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RESEARCH ARTICLE

Survival rate and prognosis of a single hormone receptor positive breast cancer

Amany M. Omar[1,2] and Shaymaa A. Sadek[1]

[1]Pathology Department, Faculty of Medicine, Minia University, Minia, Egypt
[2]Al Emadi Hospital, Doha, Qatar

ABSTRACT

Background: Historically, hormone receptor-positive breast cancers showed better outcomes. However, the prognostic significance of single hormone receptor breast cancer is still evolving. We investigated the prognosis and clinical traits of single hormone receptor-positive tumors (ER+PR- or ER-PR+), comparing them with both double hormone-positive and hormone-negative breast cancers. **Aims:** Our study aims to assess the prognostic implications of breast cancers with only one hormone receptor, compared to those with both receptors or none. **Material Subjects and Methods:** We examined the clinical and biological features of 141 women with breast carcinoma. Patients were stratified as having double HR+, single HR+ (ER+PR- and ER-PR+), and double HR- tumors. Then correlations with clinicopathological character and survival were made. **Results:** Twenty-two (15.6%) cases were single HR+ tumors, of which 19 (13.5%) were ER+PR- tumors and 3 (2.1%) were ER-PR+ tumors. In the HER2-group, only 10.5% of the ER+PR+ group showed a hazard of death, while the hazard of death was 60% and 11.1% in the single hormone receptor positive groups (ER+PR-/ER-PR+) and ER-PR-groups, respectively. Regarding HER2+ groups, none of the ER+PR+ group showed a hazard of death, while 33.3% and 40% of single hormone receptor positive groups (ER+PR-/ER-PR+) and ER-PR-groups respectively, showed statistically significant (p = 0.017) a hazard death. **Conclusion:** Our study concludes that breast tumors expressing only one hormone receptor had distinct characteristics compared to tumors expressing both receptors or none. These single hormone receptor-positive tumors showed poorer 5-year survival rates.

Keywords: Breast, Cancer, Estrogen, Progesterone, Prognosis, Receptors, Tumors

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Correspondence to
Amany M. Omar,
Pathology Department, Faculty of Medicine, Minia University, Minia, Egypt, Al Emadi Hospital, Doha, Qatar
Tel.: 97477584669
Email: sabry_amany@yahoo.com
ORCID:0000-0002-3789-0823

INTRODUCTION

Breast cancer is a significant global health issue, being the most prevalent cancer and a leading cause of cancer-related deaths in women (Akram et al., 2017; Rakha and Ellis, 2011). It's a complex disease with various molecular subtypes determined by estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2) status (Zhao and Gong, 2021). Breast cancer molecular classification based on immunohistochemical expression of ER, PR, HER2, and Ki67 yields five primary categories: luminal-A, luminal-B, HER2-negative, luminal B HER2-positive, HER2-enriched, and TNBC (triple-negative, characterized by the absence of ER, PR, and HER2 overexpression) (Kunc et al., 2018; Coates et al., 2015). This classification serves as a valuable biomarker for prognosis and guides targeted therapy decisions. The expression status of ER and PR is pivotal, as it predicts prognosis and responsiveness to endocrine therapy in breast cancer patients (Wu et al., 2020). Previously, progesterone receptor (PR) was thought to reflect estrogen receptor (ER) activity since PR is produced by ER target genes and its synthesis is regulated by ER. However, recent evidence indicates that the regulatory mechanisms controlling PR function and target genes are distinct from ER. Consequently, ER operates independently as a driver of cell proliferation in breast cancer (Liu et al., 2022; Yang et al., 2012). Single ER+ and PR+ subtypes

accounted for about 10% of all molecular subtypes of breast cancer (Li et al., 2020). Some studies found that there were no differences in prognosis between ER+PR- and ER-PR+ patients (Rakha et al., 2007; Shen et al., 2015). Others found that ER-PR+ patients had a worse prognosis compared with ER-PR cases (Li et al., 2020; Dauphine et al., 2020). Research from the National Cancer Database and the Surveillance, Epidemiology, and End Results (SEER) program concluded that single HR+ tumors had a worse prognosis than ER+PR+ tumors (Lv et al., 2020). The objective of the current study was to assess the prognostic importance of breast cancer expressing a single hormone receptor**.**

MATERIAL AND METHODS

A retrospective study was conducted on 141 female patients diagnosed with unilateral breast carcinoma at Al-Emadi Hospital, Doha, Qatar, between January 2018 and December 2022. Most cases (92.9%) were invasive ductal carcinoma, with smaller percentages of invasive lobular carcinoma (3.5%), mucoid carcinoma (1.4%), papillary carcinoma (1.4%), and medullary carcinoma (0.7%). The information was extracted retrospectively and included patients age, histologic type, tumor size, tumor grade, tumor stage, lymph node status, lymph vascular invasion, ER, PR, Her-2, and Ki67 expression, along with corresponding therapies (chemotherapy, radiotherapy, or endocrine therapy), and 5-year survival months if available. The pathologic tumor stage was assessed according to the American Joint Committee on Cancer (AJCC) 8th Staging System (Giuliano et al., 2018). Overall survival (OS) was measured from the time of surgery to the occurrence of death, specifically due to breast cancer. Patients who passed away from other causes or were still alive at the last follow-up were not considered in the analysis of survival outcomes. All biopsies from patients with breast mass were sent for histopathology examination after confirming the diagnosis of breast cancer. Immunohistochemical staining was performed using the antibodies against ER (clone: EP1) and PR (clone: 636) using the Envision flex detection system (Dako Omnis), HER2 (Hercept Test Kit DAKO), and Ki67 (clone MIB1; mouse monoclonal, Inc., Santa Clara, CA, USA). All tissue blocks were cut to provide sections of 3 µm, and then immunostaining was performed using the automated IHC Ventana staining machine (Benchmark XT; Ventana Medical Systems, Inc., Tucson, USA). For ER and PR, nuclear (not cytoplasmic) immunostaining was considered positive if equal to or more than 1% of tumor cells showed immunoreactivity, and staining intensity was scored on a 0 to 3 scale (+1 weak, +2 intermediate, and +3 strong). HER2 (membranous stain) positivity was defined as an intensity of 3+ by IHC; a score of 2+ was interpreted as equivocal. A negative test was defined as staining with a score of 0/1+. For equivocal staining, in situ hybridization (ISH) was performed; the results were positive for HER2 amplification when the ratio of HER2 to CEP17 was > 2.2. Ki-67 was considered positive when ≥ 10% of cells showed nuclear staining.

The present study was in accordance with the ethical standards of the responsible committee (ethical permission No. ETHIC-03-06/22) and according to the Helsinki Declaration of 1975, revised in 2008. Specific patient consent was not required, as we used retrospective data from medical records of patients who had already signed information release documents.

Data were checked, coded, entered, and analyzed using SPSS (The Statistical Package for Social Sciences) version 27 software. Differences in the frequencies of clinicopathological factors and subtypes were statistically analyzed using the chi-square test and Fisher's exact test. The association with 5-year survival was initially analyzed by a Kaplan-Meier plot and a log-rank test. Statistical significance was determined at a p value of ≤ 0.05.

RESULTS

Patients were divided into two age groups: less than 50 years and equal to or more than 50 years. The median (range) age at diagnosis was 49.64 (26–90) years, and the median (range) follow-up duration was 39.20 (7–76) months. Among the included patients, the percentages of ER+ PR+, ER+PR-/ER-PR+, and ER-PR- cases were 46.8%, 13.5%/2.1%, and 37.6%,

respectively. The demographic and clinicopathological characteristics of patients are listed in Table 1. Compared with other groups, ER+ PR+ tumors were more frequent in individuals 50 years of age or older (59.1%), while ER+PR-/ER-PR+ and ER-PR- tumors were more frequent in individuals less than 50 years of age, and this was statistically significant (p = 0.23). The ER+ PR+ group included the highest proportion of patients with grade II (66.7%); also, for ER+PR-/ER-PR+, the highest proportion of patients were grade II (72.7%), while in the ER-PR-group, 52.8% were grade II and 45.3% were grade III, and this was statistically significant (p = 0.042). Our results revealed that HER2 hormone receptor positivity was 19.7% in the ER+PR+, 31.8% in the ER-PR+, and 43.4% in the ER-PR-group; this was statistically significant (p = 0.020). No significant correlation was found between the different groups with tumor type, stage, lymph vascular invasion, lymph node status, and Ki proliferation index. The correlations between different hormonal receptor groups and clinicopathological data are listed in Table 2.

The overall median 5-year survival time was 39 months (range: 7 to 76 months). A significant correlation was detected between 5-year survival and tumor stage: 100% of stages I and II were alive, while 10% and 47.1% of stages III and IV had a hazard of death (p = 0.005). 93.3% of cases with absent lymph vascular invasion were alive, while 46.7% of cases with positive lymph vascular invasion had a hazard of death (p = 0.002). No significant corrections were found with other clinicopathological characters. The relationship between 5-year survival and each variable (Table 3).

In the HER2-group, it was found that only 10.5% of the ER+PR+ group had a hazard of death, while the hazard of death was 60% and 11.1% in single hormone receptor positive groups and ER-PR-groups, respectively. In the HER2+ group, it was observed that none of the ER+PR+ group had a hazard of death, while 33.3% and 40% of the single hormone receptor positive groups and the ER-PR-group, respectively, had a death hazard. This was statistically significant (p = 0.017). Survival strata by HER-2 status is reported in Table 4.

With univariate analysis by the Kaplan-Meier method, the 5-year survival graph of ER+PR-/ER-PR+ tumors were located below both the ER+PR+ tumors and the ER-PR-tumors graph in either status of HER2 status. The 5-year survival distributions for the three groups were statistically significantly different (X^2 (2) = 8.142, P = 0.017). The 5-year survival rate was 63.2%. Patients with ER-PR+/ER+ER- tumors had worse OS (5-year; 42.9%) than those with ER+PR+ (5-year; 70.2%) and ER-PR-tumors (5-year; 59.9%). (Figures 1 and 2).

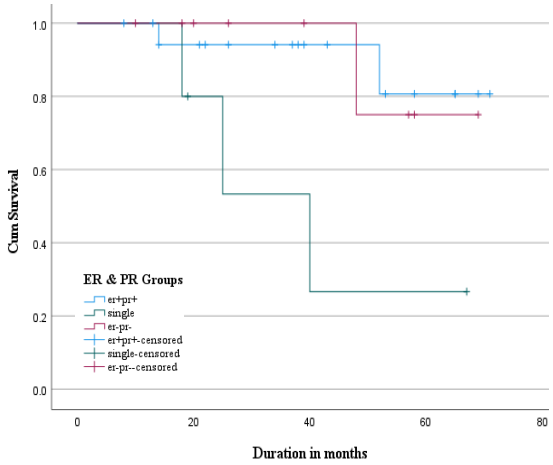

Figure 1. Kaplan-Meier Curve, 5-year survival of patients with HER2 negative tumors. The 5-year survival graph of ER+PR- /ER-PR+ tumors were located below both the ER+PR+ tumors and the ER-PR-tumors graph in HER2-group. (Univariate analysis, Kaplan-Meier method).

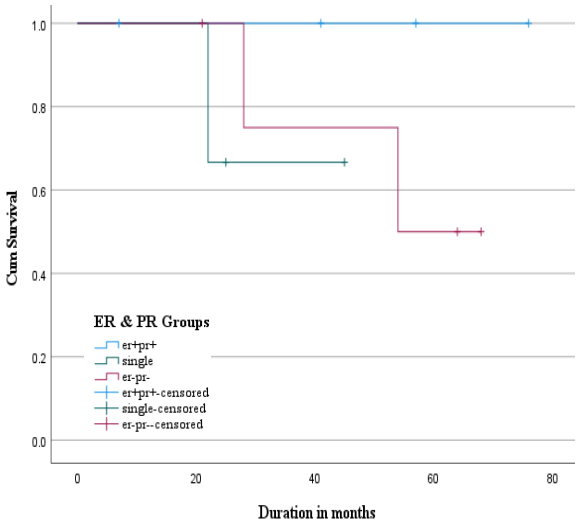

Figure 2. Kaplan-Meier Curve, 5-year survival of patients with HER2 positive tumors. The 5-year survival graph of ER+PR- /ER-PR+ tumors were located below both the ER+PR+ tumors and the ER-PR-tumors graph in HER2+ group. (Univariate analysis, Kaplan-Meier method).

Table 1. The demographic and clinicopathological characteristics

Variable (Total number 141)			Number (%)
Age in years 49.64y ±13.53 (mean±SD)		<50y	75(53.2)
		≥50y	66(46.8)
Diagnosis		Invasive duct carcinoma	131(92.9)
		Invasive lobular carcinoma	5(3.5)
		Mucinous carcinoma	2(1.4)
		Papillary carcinoma	2(1.4)
		Medullary carcinoma	1(0.7)
Grade		Grade I	7(5)
		Grade II	88(62.4)
		Grade III	46(32.6)
Stage (70 cases)		Stage I	9(12.9)
		Stage II	22(31.4)
		Stage III	20(28.6)
		Stage VI	19(27.1))
Lymph vascular invasion (69 cases)		Negative	38(55.1)
		Positive	31(44.9)
Lymph node status (69 cases)		Negative	30(43.5)
		Positive	39(56.5)
Ki67 proliferation index (129 cases)		Low Ki67	20(15.5)
		High ki67	109(84.5)
Estrogen		Negative	56(39.7)
		Positive	85(60.3)
Progesterone		Negative	69(48.9)
		Positive	72(51.1)
Hormonal receptor status		ER+ PR+	66(46.8)
		ER+ PR-	19(13.5)
		ER- PR+	3(2.1)
		ER- PR-	53(37.6)
Human epidermal growth factor-2 status		Negative	98(69.5)
		Positive	43(30.5)
Adjuvant therapy (45 cases)	Hormonal therapy	Absent	11(24.4)
		Present	34(75.6)
	Chemotherapy	Absent	7(15.6)
		Present	38(84.4)
	Radiotherapy	Absent	0(0)
		Present	45(100)
5-year Survival (45 cases)		Death	9(20)
		Alive	36(80)

DISCUSSION

Breast cancer is a complex genetic disease characterized by the accumulation of multiple molecular alterations (Rakha et al., 2010). Standard clinical management typically depends on established clinicopathological factors. While these factors generally correlate strongly with patients' prognosis and treatment outcomes, it's evident that patients with similar characteristics may experience differing outcomes and responses to therapy (Simpson et al., 2005; Hammond et al., 2010). The predictive significance of estrogen receptor expression is firmly established as the primary determinant of a patient's likelihood to respond to endocrine therapy (Coates et al., 2005; Davies et al., 2011). The additional contribution of progesterone receptor (PR) expression remains uncertain, but the assessment of PR expression is still recommended, despite some authors raising doubts about its relevance (Olivotto et al., 2004). When the combinatorial expression of ER and PR is considered, four subgroups are recognized: double HR+ (ER+/PR+), single HR+ (ER+/PR- and ER-/PR+), and double HR- (ER-/PR-). The double HR+ subgroup, representing most tumors (55%–65%), typically has the best prognosis and responds well to hormonal therapy, often classified as the Luminal A subtype in recent classification systems (Carey et al., 2006).

An early hypothesis regarding the emergence of the ER+PR-subtype in breast cancer patients suggested that dysfunctional ER was unable to induce the production of PR, resulting in the development of ER+PR-breast cancer (Wu et al., 2020). Experimental data have implied that growth factor signalling mediates PR down-regulation through the activation of the PI3K-Akt-mammalian target of the rapamycin (mTOR) pathway (Cui et al., 2005). Additionally, growth factors potentiate non-classical ER signalling, such as membrane-initiated steroid signalling (MISS) or other non-classical molecular pathways of signalling (Schiff et al., 2004). Molecular crosstalk occurs between membranous ER and the growth factor signalling pathway; at the same time, PR protein levels are down-regulated (Osborne et al., 2005). These molecular mechanisms collectively contribute to tumor progression and confer resistance to tamoxifen. However, they do not fully explain the earlier recurrence and limited responsiveness to endocrine therapy observed in ER+PR-tumors. Additional mechanisms underlying these phenomena are yet to be elucidated (Wu et al., 2020).

Table 2. Correlations between different hormonal receptor groups and clinicopathological data

Variable		ER+PR+ (total N. 66)	ER-PR+ /ER+PR- (total N. 22)	ER-PR- (total N. 53)	P-value
Age group	<50y	27(40.9)	14(63.6)	34(64.2)	0.023*
	≥50y	39(59.1)	8(36.4)	19(35.8)	
Diagnosis	IDC	58(87.9)	22(100)	51(96.2)	0.348
	ILC	4(6.1)	0(0)	1(1.9)	
	Medullary	0(0)	0(0)	1(1.9)	
	Mucinous	2(3)	0(0)	0(0)	
	Papillary	2(3)	0(0)	0(0)	
Grade	Grade I	6(9.1)	0(0)	1(1.9)	0.042*
	Grade II	44(66.7)	16(72.7)	28(52.8)	
	Grade III	16(24.2)	6(27.3)	24(45.3)	
Stage	Stage I	3(8.6)	0(0)	6(25)	0.133
	Stage II	12(34.3)	5(45.5)	5(20.8)	
	Stage III	12(34.3)	1(9.1)	7(29.7)	
	Stage VI	8(22.9)	5(45.5)	6(25)	
Lymph vascular invasion	Absent	20(55.6)	4(44.4)	14(58.3)	0.772
	Present	16(44.4)	5(55.6)	10(41.7)	
Lymph nodes status	Negative	11(31.4)	5(50)	14(58.3)	0.111
	Positive	24(68.6)	5(50)	10(41.7)	
HER-2	Negative	53(80.3)	15(68.2)	30(56.6)	0.020*
	Positive	13(19.7)	7(31.8)	23(43.4)	
Ki67 proliferation index	Low	13(20.6)	3(13.6)	4(9.1)	0.258
	High	50(79.4)	19(86.4)	40(90.9)	

**P* value less than or equal to 0.05 is considered statistically significant according to the $\chi 2$ test. IDC: invasive duct carcinoma, ILC: invasive lobular carcinoma, ER: estrogen, PR: progesterone, HER2: human epidermal growth factor receptor 2.

Table 3. Relations between survival and clinicopathological data

Variable		5-year Survival		P-value
Median 5- year survival time 39 months, (range: 7 to 76 months).		**Death (9 cases)**	**Alive (36 cases)**	
Age group	<50y	6(24)	19(76)	0.453
	≥50y	3(15)	17(85)	
Diagnosis	IDC	9(21.4)	33(78.6)	0.669
	ILC	0(0.0)	2(100)	
	Mucinous	0(0.0)	1(100)	
Grade	Grade I	0(0.0)	1(100)	0.811
	Grade II	4(23.5)	13(76.5)	
	Grade III	5(18.5)	22(81.5)	
Stage	Stage I	0(0.0)	6(100)	0.005*
	Stage II	0(0.0)	12(100)	
	Stage III	1(10)	9(90)	
	Stage VI	8(47.1)	9(52.9)	
Lymph vascular invasion	Absent	2(6.7)	28(93.3)	0.002*
	Present	7(46.7)	8(53.3)	
Lymph nodes	Negative	4(20)	16(80)	1.00
	Positive	5(20)	20(80)	
HER-2	Negative	6(18.2)	27(81.8)	0.613
	Positive	3(25)	9(75)	
Ki67 proliferation index	Low	1(20)	4(80)	1.00
	High	8(20)	32(80)	
Therapy received	Endocrinal Chemotherapy Radiotherapy	6(22.2)	21(77.8)	0.883
	Chemotherapy Radiotherapy	2(18.2)	9(81.8)	
	Endocrinal Radiotherapy	1(14.3)	6(85.7)	

**P* value less than or equal to 0.05 is considered statistically significant according to the $\chi 2$ test. IDC: invasive duct carcinoma, ILC: invasive lobular carcinoma, HER-2: human epidermal growth factor receptor 2.

Table 4. Survival strata by HER-2 status

5-year Survival		Death	Alive	Overall P-Value
HER2-	ER+PR+	2(10.5)	17(89.5)	0.017*
	ER+ER/ER-PR+	3(60)	2(40)	
	ER-PR-	1(11.1)	8(88.9)	
	Total	6(18.2)	27(81.8)	
HER2+	ER+PR+	0(0)	4(100)	
	ER+ER-/ER-PR+	1(33.3)	2(66.7)	
	ER-PR-	2(40)	3(60)	
	Total	3(21.4)	11(78.6)	

**P* value less than or equal to 0.05 is considered statistically significant according to the $\chi 2$ test. ER: estrogen, PR: progesterone, HER-2: human epidermal growth factor receptor.

On the contrary, the ER-/PR+ subgroup might indicate false-negative estrogen receptor (ER) status, potentially stemming from the inability of the ER antibody to effectively bind to the receptor for detection. This failure of binding could be attributed to various factors, such as conformational changes in the ER induced by mutations, rendering the receptor inaccessible for antibody binding. Additionally, competitive antagonism of the ER by other molecules within the tumor microenvironment may impede antibody-antigen binding, further complicating accurate ER detection. Alternatively, the ER-/PR+ subgroup could indicate falsely positive progesterone receptor (PR) status, potentially arising from cross-reactivity of anti-PR antibodies with other antigens. To mitigate the risk of false results, it is advisable to assess ER and PR status using two independent antibodies. This approach helps ensure reliability, as the epitopes recognized by different antibodies should be distinct (Chan et al., 2015).

Recent studies have highlighted a notable difference in outcomes between patients with single hormone receptor-positive breast cancer and those with either double hormone receptor-positive or double hormone receptor-negative breast cancer, implying that we should consider both ER+PR- and ER-PR+ cases as distinct from ER+PR+ ones (Hammond et al., 2010; Engl et al., 1988; Kaufmann et al., 2007).

In the present study, a total of 22 primary operated tumors (15.6%) were single hormone receptor positive, and this came in concordance with the range reported in most studies; for example, Li et al., (2020) found that single hormone receptor positive tumors represented 10% of their cases; Rakha et al., (2007) and his colleagues reported a percentage of 11%; and others reported 13–19% of their cases to be single hormone receptor positive (Dunnwald et al., 2007).

In the current study, single hormone receptor-positive breast cancer occurred more commonly in younger, premenopausal women, a finding that, in fact, was also reported by many studies comparing women with single hormone receptor expression to other phenotypes. (Grann et al., 2005; Yu et al., 2008; Kim et al., 2022). Hormone receptor expression is probably age-dependent, as Rhodes et al., (2000) and his colleagues emphasized in their study that patient age and IHC assay sensitivity were found to be the main variables influencing the frequency of receptor positivity and added that most hormone receptor cases lie in the age group above 60 years. Variations in hormone receptor expression rates across specific age groups suggest that a single hormone receptor status delineates a distinct clinicopathological entity. This status has been linked to different behaviors compared to ER+/PR+ disease. As for histological type, all single hormone receptor tumors in the present work were of invasive ductal carcinoma, no special type, and grade 2 tumors comprised most of the cases in the single hormone receptor group, a finding that was previously reported (Li et al., 2020; Rakha et al., 2007; and Yu et al., 2008).

In the current study, there was no notable correlation detected between the four hormone receptor expression groups and tumor stage, lymph-vascular invasion, or lymph node status. This observation aligns with the findings of many studies conducted on this topic (Li et al., 2020; Rakha et al., 2007; Yu et al., 2008; Kunc et al., 2018). On the other hand, Fan et al., (2015) compared ER-/RP+/HER2 negative tumors to TNBC and found that lymph node status was an independent predictive factor of poorer outcome; moreover, some authors found that ER-/PR+ tumors had lower sizes and a higher

proportion of grade 3 tumors when compared to ER-/PR- tumors (Chan et al., 2015; Bernoux et al., 1998), while other authors found lower grades when compared to ER-/PR- (Kunc et al., 2018; Bardou et al., 2003). This inconsistence may result from the sample size, statistical methods, or adjusted variables.

Our study findings align with previous research indicating that single hormone receptor-positive tumors exhibit higher expression levels of EGFR/HER2 compared to ER+ PR+ tumors (Li et al., 2020; Bardou et al., 2003; Ng et al., 2012; Cancello et al., 2013). It has been postulated that, when pathways like MAPK are excessively activated due to EGFR or c-erbB-2 overexpression, estrogen receptor (ER) expression decreases. Likewise, HER2 overexpression can also lower ER and PR expression through the PI3K/AKT/mTORC1 pathway, for instance, by reducing FOXO3a protein expression via AKT. This is why ER+/HER2+ tumors often have lower ER levels than ER+/HER2-negative tumors (Zattarin et al., 2020). On the other hand, we didn't find such a significant correlation between hormone receptor status and the Ki67 proliferative index, a finding that was also demonstrated by Rakha et al., (2007). Our study found that the 5-year survival of patients is notably lower with advanced tumor stage and positive lympho-vascular invasion. However, no significant correlation was observed between survival and other clinicopathologic features in the group under study.

Various studies, employing diverse sample sizes, ethnic populations, follow-up durations, and statistical analyses, have explored the relationship between survival and various demographic and clinicopathologic factors. Their aim is to understand the key determinants influencing breast cancer survival and prognosis, aiding in treatment decision-making. A common finding across many studies is the significant correlation between tumor stage and survival. For instance, Roder et al., (2012) found some factors, including tumor size, higher grade, positive nodal status, as well as vascular invasion and multifocality, to be correlated with decreased survival. Abbass et al., (2011) thought that tumor size and high histologic grade were independent prognostic factors for breast cancer patients. Dauphine et al., (2020) showed that, compared with the ER-positive/PR-positive group, the ER-positive/PR-negative and ER-negative/PR-positive groups were more likely to be diagnosed with high-grade cancer and have lymphovascular invasion. Another study involving 246 breast cancer patients found that the 5-year overall survival rate was influenced by factors like menopausal status, tumor size, axillary lymph node metastasis, and TNM stage (Han et al., 2020). Pascual et al., (2022) concluded that as the stage of breast cancer increases, the survival rate worsens. Therefore, they emphasized the importance of reinforcing early detection breast cancer programs and developing rapid diagnosis protocols.

In terms of evaluating hormonal status concerning patients' 5-year survival, categorized by HER2 status, our study found that ER and PR expression profiles were significantly linked to 5-year survival regardless of HER2 status. Specifically, ER+PR+ tumors exhibited better 5-year survival compared to single hormone-positive and ER-PR-cases, regardless of HER2 expression. Additionally, when considered alone, single hormone receptor-expressing tumors with positive HER2 expression displayed better 5-year survival rates than the HER2-negative group. Furthermore, our study revealed that patients with single hormone receptor expression had the poorest 5-year survival rates compared to both the double hormone-positive and double hormone-negative groups. These findings in fact come in tune with those of other authors emphasizing the prognostic value of hormone receptor status; Roder et al., (2012) reported ER negative status to be correlated with worsened survival. In the study of Zhao and Gong, (2021) and his colleague, patients with ER+PR- and ER-PR+ had worse prognoses than those with ER+PR+. Similarly, Dauphine et al., (2020) reported that single hormone receptor-positive breast cancer subtypes (ER+PR- and ER-PR+) tend to exhibit unfavourable characteristics and poorer survival outcomes compared to the ER+PR+ subtype. They noted

that the ER-PR+ subtype's outcomes are like those of ER-PR-cancers. Therefore, they suggested that single hormone receptor-positive subtypes should be regarded as clinically distinct from ER+PR+ disease. Wu et al., 2020 found that even in hormone receptor-positive breast cancer cases, including those that are lymph node-negative and HER2-negative, both ER+PR- and ER-PR+ tumors are linked to a poor prognosis despite receiving endocrine therapy.

Rakha et al., (2007) found that there was no significant difference in survival analyses between the ER+PR- and ER-PR+ groups in terms of disease-free interval and overall survival. However, compared to the double-negative phenotype, ER+/PR- tumors were associated with a better outcome, while no such survival advantage was observed for ER-/PR+ tumors. Furthermore, among patients with ER+ tumors who received adjuvant hormonal therapy, the absence of PR (ER+/PR) was identified as an independent predictor of recurrence development, shorter survival, and consequently, a poorer response to hormonal therapy.

Moreover, Wu et al., (2020) have identified clinically and biologically distinct features of single HR+ tumors (ER-PR+ and ER-PR-) through comparison with both ER+PR+ and ER-PR- tumors. These differences were only significant in HER2 negative tumors, not in HER2 positive tumors. Single HR+ tumors without HER2 overexpression (ER+PR-HER2- or ER-PR+HER2-) were associated with poorer survival than ER+PR+HER2-tumors and had comparable poor survival to ER-PR-HER2-tumors (triple-negative breast cancer).

To sum up, various studies considered the single hormone receptor positive group to be midway between the ER+PR+ and ER-PR- groups concerning survival; others found equal survival between single hormone receptor positive tumors and triple negative breast cancer; and others concluded worse survival for ER-PR+ tumors than ER-PR-tumors. We concluded that decreased 5-year survival for single hormone receptor-expressing tumors was even worse than double hormone-negative ones. These inconsistent findings could be attributed to different sample sizes, different treatment strategies resulting in different outcomes, and varied follow-up durations.

CONCLUSION

The loss of either ER or PR helps to identify high-risk hormone receptor-positive patients. These two types of tumors (ER+PR- and ER-PR+) require a more aggressive therapeutic strategy. To improve the survival of patients with these tumors, additional research efforts should be directed towards identifying the most effective endocrine therapy strategies or developing targeted therapies tailored to benefit patients with these tumors, ultimately aiming to improve their survival outcomes.

DECLARATION OF CONFLICT OF INTEREST

No conflict of interest.

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AUTHERS CONTRIBUTION

Both authors were shared in manuscript design, content, literature search, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript revision.

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