression profiling in 465 primary breast cancers, demonstrated that the average ESR1 expression was significantly higher in the ≥10% ER-positive patients relative to the 1%–9% or ER-negative patients. Leveraging the PAM50 classifier, 8% of 1%–9% ER-positive patients were identified as luminal B and 48% of 1%–9% ER-positive patients were identified as basal-like [13]. These findings indicated the biological difference between ER-low and ER-high breast tumors.

The clear threshold for withholding endocrine therapy is still controversial. A lower cut-off value for defining ER positivity means raised chance of receiving less toxic endocrine therapy. However, if the benefits of endocrine therapy are absent in patients with ER-low breast cancer, these patients will experience unnecessary adverse effect from endocrine therapy. The benefit-harm assessment of endocrine therapy is important for these patients.

There are several limitations of our study. First, due to the limited sample size of patients with ER-low tumors, we cannot assess the optimal threshold of ER positivity for endocrine therapy. Second, in some subgroups, the relatively small number of patients and events might weaken the statistical power. Third, although minority (4.9%) of tissues were fixed and paraffin-embedded in other medical centers, the IHC staining of ER for all slides was conducted in our institution. As all steps were performed according to the standard operating procedures, we thought the potential heterogeneity in process of tissue embedding might not affect results.

5. Conclusion

Our study provides support that ER-low patients had more aggressive clinical behaviors and worse survival outcome than ER-high patients. ER-low patients appeared to benefit less from endocrine therapy. The benefit of endocrine therapy for ER-low patients needs to be further explored in randomized studies.

Ethics statement

Institutional review board approval was acquired from the Clinical Test and Biomedical Ethics Committee of our institution.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2022.03.002.

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