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THE SMALLEST SUBTYPE IN THE SEER DATABASE: ESTROGEN RECEPTOR NEGATIVE PROGESTERONE RECEPTOR POSITIVE BREAST CANCER

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Abstract – *Objective:* *Limited data are available regarding estrogen receptor (ER) negative progesterone receptor (PR) positive (ER-PR+) breast cancer, resulting in difficult treatment decision and survival forecast for this breast can-cer subtype. This study aimed at evaluating the clinical characteristics and survival outcomes of patients with ER-PR+ breast cancer, taking into account human epidermal growth factor receptor 2 (HER2) status.*

Patients and Methods: *We identified female breast cancer patients from the Surveillance, Epidemiology, and End Results (SEER) database with a median follow-up period of 60 months from 2010 to 2012, and these patients were classified into four subtypes according to ER and PR expression, as ER+PR+, ER+PR–, ER–PR+, and ER–PR–. ER+PR– subtype was further stratified based on HER2 status. Kaplan-Meier survival plots and Cox regression models were applied to evaluate overall survival (OS) and breast cancer specific survival (BCSS) outcomes differences among breast cancer subtypes.*

Results: *Of 140,072 female breast cancer patients included in the study, 98,721 (70.48%) were ER+PR+, 16,581 (11.84%) were ER+PR-, 1,579 (1.01%) were ER-PR+, and 23,241 (16.59%) were ER-PR–. ER-PR+ patients had significantly poorer OS and BCSS than ER+PR+ and ER+PR- patients. Compared to those diagnosed with other subtypes, ER-PR+ patients were more likely to be younger, and to have higher rate of HER2 positive status, stage IV tumor, positive lymph node status, and tumor size of 21-50 mm. HER2 negativity was found to be a significant predictor of poor prognosis in terms of both OS and BCSS in ER-PR+ patients.*

Conclusions: *We found that ER-PR+ tumors represented the smallest distinct biological subtype, with poorer survival outcomes compared to ER+PR+ and ER+PR- subtypes. Moreover, ER-PR+ patients with HER2 negative breast cancer were associated with poorer OS and BCSS compared to ER-PR+ patients with HER2 positive breast cancer. These findings may help to optimize treatment and improve outcomes for ER-PR+ patients.*

KEYWORDS: *Breast cancer, Estrogen receptor, Progesterone receptor, Prognosis, Survival, SEER.*

INTRODUCTION

Breast cancer is known to be a heterogeneous disease with highly varying pathologic, molecular, and clinical features[1]. Hormone receptor status is one of the crucial factors in the diagnosis, treatment and prognostication of the disease[2].

Breast cancers are classified into four subtypes of hormone receptor status, based on estrogen receptor (ER) and progesterone receptor (PR) expression, namely ER+PR+, ER+PR−, ER−PR+, and ER−PR−. While most previous studies have reported relatively consistent results about clinical characteristics and survival outcomes of ER+PR+,

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ER+PR−, and ER−PR− subtypes[1,3,4], there is a poorer understanding of ER−PR+ subtype, due to its rarity[5]. Some studies have questioned the existence of ER-PR+ breast cancer, claiming that it is a technical artifact[6,7], whereas others have proposed that it is a unique subtype with distinct biological and clinical characteristics[1,8]. Yet, to our knowledge, apart from Parise et al[8], previous studies have one common limitation, i.e., the evaluation of the clinical characteristics and survival outcomes of ER-PR+ tumors neglected to classify this subtype with respect to human epidermal growth factor receptor 2 (HER2) status.

In this study, we aimed to evaluate the clinical characteristics and survival outcomes of patients with ER-PR+ breast cancer, based on the cases from the Surveillance, Epidemiology, and End Results (SEER) database, considering HER2 status. This involved the comparison of ER-PR+ subtype to ER+PR+, ER+ PR, and ER-PR- subtypes, and examining clinicopathological and survival differences between HER2 positive and HER2 negative tumors in ER-PR+ subtype.

PATIENTS AND METHODS

Data Source

We used the United States (US) National Cancer Institute's SEER database released in November 2018. The SEER database is characterized by broad, high quality, coverage of cancer incidence and survival, covering around 30% of the population of the US. Data collection on ER and PR status started in 1973, but incorporated information on HER2 status only in 2010. To account for HER2 status and to allow for a meaningful follow-up time, we collected information on female patients with a diagnosis of primary breast cancer from 2010 to 2012. The follow-up time was up to 83 months with a median of 60 months. Only the first malignant primary cancer cases were included, and patients were excluded if the following data were unavailable: cause of death, number of survival months, and hormone status. Patients with a diagnosis of stage 0 were also excluded. We identified 140,072 patients who met the study criteria.

We analyzed clinicopathological characteristics of breast cancer patients, including age at diagnosis (<40, 40-49, and >50 years), stage (I, II, II, and IV), grade (well-differentiated, moderately differentiated, poorly differentiated, undifferentiated, and unknown), tumor size (<20 mm, 21-50 mm, >50 mm, and unknown), lymph node status (negative lymph nodes, positive lymph nodes, and unknown), surgery (performed, not performed, unknown), HER2 status (positive, negative, and unknown or other), radiotherapy (yes and no/unknown), and chemotherapy (yes and no).

Statistical Analysis

We used the chi-square test to analyze the association between hormone receptor status and other clinicopathologic variables. We compared the overall survival (OS) and the breast cancer specific survival (BCSS) of the patients using Kaplan–Meier analysis. OS was defined as the interval from diagnosis to death from any cause, or the date of last follow-up (December 31, 2015). BCSS was defined as the interval from diagnosis to death due to breast cancer. We used log-rank test to determine the significance of differences between two or more survival curves. We performed a univariate Cox regression model to examine survival outcomes differences among breast cancer subtypes. We then performed multivariate Cox regression analyses to examine patients' BCSS time, as well as OS time, using the significant predictors of univariate analyses as control variables. Hazard ratios and 95% confidence intervals were reported.

Differences between HER2 positive and HER2 negative tumors in ER-PR+ patients were assessed by the Chi square test. Univariate and multivariate Cox regression models were fitted for the evaluation of the prognostic impact of HER2 expression in ER-PR+ cohort. All tests were two-sided, and $p < 0.05$ was considered statistically significant. In the univariate and multivariate analyses, cases with missing relevant covariables were excluded. We used R statistical software, version 3.6.1 (R Foundation for Statistical Computing) for all analyses and to create Kaplan–Meier survival plots.

RESULTS

Clinicopathological Characteristics of Breast Cancer Patients

Table 1 summarizes clinicopathological characteristics of breast cancer patients according to ER and PR status. Among 140,072 patients who met our inclusion criteria, there were 1,579 (1.01%) with ER-PR+ breast cancer, 23,241 (16.59%) with ER-PR- breast cancer, 16,581 (11.84%) with ER+PR- breast cancer and 98,721 (70.48%) with ER+/PR+ breast cancer.

ER-PR+ patients were more likely to be under 40 years than the patients in other subtypes

TABLE 1. Clinicopathological Characteristics of Female Breast Cancer Patients with ER-PR+, ER-PR-, ER+PR-, and ER+PR+ tumors (N=140,072).

Characteristic	*ER-PR+ (N=1,529 1.01%)*	*ER-PR- (N=23,241 16.59%)*	*ER+PR- (N=16,581 11.84%)*	*ER+PR+ (N=98,721 70.48%)*	*p-value*
Age at diagnosis					**<0.001**
<40	154 (10.1)	1,995(8.6)	841(5.1)	4,484 (4.5)	
40-49	367 (24.0)	4,513(19.4)	2,050 (12.4)	17,627 (17.9)	
>50	1,008 (65.9)	16,733 (72.0)	13,690 (82.6)	76,610 (77.6)	
Stage					**<0.001**
I	513 (33.6)	8114 (34.9)	7361 (44.4)	53,606 (54.3)	
II	637 (41.7)	9412 (40.5)	5635 (34.0)	30,612 (31.0)	
III	251 (16.4)	4020 (17.3)	2333 (14.1)	10,181 (10.3)	
IV	128 (8.4)	1695 (7.3)	1252 (7.6)	4322 (4.4)	
Grade					**<0.001**
Well differentiat-ed	34 (2.2)	440 (1.9)	2543 (15.3)	26,855 (27.2)	
Moderately dif-ferentiated	281 (18.4)	4171 (17.9)	6178 (37.3)	47,449 (48.1)	
Poorly differenti-ated	1105 (72.3)	17,014 (73.2)	6747 (40.7)	19,830 (20.1)	
Undifferentiated	14 (0.9)	269 (1.2)	93 (0.6)	224 (0.2)	
Unknown	95 (6.2)	1347 (5.8)	1020 (6.2)	4363 (4.4)	
Tumor Size					**<0.001**
≤20 mm	622 (40.7)	9666 (41.6)	8610 (51.9)	61,487 (62.3)	
21-50 mm	654 (42.8)	9517 (40.9)	5645 (34.0)	28,335 (28.7)	
>50 mm	170 (11.1)	2875 (12.4)	1610 (9.7)	6279 (6.4)	
Unknown	83 (5.4)	1183 (5.1)	716 (4.3)	2620 (2.7)	
Surgery					**<0.001**
Performed	1360 (88.9)	21,242 (91.4)	15,091 (91.0)	93,016 (94.2)	
Not performed	149 (9.7)	1784 (7.7)	1381 (8.3)	5280 (5.3)	
Unknown	20 (1.3)	215 (0.9)	109 (0.7)	425 (0.4)	
Lymph node					**<0.001**
Positive	602 (39.4)	9051 (38.9)	5927 (35.7)	31,032 (31.4)	
Negative	907 (59.3)	14,021 (60.3)	10,509 (63.4)	67,168 (68.0)	
Unknown	20 (1.3)	169 (0.7)	145 (0.9)	521 (0.5)	
HER2 Status					**<0.001**
Positive	422 (27.6)	6239 (26.8)	3788 (22.8)	9733 (9.9)	
Negative	1020 (66.7)	15,977 (68.7)	11,946 (72.0)	84,365 (85.5)	
Unknown or other	87 (5.7)	1025 (4.4)	847 (5.1)	4623 (4.7)	
Radiation					**<0.001**
Yes	752 (49.2)	11,057 (47.6)	8220 (49.6)	52,193 (52.9)	
No/ Unknown	777 (50.8)	12,184 (52.4)	8361 (50.4)	46,528 (47.1)	
Chemotherapy					**<0.001**
Yes	1058 (69.2)	16,856 (72.5)	8348 (50.3)	33,044 (33.5)	
No /Unknown	471 (30.8)	6385 (27.5)	8233 (49.7)	65,677 (66.5)	
Status					**<0.001**
Alive	1139 (74.5)	17202 (74.0)	13,004 (78.4)	85,457 (86.6)	
Dead	390 (25.5)	6039 (26.0)	3577 (21.6)	13,264 (13.4)	

The statistically significant *p*-values were indicated with bold characters. The chi-square test was used for *p*-value calculation.

of breast cancer (Table 1; 10.4% *vs.* 8.6%, 5.1%, 4.5%, $p<0.001$). Compared to other subtypes, ER-PR+ patients had a higher rate of stage IV tumor (Table 1; 8.4% *vs.* 7.3%, 7.6% and 4.4%, $p<0.001$), tumor size of 21-50 mm (Table 1; 42.8% *vs.* 40.9, 34.0, and 28.7, $p < 0.001$), HER2 positive status (Table 1; 27.6% *vs.* 26.8%, 22.8%, and 9.9%, $p < 0.001$), and positive lymph node status (Table 1; 39.4% *vs.* 38.9%, 35.7%, and 31.4%, $p<0.001$). Moreover, ER-PR+ patients were more likely to receive chemotherapy (Table 1; 69.2% *vs.* 50.3 and 33.5%, compared to those diagnosed with ER+PR- and ER+PR+ subtypes (Table 1; 72.3% *vs.* 40.7% and 20.1%, $p<0.001$). ER-PR+ patients had much higher rates of poorly differentiated tumor grade than ER+PR- and ER+PR+ patients (Table 1; 72.3% *vs.* 40.7% and 20.1%, $p< 0.001$). Proportions of poorly differentiated grade and larger size (>50 mm) were lower in ER- PR+ tumors than those observed in ER-PR- tumors (Table 1; 72.3% *vs.* 73.2%, $p<0.001$ and 11.1% *vs.* 12.4%, $p< 0.001$).

TABLE 2. Cox Regression Analyses of Factors Associated with OS.

	OS (Univariate)			OS (Multivariate)		
Category	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Hormone Receptor Status						
ER-PR+	Ref			Ref		
ER-PR-	1.03	(0.91, 1.15)	0.65	0.94	(0.83, 1.05)	0.275
ER+PR-	0.77	(0.69,0.87)	**<0.001**	0.73	(0.65, 0.82)	**<0.001**
ER+PR+	0.45	(0.40, 0.51)	**<0.001**	0.51	(0.46, 0.58)	**<0.001**
Age						
<40	Ref					
40-49	0.64	(0.59, 0.69)	**<0.001**	0.86	(0.79, 0.93)	**<0.001**
>50	1.21	(1.13, 1.29)	**<0.001**	1.87	(1.75, 2.01)	
Stage						
I	Ref					
II	2.00	(1.92, 2.07)	**<0.001**	1.27	(1.19, 1.35	**<0.001**
II	4.36	(4.19, 4.54)	**<0.001**	2.70	(2.50, 2.92)	**<0.001**
IV	17.24	(16.47, 18.03)	**<0.001**	6.27	(5.78, 6.81)	**<0.001**
Grade						
Well differentiated	Ref					
Moderately differentiated	1.47	(1.40, 1.54)	**<0.001**	1.08	(1.03, 1.13)	**<0.001**
Poorly differentiated	2.63	(2.51, 2.75)	**<0.001**	1.43	(1.36,1.51)	**<0.001**
Undifferentiated	2.94	(2.43, 3.55)	**<0.001**	1.35	(1.12,1.64	**<0.001**
Tumor size						
>=20 mm	Ref					
21-50 mm	2.49	(2.41, 2.57)	**<0.001**	1.40	(1.32,1.47)	**<0.001**
>50 mm	5.29	5.08, 5.51)	**<0.001**	1.69	(1.59,1.80)	**<0.001**
Surgery						
Performed	Ref					
Not performed	8.23	(7.92, 8.56)	**<0.001**	2.70	(2.56,2.83)	**<0.001**
Lymph node						
Positive	Ref					
Negative	0.43	(0.42, 0.44)	**<0.001**	0.93	(0.89,0.97)	**<0.001**
HER2 Status						
Positive	Ref					
Negative	0.93	(0.90, 0.97)	**<0.001**	1.59	(1.52,1.65)	**<0.001**
Radiation						
Yes	Ref					
No	1.88	(1.83, 1.94)	**<0.001**	1.65	(1.60,1.70)	**<0.001**
Chemotherapy						
Yes	Ref					
No	0.97	(0.94, 1.00)	0.0634			

The statistically significant *p*-values were indicated with bold characters.

Univariate and Multivariate Analyses

Univariate Cox model showed that ER and PR status, patient age, stage, grade, tumor size, lymph node, surgery, HER2 and radiation treatment significantly affected OS (Table 2; $p<0.001$). Chemotherapy treatment was found to be statistically insignificant (Table 2; $p=0.0634$). All prognostic factors were found to be significant predictors of BCSS in univariate Cox model (Table 3; $p<0.001$). Factors associated with a worse prognosis included high stage, high tumor grade, larger tumor size, positive lymph node, HER2 negativity, and lack of surgery radiation or chemotherapy treatments.

Multivariate Cox model demonstrated that patients with ER-PR+ tumor have poorer OS than patients with ER+PR- (Table 2; HR=0.73, 95% CI: (0.65, 0.82), $p<0.001$) and ER+PR+ tumors (Table 2; HR=0.51, 95% CI: (0.46,0.58), $p<0.001$), after adjusting for significant predictors of the univariate model.

We observed a similar BCSS outcome to the OS one, as shown in Table 3. ER-PR+ patients had a poorer BCSS than patients with ER+PR- tumor (HR=0.68, 95% CI: (0.60, 0.79), $p<0.001$) and ER+PR+ tumor (HR=0.37, 95% CI: (0.32, 0.43), $p<0.001$). There was no statistically significant OS and BCSS time difference between patients with ER-PR+ tumors and those with ER-PR- tumors (Table 2; $p=0.275$, Table 3; $p=0.871$).

TABLE 3. Cox Regression Analyses of Factors Associated with BCSS.

	BCSS (Univariate)			BCSS (Multivariate)		
Category	***HR***	***95% CI***	***p-value***	***HR***	***95% CI***	***p-value***
Hormone Receptor Status						
ER-PR+	Ref			Ref		
ER-PR-	1.06	(0.92, 1.21)	0.435	0.99	(0.86, 1.13)	0.871
ER+PR-	0.68	(0.59,0.78)	**<0.001**	0.68	(0.60, 0.79)	**<0.001**
ER+PR+	0.29	(0.26, 0.33)	**<0.001**	0.37	(0.32, 0.43)	**<0.001**
Age						
<40	Ref			Ref		
40-49	0.58	(0.54, 0.63)	**<0.001**	0.87	(0.80, 0.95)	**<0.001**
>50	0.69	(0.64, 0.74)	**<0.001**	1.20	(1.11, 1.29)	**<0.001**
Stage						
I	Ref			Ref		
II	4.01	(3.76, 4.28)	**<0.001**	1.65	(1.52, 1.79)	**<0.001**
II	12.57	(11.79, 13.41)	**<0.001**	2.81	(2.57, 3.06)	**<0.001**
IV	57.45	(53.76, 61.38)	**<0.001**	2.47	(1.96, 3.11)	**<0.001**
Grade						
Well differentiated	Ref			Ref		
Moderately differentiated	2.74	(2.52, 2.98)	**<0.001**	2.23	(2.03, 2.44)	**<0.01**
Poorly differentiated	7.30	(6.74, 7.91)	**<0.001**	6.02	(5.43, 6.68)	**<0.001**
Undifferentiated	8.03	(6.40, 10.09)	**<0.001**	17.92	(16.11, 19.95)	**<0.001**
Tumor size						
>=20 mm	Ref			Ref		
21-50 mm	4.25	(4.05, 4.46)	**<0.001**	1.38	(1.29,1.47)	**<0.001**
>50 mm	11.27	(10.68, 11.89)	**<0.001**	1.69	(1.58,1.81)	**<0.001**
Surgery						
Performed	Ref			Ref		
Not performed	11.69	(11.17, 12.23)	**<0.001**	2.69	(2.54,2.85)	**<0.001**
Lymph node						
Positive	Ref			Ref		
Negative	0.23	(0.22, 0.24)	**<0.001**	0.73	(0.69,0.77)	**<0.001**
HER2 Status						
Positive	Ref			Ref		
Negative	0.78	(0.74, 0.82)	**<0.001**	1.70	(1.62,1.80)	**<0.001**
Radiation						
Yes	Ref			Ref		
No	1.64	(1.57, 1.70)	**<0.001**	1.28	(1.23,1.33)	**<0.001**
Chemotherapy						
Yes	Ref			Ref		
No	0.50	(0.48, 0.52)	**<0.001**	1.49	(1.43, 1.56)	**<0.001**

The statistically significant *p*-values were indicated with bold characters.

Survival Analyses according to ER PR status

We next compared the survival differences among four subtypes. ER-PR+ breast cancer patients had significantly worse OS and BCSS compared to ER+PR- or ER+PR+ patients (Figure 1; all log-rank $p<0.0001$).

The effect of HER2 Status on Patients with ER-PR+ Tumors

We subdivided ER-PR+ tumors into two, according to HER2 status: 422 HER2 positive and 1020 HER2 negative ER-PR+ patients (Table 4). In ER-PR+ patients, HER2 expression was significantly associated with grade, stage, tumor size, lymph node status, surgery, radiotherapy, and chemotherapy. Only age was not significantly different between HER2 positive and HER2 negative patients (Table 4; $p=0.321$). HER2 positive patients showed higher rates of stage 3 and stage 4 tumors (Table 4, 19.6% *vs.* 13.4% and 7.6% *vs.* 5.3%, $p<0.001$) and tumor size of 21-50 mm (46.0% *vs.* 42.5% $p=0.0013$) and received more frequent chemotherapy than HER2 negative patients (76.3% *vs.* 68.9%, $p=0.005$).

We next examined the influence of HER2 status on OS and BCSS in ER-PR+ cohort. All

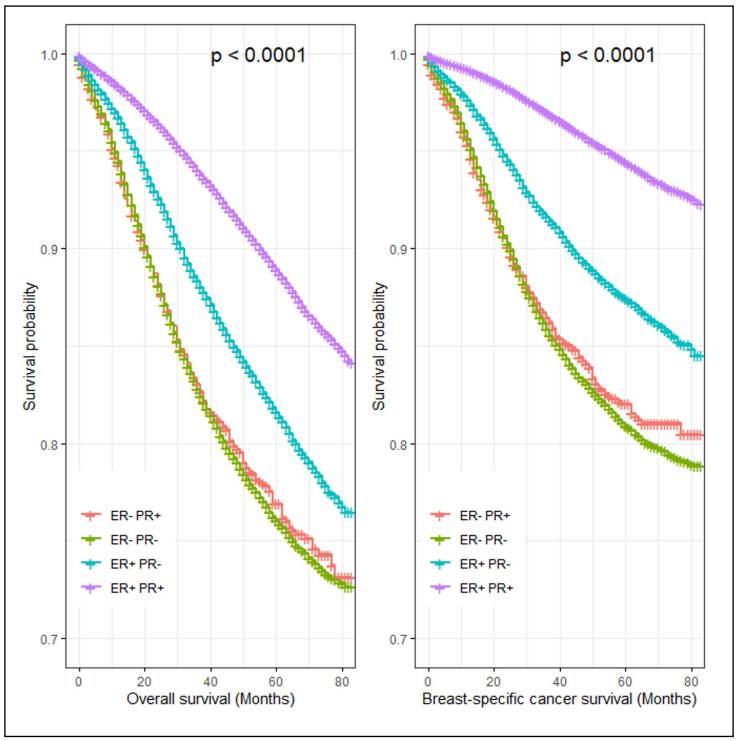

Fig. 1. Survival according to ER and PR status.

prognostic factors apart from age and grade were found to be significant predictors of OS and BCSS in univariate Cox regression analyses. The multivariate Cox regression analysis showed that HER2 negativity is a significant predictor of poor prognosis in terms of both OS and BCSS in ER+PR- patients (Table 5; HR=2.43, 95% CI: (1.81, 3.21), p<0.001, Table 6; HR=2.96, 95% CI: (2.09, 4.18), p<0.001).

Kaplan-Meier analysis showed that ER-PR+ patients with HER2 positivity had significantly better OS and BCSS values than those with HER2 negativity (Figure 2; p=0.004 and p=0.005), confirming the negative impact of negative HER2 expression in ER-PR+ tumors.

DISCUSSION

Using the SEER database, we analyzed clinical characteristics and survival outcomes of ER-PR+ tumors in comparison with ER+PR+, ER+PR-, and ER-PR- tumors. Large cohort studies have shown that the frequency of ER-PR+ subtype ranges from 1% to 4% among all invasive breast cancers[9-11]. This rare incidence makes ER-PR+ the smallest subtype, with consequently relatively less well-known characteristics and prognosis. In our study, 1.01% of total cases were ER-PR+.

HER2 Status

The amplification or overexpression of HER2 has prognostic and therapeutic significance[12,13]. Patients with HER2 positivity have low hormone receptors because of the negative association between hormone receptors and HER2[14]. It has been revealed that HER2 positivity contributes to relative resistance to endocrine therapies[15]. The use of trastuzumab plus chemotherapy has been shown to dramatically improve prognosis at all stages[14-16].

Previous studies[1,17] suggested that ER-PR+ tumors exhibit higher expression in HER2 than ER+PR+ and ER+PR- tumors. In our study, ER-PR+ subtype showed higher HER2 positivity than the other three. Our findings were consistent with a recent large cohort study showing that ER-PR+ subtype had the highest proportion of HER2 positive tumors[18].

Parise et al[8] classified ER−PR+ breast cancer subtype as HER2 positive and HER2 negative and found similar survival outcomes for the groups. Yet, the results of this study reflect the natural history of HER2 positive patients because they were not treated with the anti HER2 agent, trastuzumab.

In the present study, we subdivided ER-PR+ subgroup with respect to HER2 status and found that only age is independent from HER2 status; the following were significantly associated with HER2 status: stage, grade, tumor size, lymph node status, and radiotherapy and chemotherapy

TABLE 4. Clinicopathological Characteristics of Female Breast Cancer Patients with ER-PR+tumor (N=1,442).

	HER2 positive (N=422)	*HER2 negative (N=1,020)*	*p-value*
Age at diagnosis			0.321
<40	52 (12.3)	101 (10.0)	
40-49	94 (22.4)	250 (24.6)	
>50	276 (65.3)	669 (65.4)	
Stage			**<0.001**
I	119 (28.9)	355 (35.6)	
II	169 (44.0)	444 (45.7)	
III	91 (19.6)	147 (13.4)	
IV	43 (7.6)	74 (5.3)	
Grade			**<0.001**
Well differentiated	6 (1.4)	23 (2.3)	
Moderately differentiated	97 (23.0)	166 (16.3)	
Poorly differentiated	282 (66.8)	777 (76.2)	
Undifferentiated	1 (0.2)	12 (1.2)	
Unknown	36 (8.5)	42 (4.1)	
Tumor Size			**0.013**
≤20 mm	154 (36.5)	436 (42.7)	
21-50 mm	194 (46.0)	434 (42.5)	
>50 mm	46 (10.9)	115 (11.3)	
Unknown	28 (6.6)	35 (3.4)	
Surgery			**0.004**
Performed	362 (85.8)	929 (91.1)	
Not performed	51 (12.1)	84 (8.2)	
Unknown	9 (2.1)	7 (0.7)	
Lymph node			**<0.001**
Positive	207 (49.1)	366 (35.9)	
Negative	209 (49.5)	643 (63.0)	
Unknown	6 (1.4)	11 (1.1)	
Radiation			**0.046**
Yes	192 (45.5)	523 (51.3)	
No/Unknown	230 (54.5)	497 (48.7)	
Chemotherapy			**0.005**
Yes	322 (76.3)	703 (68.9)	
No/Unknown	100 (23.7)	317 (31.1)	
Status			**0.006**
Alive	336 (79.6)	741 (72.6)	
Dead	86 (20.4)	279 (27.4)	

The chi-square test was used for p value calculation.
The statistically significant *p*-values were indicated with bold characters.

treatments. Furthermore, HER2 negativity was a significant predictor of poor prognosis in terms of both OS and BCSS in this smallest subtype.

Over the past 2 decades, the use of trastuzumab and other targeted therapies dramatically improved the prognosis for HER2 positive breast cancer[13-15]. However, the ability to assess long-term survival is limited because the SEER database has no records of HER2 status of breast cancer patients before 2010.

Age

Previous studies[1,19,20] have shown the association between ER-PR+ subtype and younger age. In this study, among four subtypes, ER-PR+ has the highest proportion of diagnosed patients under 40 years of age. This finding may be due to younger, menstruating women's higher estrogen levels, which downgrade ER expression[21].

Grade, Stage, and Size

Previous studies showed that, compared to ER+PR+ and ER+PR- tumors, ER−PR+ tumors exhibit more unfavorable clinicopathologic features, such as higher grade, higher stage, and larger tumor size, and compared to ER-PR- tumors, they exhibit fewer unfavorable features[22,23].

Consistent with the previous studies, in the SEER database, proportions of poorly differentiated grade and larger size (>50 mm) were high-

TABLE 5. Cox regression analyses of OS in ER-PR+ patients.

	OS (Univariate)			OS (Multivariate)		
Category	***HR***	***95% CI***	***p-value***	***HR***	***95% CI***	***p-value***
HER-2 Status						
Positive	Ref			Ref		
Negative	1.43	(1.09, 1.88)	**0.009**	2.43	(1.81, 3.25)	**<0.001**
Age						
<40	Ref					
40-49	1.09	(0.64, 1.85)	0.759			
>50	1.42	(0.88, 2.28)	0.149			
Stage						
I	Ref			Ref		
II	2.26	(1.60, 3.17)	**<0.001**	1.56	(0.89, 2.76)	**0.122**
II	4.17	(2.87, 6.07)	**<0.001**	3.46	(1.80, 6.65)	**<0.001**
IV	21.93	(14.86, 32.35)	**<0.001**	10.87	(5.57, 21.23)	**<0.001**
Grade						
Well differentiated	Ref					
Moderately differentiated	2.99	(0.73, 12.26)	0.128			
Poorly differentiated	3.52	(0.88, 14.16)	0.076			
Undifferentiated	4.02	(0.67, 24.06)	0.127			
Tumor size						
>=20 mm	Ref			Ref		
21-50 mm	2.46	(1.85, 3.27)	**<0.001**	1.62	(1.03, 2.55)	**0.037**
>50 mm	5.77	(4.13, 8.05)	**<0.001**	1.72	(1.04, 2.85)	**0.036**
Surgery						
Performed	Ref			Ref		
Not performed	7.31	(5.52, 9.69)	**<0.001**	3.10	(2.16, 4.44)	**<0.001**
Lymph node						
Positive	Ref			Ref		
Negative	0.43	(0.34, 0.54)	**<0.001**	0.73	(0.53, 0.99)	**0.044**
Radiation						
Yes	Ref			Ref		
No	1.80	(1.42, 2.27)	**<0.001**	1.33	(1.03, 1.72)	**0.0274**
Chemotherapy						
Yes	Ref			Ref		
No	1.88	(1.50, 2.37)	**<0.001**	2.58	(2.00, 3.32)	**<0.001**

The statistically significant *p*-values were indicated with bold characters.

er in ER- PR+ tumors than those observed in ER+PR- and ER+PR+ tumors, but the opposite relationships were observed when matched with ER-PR- tumors. We also observed that ER-PR+ tumors had a higher rate of stage IV and size of 21-50 mm than the other subtypes.

Lymph Node Status

Lymph node status is a very important prognostic and therapeutic variable[24]. Most studies reported similar incidence of regional lymph node involvement in breast cancer subtypes[7,24,25], but in our study, we found that ER-PR+ subtype is more likely to be lymph node positive than the others. This finding can be better understood through more comprehensive studies.

Radiotherapy, Chemotherapy, and Surgery

In the current study, ER-PR+ patients were more likely to receive chemotherapy, radiation, and surgery than patients with other subtypes.

OS and BCSS

Basing their research on 1,944 primary invasive breast cancer cases with a median follow-up duration of 108 months, Rakha et al[1] found that ER-PR+ and ER+PR- subtypes have similar OS; ER+PR+ subtype showed the best OS, and ER-PR- subtype, the worst. Bordou et al[3] examined two large databases consisting of 5,427 and 10,444 breast cancer cases, respectively. In their study, no significant

TABLE 6. Cox regression analyses of BCSS in ER-PR+ patients.

	BCSS (Univariate)			BCCS (Multivariate)		
Category	***HR***	***95% CI***	***p-value***	***HR***	***95% CI***	***p-value***
HER-2 Status						
Positive	Ref			Ref		
Negative	1.57	(1.13, 2.17)	**0.0066**	2.96	(2.09, 4.18)	**<0.001**
Age						
<40	Ref					
40-49	1.09	(0.64, 1.85)	0.759			
>50	1.42	(0.88, 2.28)	0.149			
Stage						
I	Ref			Ref		
II	2.56	(1.63, 4.02)	**<0.001**	1.64	(0.83, 3.26)	0.151
II	6.89	(4.34, 10.93)	**<0.001**	4.81	(2.23, 10.35)	**<0.001**
IV	34.61	(21.52, 55.64)	**<0.001**	15.35	(7.02, 33.57)	**<0.001**
Grade						
Well differentiated	Ref					
Moderately differentiated	2.00	(0.48, 8.30)	0.34			
Poorly differentiated	2.62	(0.65, 10.57)	0.175			
Undifferentiated	3.89	(0.65, 23.29)	0.137			
Tumor size						
>=20 mm	Ref			Ref		
21-50 mm	2.78	(1.96, 3.95)	**<0.001**	1.61	(0.96, 2.68)	0.0685
>50 mm	8.34	(5.67, 12.26)	**<0.001**	1.90	(1.08, 3.319	**0.0240**
Surgery						
Performed	Ref			Ref		
Not performed	8.18	(5.98, 11.17)	**<0.001**	3.19	(2.12, 4.80)	**<0.001**
Lymph node						
Positive	Ref			Ref		
Negative	0.31	(0.24, 0.42)	**<0.001**	0.68	(0.47, 0,98)	**0.0409**
Radiation						
Yes	Ref			Ref		
No	1.60	(1.22, 2.08)	**<0.001**	1.28	(0.95, 1.72)	0.093
Chemotherapy						
Yes	Ref			Ref		
No	1.41	(1.07, 1.86)	**0.0143**	2.09	(1.54, 2.83)	**<0.001**

The statistically significant *p*-values were indicated with bold characters.

difference in survival between ER−PR+ and ER−PR− subtypes was noted in either database.

In the analysis of a cohort of 155,175 breast cancer patients, Dunnwald et al[4] observed that ER−PR− subtype has the highest breast cancer specific risk, followed by ER-PR+, ER+PR-, and ER+PR+ subtypes. Bae et al[26] analyzed 6,980 invasive ductal carcinoma cases with median follow-up of 45 months. The authors detected similar survival outcomes among hormone receptor subtypes in patients with HER2 expression. In HER2 negative breast cancer patients, ER-PR+ tumors had poorer survival outcomes compared to ER+PR+ tumors, and comparable survival outcomes with ER+PR- and ER-PR- tumors. Li et al[27] examined two big databases, SEER of 161,972 breast cancer cases, and Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) of 1,412 cases, with median follow-up durations of 21 months and 123 months, respectively. In the SEER database, ER-PR+ tumors had worse OS and BCSS than ER+PR+ and ER+PR- tumors. In contrast, an analysis of the METABRIC database, which included longer-term follow-up data, revealed no such differences in OS among these three subtypes, due perhaps to the greater incidence of death due to other factors, which can be attributed to the length of the follow-up.

Hwang et al[28] analyzed 810,587 female breast cancer patients from SEER database with median follow-up time of 94.2 months and found that the ER+PR+ subtype has the best prognosis, followed by ER+PR−, ER−PR+, and ER−PR− subtypes, respectively.

In a recent study based on 823,399 patients from SEER database, ER-PR- subtype was found

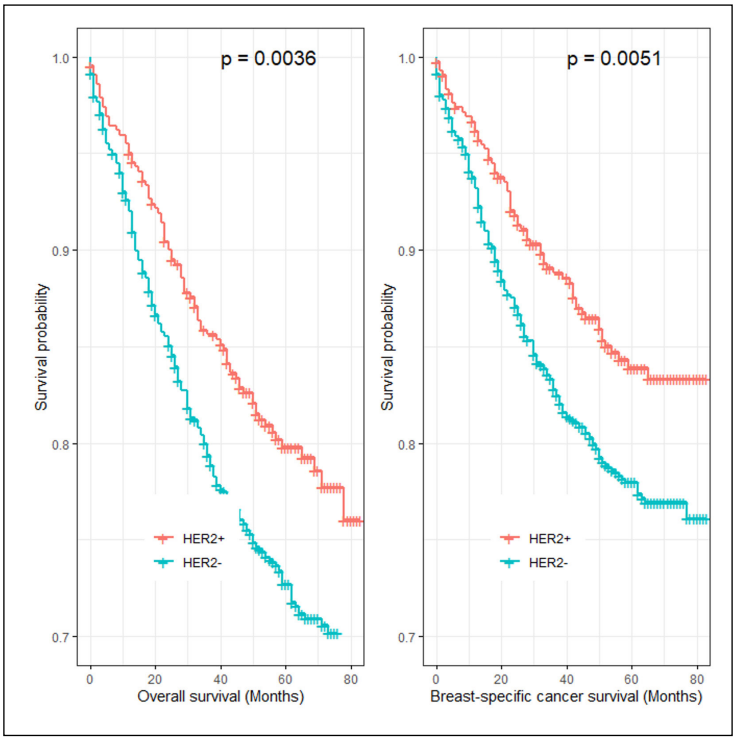

Fig. 2. Survival of ER-PR+ patients according to HER2 status.

to have the highest risk of breast cancer specific death, followed by ER-PR+, ER+PR− and ER+PR+ subtypes, respectively[18].

In the present study, consistent with other studies, we observed that patients with ER+PR+ tumors have longer OS and BCSS than patients with ER-PR+ tumors over the short-term follow-up period[1,3,4,18,24,25]. In our study, ER-PR+ patients had worse OS and BCSS outcomes than patients with ER+PR- and ER+PR+ tumors. On the other hand, we observed similar BCSS and OS outcomes in ER−PR+ and ER-PR- breast cancer patients.

CONCLUSIONS

Based on a large number of breast cancer cases from the SEER database, our evaluation of the clinical characteristics and survival outcomes of patients with ER– PR+ tumors suggested that these tumors represent the smallest distinct biological subtype and have poorer survival outcomes than ER+PR+ and ER+PR– subtypes. There was no survival time difference between ER-PR+ and ER-PR- subtypes. ER-PR+ patients were more likely to be younger than 40 years of age, and our results showed a higher rate of HER2 positive status, stage IV, tumor size of 21-50 mm, and positive lymph node status than for the other subtypes. In ER-PR+ patients, we found significant association between HER2 status and stage, grade, tumor size, lymph node status, and radiotherapy and chemotherapy treatments, and patients in this smallest subtype with HER2 negativity showed poorer OS and BCSS than those with HER2 positivity. The strengths of this study include the large number of patients assessed and the ability to adjust for multiple control variables, including HER2 expression. The assessment of HER2 status provides valuable information for prognosis, and for the evaluation of the benefits of trastuzumab and other targeted therapies. However, information on HER2 status was not available in the SEER database until 2010, thus limiting the available follow-up time. Therefore, it is of crucial importance to repeat this analysis in the future to allow for a longer period of follow-up, and also to validate these results by using other cancer databases. In this study, we evaluated the clinical characteristics and survival outcomes of patients with ER-PR+ breast cancer and found the existence of a distinct ER-PR+ subtype. Our findings may help to optimize treatment and improve outcomes for ER-PR+ patients.

Conflict of interest:

The authors declare no conflict of interest

Ethical Committee:

The study was conducted according to Helsinki declaration and SEER Database Policy.

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