A Real-World-Data Retrospective Cohort Study of Low Estrogen Receptor Positive Early Breast Cancer: Natural History and Treatment Outcomes.

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Abstract

Purpose

Estrogen receptor–positive (ER⁺) breast cancer (BC) is a heterogeneous disease with an ongoing debate regarding the optimal cutoff point for clinically relevant ER expression. We used a real-world database to assess prognostic and predictive values of lower ER expression levels on treatment outcomes with endocrine therapy.

Methods

We used a nationwide electronic health record– (EHR-) derived deidentified database. Descriptive statistics were used to evaluate the correlation between ER expression, tumor characteristics, and treatment patterns among patients with early-stage BC. We used Kaplan-Meier survival curves to estimate relapse-free survival (RFS) and overall survival (OS). To assess an optimal ER expression level cut point, correlations between ER⁺ expression and clinical outcomes were performed.

Results

Among 4697 patients with early-stage BC, 83 (1.76%) had ER⁺-low BC (ER expression, 1%-9.99%), and 36 (0.8%) had ER⁺-intermediate BC (10%-19.9%). ER⁺-low tumors were associated with higher tumor grade, larger size and higher axillary tumor burden than ER⁺-high tumors ($\geq 20\%$ ER expression). African Americans had a higher prevalence of both triple-negative BC (TNBC; 21%) and ER⁺-low BC (22%) than ER⁺-high tumors (8%). Patients with ER⁺-low and ER⁺-intermediate tumors had survival outcomes similar to patients with TNBC and worse survival outcomes than patients with ER⁺-high tumors ($P < .001$). No significant correlations between endocrine therapy and RFS or OS were observed among patients with either ER⁺-low or ER⁺-intermediate BCs. Further tumors with $< 20\%$ ER expression were associated with worse outcomes.

Conclusions

Patients with ER expression levels $< 20\%$ derive minimal benefit from endocrine therapies.

Introduction

Breast cancer (BC) is the most common malignancy worldwide. In 2020, an estimated 279 100 new cases were diagnosed in the United States alone [1]. Hormone receptor–positive (HR⁺) BC is the most common subset (~ 60%) and is defined by the 2010 American Society of Clinical Oncology (ASCO) and College of American Pathology (CAP) guidelines as a tumor with at least 1% of cancer nuclei that stain positive for HRs for estrogen or progesterone by immunohistochemistry [2]. Notwithstanding the clinical importance of pathological assessments of both HRs, decisions pertaining to endocrine therapy (ET) are largely based on expression levels of estrogen receptors (ERs), and progesterone receptors are accepted as a prognostic biomarker.

The current definition of ER positivity presents an obvious caveat, as it does not encompass the biological heterogeneity inherent in the wide distribution of ER expression levels between tumors. Moreover, it suggests that

patients with BCs with varying levels of ER expression have similar natural histories and derive similar benefit from approved and developing ETs. This is an incorrect premise. Data show that patients with tumors harboring lower levels of ERs have a poor prognosis similar to patients with strictly defined triple-negative BC (TNBC); patients with TNBC have a 3-year absolute risk of BC recurrence of 30% despite multimodality therapy [3–5]. The results of a meta-analysis of 21 457 patients with early-stage BC showed that ER⁺-low status (i.e., ligand-based assay, HR < 10 fmol/mg cytosol protein) was not significantly correlated with clinical benefit from adjuvant ET [6]. Current guidelines for ER testing in BCs, published by ASCO and CAP, define ER⁺-low tumors as cancer with 1–10% staining for ERs and affirms the optimal cut point for ER positivity using the universally adopted immunohistochemistry scoring system [7]. It is remarkable that this revision recognizes that most of the trials supporting the benefit of adjuvant ET for early ER⁺ BC conducted in the 1990s used quantitative measures of HRs that are no longer routinely used.

Albeit their poor prognosis and apparent lack of benefit from ETs, treatment development for patients with BCs with lower levels of ERs has been stagnant as these patients are not allowed to participate in clinical trials for patients with TNBC under the assumption of better outcomes and benefit from endocrine therapies. This is important as *Developmental Therapeutics* have gained momentum and continues to develop treatments targeted to strictly defined subsets of BCs (i.e., TNBC vs. ER⁺ BCs). This is evidenced by a new surge in clinical trials that assess the efficacy of new agents targeting ERs (e.g., selective estrogen receptor modulators [SERMs] and degraders [SERDs]) [8].

We conducted a large real-world retrospective study of patients with early-stage BC to improve current understanding of the prevalence and natural history of tumors with lower levels of ER expression and treatment patterns of patients with this disease. Moreover, we retrospectively assessed the prognostic and predictive values of an alternative definition of ER⁺-low BC in relation to treatment outcomes with ET.

Methods

Data source

This retrospective cohort study used the nationwide Flatiron Health electronic health record– (FEHR-) derived deidentified database. This is a real-world longitudinal database that comprises deidentified patient-level structured and unstructured data, which were curated via technology-enabled abstraction [9, 10]. The database originated from approximately 280 US cancer clinics (~ 800 sites of care). The majority of patients were from community oncology settings, and relative community/academic proportions may vary depending on study cohort.

Our cohort (N = 9386) included patients with early-stage BC diagnosed between January 2011 and May 2020. Institutional Review Board approval of the study was obtained prior to study conduct and included a waiver for informed consent. The data were deidentified and subject to obligations to prevent reidentification and protect patient confidentiality. The dataset included patient-related and tumor-related variables, including epidemiological, clinical, and pathological data as well as age at diagnosis, race, ethnicity, menopausal status, tumor size, grade, Ki-67 (%), number of lymph nodes involved, chemotherapy, and ET histories. HRs and human epidermal growth factor receptor 2 (HER2) expressions were assessed locally in accordance with standard immunohistochemistry nuclei staining by a local pathologist. Expression of HRs and HER2 was measured as the percent of nuclei staining and membrane staining, respectively. HER2 amplification was assessed according to locally assessed fluorescent in situ hybridization.

Recurrence-free survival (RFS) was defined as the time in months from the date of first treatment to the date of diagnosis of metastasis, first local recurrence, or death, whichever occurred first; patients without these data were censored at the last date known alive. Overall survival (OS) was defined as the time from the date of first treatment to the date of death; patients without these data were censored at the last date known alive.

Real-world cohort key inclusion and exclusion criteria

Inclusion criteria used to select cases from the FEHR BC cohort included having a diagnosis of histologically proven stage I-III BC and receiving surgical treatment for BCs with curative intent. Exclusion criteria were having carcinoma *in situ*, metastatic BC and having HER2⁺ BC. Patients who received chemotherapy before or after surgical treatment were classified as having received perioperative chemotherapy. Information on perioperative chemotherapy, ET, and radiation therapy was abstracted. Because of the diversity in the number of chemotherapy regimens, these regimens were classified as anthracycline- and taxane-containing, anthracycline-only and taxane-only regimens, and *other*. Patients were followed from the date of resection (index date) until the date of biopsy-proven tumor recurrence, death, or last follow-up. Patients with > 90 days between diagnosis and first Flatiron Health–reported structured activity were excluded to avoid missing treatment data. Furthermore, any patient with < 90 days of follow-up from the index date was excluded.

Statistical methods

Among 9386 early-stage BC patients, 3490 had missing or incomplete ER, PR, or HER2 status and/or did not have at least 90 days of follow-up. A further 1299 patients had HER2⁺ BC and were also excluded from the final analysis, leaving 4697 evaluable patients (634 with TNBC and 4063 with ER⁺ BC).

Initially, descriptive characteristics were described by using means (standard deviations) and medians (ranges) for continuous variables and frequencies for categorical variables. The ER⁺-low and ER⁺-intermediate cohorts were compared using the Kruskal-Wallis test for continuous variables and Fisher exact test for categorical variables.

A training dataset and test dataset were established by dividing the ER⁺ dataset into two-thirds training and one-third test data. The range of ER percent staining values was divided into 10 levels, with 10% increments. A cut point analysis was performed on the training dataset using the Contal and O'Quigley method [11], which enabled us to assess the optimum cut point of ER⁺ staining, which was correlated with RFS using Cox proportional hazards regression. Because the analysis did not identify a cut point that was adequately and significantly differentiated from other cut points, we used 20% as a clinically reasonable cut point ($P < .0001$). New exploratory ER⁺-low and ER⁺-high groups were defined by this cut point (1%-19.9% vs $\geq 20\%$).

We then performed Kaplan-Meier survival curves for RFS and OS for both the training and test sets. Furthermore, a multivariable Cox proportional hazards survival analysis was used on the training set and adjusted for age, radiotherapy, and ET. This model was then used on the test set, and the c-statistic was used to check for model fit. Hazard ratios and 95% confidence intervals are reported. All analyses were performed in SAS v 9.4 (Cary, NC).

Results

In the total cohort of 9386 patients with early-stage BC, only 4697 were evaluable (634 with TNBC and 4063 with ER⁺ BCs). Only 83 cases were classified as ER⁺ low (ER expression 1%-9.99%). Median follow-up was 63 (range, 24–84) months.

Baseline demographics and clinical, treatment, and outcome patterns

The majority (72%) of patients were White, and African Americans represented 10% of the cohort analyzed. There were 38 males in this dataset. Median age in years at diagnosis of BC was 63 (range, 24–84 years), and most women were postmenopausal (72%). Eighty-two percent of patients had invasive ductal carcinomas, 12% had lobular carcinomas, and 47% had grade 2 tumors. Up to 63% of patients received adjuvant radiation therapy, and 37% underwent mastectomies (Table 1). Patients with ER⁺ tumors had significantly longer RFS and OS than patients with TNBC (Fig. 1).

Table 1
Cohort description

Characteristics		Group			
		Triple negative n = 634 (%)	ER ⁺ low n = 83 (%)	ER ⁺ intermediate n = 36 (%)	ER ⁺ high n = 3944 (%)
Gender	Female	634 (100)	83 (100)	36 (100)	3906 (100)
	Male	0 (0)	0 (0)	0 (0)	38 (0.96)
Race	Asian	9 (1.52)	1 (1.35)	1 (2.78)	112 (3.09)
	Black or African American	122 (20.61)	16 (21.62)	6 (16.67)	288 (7.95)
	Hispanic or Latino	1 (0.17)	0 (0)	0 (0)	8 (0.22)
	Other	72 (12.16)	7 (9.46)	5 (13.89)	549 (15.16)
	White	388 (65.54)	50 (67.57)	24 (66.67)	2664 (73.57)
Ethnicity	Hispanic or Latino	51 (8.04)	7 (8.43)	3 (8.33)	247 (6.26)
	Non-Hispanic	583 (91.96)	76 (91.57)	33 (91.67)	3697 (93.74)
Menopausal Status	N/A - patient is male	0 (0)	0 (0)	0 (0)	37 (0.94)
	Perimenopausal	16 (2.52)	1 (1.2)	2 (5.56)	95 (2.41)
	Postmenopausal	436 (68.77)	54 (65.06)	24 (66.67)	2886 (73.17)
	Premenopausal	126 (19.87)	21 (25.3)	5 (13.89)	691 (17.52)
	Unknown/not documented	56 (8.83)	7 (8.43)	5 (13.89)	235 (5.96)
Histology	Ductal	581 (91.79)	75 (90.36)	31 (86.11)	3142 (79.77)
	Lobular	10 (1.58)	3 (3.61)	2 (5.56)	564 (14.32)
	Mixed	9 (1.42)	1 (1.2)	1 (2.78)	96 (2.44)
	Other	33 (5.21)	4 (4.82)	2 (5.56)	137 (3.48)
Tumor Grade	Grade 1	10 (1.58)	4 (5)	3 (8.33)	1127 (28.82)
	Grade 2	113 (17.91)	15 (18.75)	11 (30.56)	2108 (53.9)
	Grade 3	508 (80.51)	61 (76.25)	22 (61.11)	676 (17.28)
KI-67	< 20%	28 (8.95)	10 (25)	1 (6.67)	1122 (58.9)
	≥ 20%	285 (91.05)	30 (75)	14 (93.33)	783 (41.1)
Clinical T stage	1	110 (35.6)	14 (38.89)	5 (33.33)	764 (59.09)
	2	135 (43.69)	16 (44.44)	7 (46.67)	379 (29.31)
	3,4	64 (20.71)	6 (16.67)	3 (20)	150 (11.6)

Characteristics		Group			
		Triple negative n = 634 (%)	ER ⁺ low n = 83 (%)	ER ⁺ intermediate n = 36 (%)	ER ⁺ high n = 3944 (%)
Clinical N stage	0	160 (54.98)	19 (59.38)	9 (64.29)	907 (76.22)
	1	100 (34.36)	10 (31.25)	4 (28.57)	224 (18.82)
	2,3	31 (10.65)	3 (9.38)	1 (7.14)	59 (4.96)
Radiotherapy	No/unknown	237 (37.38)	29 (34.94)	14 (38.89)	1429 (36.23)
	Yes	397 (62.62)	54 (65.06)	22 (61.11)	2515 (63.77)
Chemotherapy	Other	13 (3.04)	0 (0)	2 (7.14)	66 (6.8)
	Anthracycline without taxane	12 (2.81)	0 (0)	3 (10.71)	41 (4.23)
	Taxane without anthracycline	132 (30.91)	15 (29.41)	4 (14.29)	442 (45.57)
	Taxane and anthracycline	270 (63.23)	36 (70.59)	19 (67.86)	421 (43.4)
Surgery	Mastectomy	330 (54.1)	42 (50.6)	20 (55.56)	2493 (64.59)
	Other	280 (45.9)	41 (49.4)	16 (44.44)	1367 (35.41)
Endocrine therapy	No	605 (95.43)	54 (65.06)	18 (50)	1673 (42.42)
	Yes	29 (4.57)	29 (34.94)	18 (50)	2271 (57.58)
Age at diagnosis	Mean	58.5	55.62	59.53	62.62
	Median	58.67	54.91	60.65	63.92
	Minimum	24.03	26.99	31.05	25.07
	Maximum	84.24	80.06	81.46	84.33
	Standard deviation	12.35	13.33	11.66	11.92
Follow-up Time (months)	Mean	58.5	55.62	59.53	62.62
	Median	58.67	54.91	60.65	63.92
	Minimum	24.03	26.99	31.05	25.07
	Maximum	84.24	80.06	81.46	84.33
	Standard deviation	12.35	13.33	11.66	11.92
Abbreviations: Estrogen Receptor, ER.					
Triple negative defined as ER and PR < 1% staining; ER ⁺ low 1%-9.99% staining; ER ⁺ intermediate 10%-19.99%; ER ⁺ high ≥ 20% staining.					

Distribution of ER expression and pathological characteristics

A total of 4063 patients with ER⁺/HER2⁻ early-stage BC were included in our analysis, of whom 83 (1.8%) had ER⁺-low (ER staining, 1%-9.99%) and 36 (0.8%) had ER⁺-intermediate (ER staining 10%-19.99%) BC. Both TNBC and ER⁺-low tumors were more commonly observed among patients < 60 years of age; however, patients with higher ER expression were typically older. African American patients had a higher frequency of both TNBC (21%) and ER⁺-low (22%) BC than ER⁺-high (8%) tumors. The majority of ER⁺-high tumors had low to intermediate histological grades, whereas most tumors with lower levels of ER expression were grade 3 (Table 1). Patients with ER⁺-high tumors were also diagnosed with smaller tumors and lower axillary tumor burden than those with ER⁺-low tumors.

Clinical outcomes of patients with ER⁺-low and -intermediate early-stage BCs

There was no statistically significant difference between the epidemiological, clinical, and pathological characteristics of patients with ER⁺-low and ER⁺-intermediate tumors (Table 2). Surgical and radiation treatment patterns were similar between these two groups. More patients in the ER⁺-intermediate group received adjuvant ET (unadjusted $P = .005$). Furthermore, more patients with ER⁺-low tumors received adjuvant chemotherapy with both anthracycline- and taxane-containing perioperative regimens (unadjusted, $P = .009$). In univariate analyses, patients with ER⁺-low and ER⁺-intermediate tumors had OS and RFS similar to patients with TNBC (Fig. 2). Because of the low number of patients in the ER-low and ER-intermediate groups, multivariate analyses were not conducted.

Table 2
Comparison between ER low+ and ER intermediate+ groups

Characteristics		Group		
		ER ⁺ low n = 83	ER ⁺ intermediate n = 36	P value*
Ethnicity	Hispanic or Latino	7 (8.43)	3 (8.33)	1.000
	Non-Hispanic	76 (91.57)	33 (91.67)	
Race	Asian	1 (1.35)	1 (2.78)	.727
	Black or African American	16 (21.62)	6 (16.67)	
	Other	7 (9.46)	5 (13.89)	
	White	50 (67.57)	24 (66.67)	
Menopausal Status	Perimenopausal	1 (1.2)	2 (5.56)	0.214
	Postmenopausal	54 (65.06)	24 (66.67)	
	Premenopausal	21 (25.3)	5 (13.89)	
	Unknown/not documented	7 (8.43)	5 (13.89)	
Histology	Ductal	75 (90.36)	31 (86.11)	0.694
	Lobular	3 (3.61)	2 (5.56)	
	Mixed	1 (1.2)	1 (2.78)	
	Other	4 (4.82)	2 (5.56)	
Tumor Grade	Grade 1	4 (5)	3 (8.33)	0.229
	Grade 2	15 (18.75)	11 (30.56)	
	Grade 3	61 (76.25)	22 (61.11)	
KI67	< 20%	10 (25)	1 (6.67)	0.255
	>=20%	30 (75)	14 (93.33)	
Clinical T stage	1	14 (38.89)	5 (33.33)	1.000
	2	16 (44.44)	7 (46.67)	
	3,4	6 (16.67)	3 (20)	
Clinical N stage	0	19 (59.38)	9 (64.29)	1.000
	1	10 (31.25)	4 (28.57)	
	2,3	3 (9.38)	1 (7.14)	
Primary Radiotherapy	No/unknown	29 (34.94)	14 (38.89)	0.684
	Yes	54 (65.06)	22 (61.11)	
Surgery	mastectomy	42 (50.6)	20 (55.56)	0.691

Characteristics		Group		
		ER ⁺ low n = 83	ER ⁺ intermediate n = 36	P value*
	other	41 (49.4)	16 (44.44)	
Endocrine therapy	Yes	42 (50.6)	8 (22.22)	0.005
	No	41 (49.4)	28 (77.78)	
Chemotherapy	Other	0 (0)	2 (7.14)	0.009
	Anthracycline without taxane	0 (0)	3 (10.71)	
	Taxane without anthracycline	15 (29.41)	4 (14.29)	
	Taxane and anthracycline	36 (70.59)	19 (67.86)	
Age (years)	Mean	55.62	59.53	.130
	Median	54.91	60.65	
	Minimum	26.99	31.05	
	Maximum	80.06	81.46	
	Standard deviation	13.33	11.66	
Follow-up (months)	Mean	55.62	59.53	.130
	Median	54.91	60.65	
	Minimum	26.99	31.05	
	Maximum	80.06	81.46	
	Standard deviation	13.33	11.66	
Abbreviations: ER, Estrogen Receptor, ER				
** ER ⁺ low 1%-9.99% staining and ER ⁺ intermediate 10%-19.99% staining.				
* The non-parametric <i>P</i> value is calculated by the Kruskal-Wallis test for numerical covariates and Fisher exact test for categorical covariates.				

Sensitivity analyses of ER cut point

Kaplan-Meier survival curves for both RFS and OS showed that patients with tumors harboring ER expression levels between 1% and 19.9% had significantly poorer outcomes than patients with expression rates $\geq 20\%$ (Fig. 3). Furthermore, a multivariable Cox proportional survival analysis was performed on the training set and showed a statistically significant correlation between higher expression of ERs ($\geq 20\%$) and improved RFS (HR, 0.55; 95% CI, 0.33–0.96; $P = .02$) and OS (HR, 0.5; 95% CI, 0.27–0.9; $P = .02$) (Harrell's c statistics, 0.677 for RFS and 0.698 for OS) (Table 3). Univariate analyses showed no significant treatment effect of ET on RFS and OS when comparing patients with tumor ER expression between 1% and 9.99% and 10% and 19.99% (Table 4).

Table 3
Cox proportional hazards regression

Recurrence-free survival analysis of maximum likelihood estimates									
Parameter		Degree of freedom	Parameter estimate	Standard error	Chi-Square	P value	Hazard ratio	95% Hazard ratio confidence limits	
*ER ⁺ low/Her2 ⁻	Ref ER ⁺ low/Her2 ⁻	1	-0.59231	0.26311	5.0678	.0244	0.553	0.330	0.926
Age under 50	Ref (50 or above)	1	-0.14587	0.15137	0.9286	.3352	0.864	0.642	1.163
Endocrine therapy	Ref (no)	1	-0.89719	0.17325	26.8186	< .0001	0.408	0.290	0.573
Primary radiotherapy	Ref (no)	1	-0.55534	0.11269	24.2846	< .0001	0.574	0.460	0.716
Fitting model to the test set, at 3 years recurrence-free survival, Harrell's c-statistic = 0.677.									
Overall Survival Analysis of Maximum Likelihood Estimates									
ER ⁺ High/Her2 ⁻	Ref (ER ⁺ low/Her2 ⁻)	1	-0.69144	0.30380	5.1799	.0228	0.501	0.276	0.908
Age under 50	Ref (50 or above)	1	-0.60046	0.20565	8.5258	.0035	0.549	0.367	0.821
Endocrine therapy	Ref (no)	1	-0.79007	0.20488	14.8702	.0001	0.454	0.304	0.678
Primary radiotherapy	Ref (no)	1	-0.63333	0.13218	22.9577	< .0001	0.531	0.410	0.688
Fitting model to the test set, at 3 years overall survival, Harrell's c-statistic = 0.698.									
Abbreviations: CI, confidence interval, CI; ER, estrogen receptor; Ref, reference.									
*ER ⁺ low 1%-19.9% staining; ER ⁺ high ≥ 20% staining.									

Table 4
Endocrine therapy treatment effect (univariate analysis)

Parameter	Recurrence free survival				Overall survival		
	Patients, no.	Events, no.	HR (95% CI)	<i>P</i> value	Events, no.	HR (95% CI)	<i>P</i> value
Patient who received ET							
ER low (1-9.99%)	41	5	Ref	Ref	3	Ref	Ref
ER intermediate (10–20%)	28	5	1.47 (0.42, 5.08)	.545	5	2.57 (0.61, 10.77)	.196
Patient who did not receive ET							
ER low (1-9.99%)	42	16	Ref	Ref	10	Ref	Ref
ER intermediate (10–20%)	8	2	0.38 (0.05, 2.86)	.346	1	n/a	n/a
Abbreviations: CI, confidence interval; ER, estrogen receptor; HR, hazard ratio; n/a, not applicable; Ref, reference, inadequate sample size to estimate.							

Discussion

ER⁺ BC is a heterogeneous disease, not only in its natural history but also in reference to its wide distribution of ER expression levels between tumors; cases of low expression represent a small proportion of cases of BC. The optimal cut point that indicates reliable prognostic ER expression and predictive information of ET benefit remains to be determined. Historically, any level of ER expression has been considered to be positive, which is counterintuitive and misleading, as tumors harboring lower levels of ERs will likely not respond to ET. In parallel, tumors with low expression rates of ERs are universally excluded from contemporary clinical trials for patients with TNBC. The corollary is that the ER⁺-low BC subset remains an orphan disease. With an increasing number of clinical trials aiming to develop new ETs (e.g., SERDs and SERMs), a better understanding of the natural history of and possible benefit from ET remains an unmet need in developmental therapeutics for patients with ER⁺-low BCs.

We conducted a large real-world retrospective cohort study of 4697 participants with early-stage ER⁺ BC or TNBC. In this cohort, the natural history of patients with early stage BCs was similar to previously published literature [12]. Our results suggest that ER⁺-low BC (expression, 1%-9.99%) represents a small subset (1.8%) of patients with ER⁺ BC. These tumors presented pathological features and prognosis similar to those of patients with TNBC. We retrospectively assessed a new cut point for the definition of ER⁺-low BC. Patients with tumors harboring ER expression rates between 10% and 19.9% (intermediate levels) presented similar clinicopathological features, natural histories, and treatment patterns to those with ER⁺-low BCs (1%-9.99%); however, anthracycline- and taxane-containing chemotherapy regimens were more commonly administered to patients with tumors with ER expression levels < 10%. Moreover, ET was not associated with clinically meaningful improvement of RFS and OS among either patients with 1–9.99% ER expression or patients with 10–20% ER expression. We also observed that an incremental expression of ER is associated with improved outcomes, further suggesting that the binary categorization of ER expression represents a simplification of continuous biological phenomena.

Our study has limitations inherent to retrospective cohort studies. There were missing data, which prevented us from including important variables, such as chemotherapy and nodal staging, into our adjusted analyses. Assessments of ER expression were not centrally reviewed. Additionally, the number of ER⁺-low and ER⁺-intermediate tumors was relatively small compared to other subtypes, limiting exploratory statistical comparisons and multivariable adjustments. Nonetheless, this is a large retrospective study that uses real-world data, which thereby increases the external validity of our findings. Given the low frequency of ER⁺-low tumors, the conduction of large prospective studies assessing the prognostic and predictive value of lower ER expression is practically unfeasible. This study therefore fills an important gap in our knowledge of the natural history of ER⁺-low and ER⁺-intermediate tumors.

Conclusions

Findings from this real-world retrospective study suggest that patients with ER expression rates < 20% have poor outcomes and derive minimal benefit from ETs. Future clinical trials for patients with TNBC should allow for participation of patients with ER-low BCs.

Declarations

Funding: Shula's Foundation.

Ethical Approval: Institutional Review Board approval of the study protocol was obtained from WCG IRB prior to study conduct and included a waiver of informed consent.

Informed Consent: This article does not contain any studies with human participants which would require informed consent.

Availability of data and materials: The data that support the findings of this study have been originated by Flatiron Health, Inc. These de-identified data may be available upon request and are subject to a license agreement with Flatiron Health; interested researchers should contact DataAccess@flatiron.com to determine licensing terms.

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Figures

A. Recurrence free survival

B. Overall survival

Figure 1

Clinical outcomes of patients with ER+ and TNBC BCs. Triple negative defined as ER/PR < 1% staining and HER2- (i.e., IHC 0/1+ and non-amplified); ER+ $\geq$ 1% staining. Abbreviations: Breast cancer, BC; Estrogen Receptor, ER; Human Epidermal growth factor receptor 2, HER2; immunohistochemistry (IHC).

A. Recurrence free survival

B. Overall survival

Figure 2

Clinical outcomes of patients with TN, low-, intermediate- and High-ER+ BCs. Triple negative defined as ER and PR < 1% staining, ER+ low 1-9.99% staining, ER+ inter, 10-19.99%, ER+ high $\geq$ 20% staining. Abbreviations: Breast cancer, BC; Estrogen Receptor, ER; Human Epidermal growth factor receptor 2, HER2; triple negative, TN.

Figure 3

Clinical outcomes of patients with ER low positive vs. ER high positive BCs. ER+ low 1-19.9% staining and ER+ high $\geq$ 20% staining. Abbreviations: Breast cancer, BC; Estrogen Receptor, ER.