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Original Article

Is there a correlation between estrogen receptor expression level and early breast cancer survival? A Retrospective Study.

Ayman Rasmy [1,2] , Ahmed Zeeneldin [3,4] , Walid Abozeed [5] , Saeed Al–Ghamdi[2] and Shereef Elsamany [3,6]

[1]Medical Oncology. Zagazig University. Egypt
[2]Medical Oncology, King Saud Medical City, KSA
[3]Medical Oncology, Oncology Center, King Abdullah Medical City, Makkah, KSA
[4]Medical Oncology, National Cancer Institute, Cairo University, Egypt
[5]Clinical Oncology, Mansoura University, Mansoura, Egypt
[6]Medical Oncology, Oncology Center, Mansoura University, Mansoura, Egypt

Abstract

Introduction: The optimal cut–off of ER–positivity is still debatable; however, adjuvant hormonal therapy is usually given if ER expression ≥ 1%. The present study aims to assess clinicopathological features and survival outcome of patients with low compared to higher ER expression level.

Methods: In this retrospective, we checked non–metastatic hormonal receptors–positive, HER2 negative breast cancer patients who presented to three Hospitals in Egypt and Saudi Arabia between 2020–2022. Different clinicopathological factors and data of relapse were checked in patients' medical records. These data were compared in patients with ER–Low (1–10%) Vs. ER–High (>10%) expression level.

Results: We included 419 patients who met the eligibility criteria of the study. Only 3.3% of patients had ER–Low. Compared to ER–High group, the ER–Low expression were more likely to have grade 3 tumours (64.3% vs. 21.0%, p=<0.0001), PR–negative (64.3% vs. 16.3%, p= <0.0001). Furthermore, younger age (≤ 50 years) was more frequent in ER–Low group compared to ER–High patients (71.4% vs. 42.5%, respectively, p=0.032). Likewise, ER–High patients were more likely to have high ER–staining intensity (74.1% vs. 0.0%, p<0.0001). Disease free survival (DFS) was numerically improved in patients with ER–High, but without statistical significance. After adjustment of different clinicopathological prognostic factors, DFS benefit in ER–High group was more definite (HR=3.59, 95% CI 1.11–11.55, p=0.032).

Conclusion: ER–low (1–10 %) expression was rare in the study group. Low ER expression was linked with more aggressive features at diagnosis and seems to have worse DFS which was more pronounced after adjustment for different clinic–pathological factors.

Introduction

Since the mid–1970s, steroid hormone receptors, such as Estrogen receptor (ER) and progesterone receptor (PR), have been worked with as crucial markers for endocrine therapy and prognosis in breast cancer. In one cohort study, statistically significant differences were observed between the survival rates of patients with single hormone receptor–positive BC and those with double hormone receptor–positive/negative BC. ER–positive/PR–negative tumours were more prevalent among those aged 60 or older (57.1%), whereas ER–negative/PR–positive tumours were more prevalent among those aged 30 to 49 years (37.7%) [(1)].

In breast cancer, the expression of ER serves a crucial role in carcinogenesis and disease progression. Recently, malignancies with low levels (1–10%) of ER expression have been classified separately as ER low positive (ER^{low}). ER^{low} breast cancer exhibited unique clinicopathological characteristics. ER^{low} tumours appeared to have higher recurrence rates than ER^{high} tumours, and hormonal therapy had no apparent impact on them [(2)].

Correspondence: Ayman Rasmy,
Al Imam Turki Ibn Abd Allah Ibn Muhammad,
Ulaishah, Riyadh 12746, Saudi Arabia,
E–mail: ay_rasmy@yahoo.com

Breast cancer is simply classified into different subtypes based on ER/PR and HER2 expression in addition to Ki67 level. Approximately, 70% of breast cancer patients are positive for hormonal receptors [3]. According to the American Society of Clinical Oncology/ College of American Pathologists (ASCO/CAP), breast cancers with ER ≥ 1% are labelled as ER–positive [4]. However, the optimal cut–off for hormonal receptors positivity is still debatable and several studies reported that a higher cut–off should be adopted [5]. In a retrospective assessment of more than 9,000 patients, 80.5% had tumours that were ER–positive ≥10%, 2.6% were ER–positive 1%–9% while 16.9% were ER–negative [6]. Patients with ER–1%–9% positive tumours had worse survival compared to those with ER ≥10% tumours. Meanwhile, patients with ER–1%–9% tumours had similar survival to ER–negative patients with comparable rates of pathological complete response after neoadjuvant chemotherapy [6].

Since 1998, Fisher B. and his colleagues have demonstrated that early ER positive breast cancer patients can be treated more successfully with breast conserving surgery (BCS) in combination with radiation therapy, adjuvant chemotherapy, and/or endocrine hormonal therapy (EHT) than with radical mastectomy. This paradigm included adjuvant chemotherapy for the majority of Positive patients, despite providing little benefit to the vast majority of patients [7].

Additionally, according to the St. Gallen International Expert Consensus 2015, ER expression rates between 1% and 9% are believed to be clearly positive, and endocrine treatment alone is ineffective for patients with these levels [8]. In the meantime, numerous studies have shown that patients with strong hormone receptor (HR)–positive tumours are less responsive to systemic chemotherapy than patients with HR–negative tumours, which may indicate that the level of ER expression is related to the extent of response to chemotherapy. [9–10]

Therefore, in patients with ER–positive, HER2–negative breast cancer, the optimal cut–off for HR–positivity may need to be re–defined for better classification of patients to guide therapeutic strategies. In this retrospective study, we aim to identify clinicopathological features and survival outcome of non–metastatic HR–positive, HER2–negative breast cancer patients with ER–positive >10% compared to those with ER 1–10% tumours from three institutes in Saudi Arabia.

METHODS

Study Design:

In this retrospective study, we recruited patients with HR–positive, HER2–negative breast cancer from three centres in Egypt and Saudi Arabia between 2020–2022 who had no evidence of metastasis at the time of diagnosis. We checked the percentage of ER and PR positivity. Different clinicopathological factors were checked. The primary endpoint of the study is disease free survival (DFS) defined as the time from the date of breast surgery to the date of first documented tumour relapse or death. Clinicopathological parameters and DFS were correlated with the percentage of ER expression (ER more than 10% will be described as the ER–High group, while ER with 1–10% will be referred to as the ER–Low group).

Study population:

We enrolled ER–positive, HER2–negative breast cancer patients diagnosed in the 3 contributing hospitals from 2020–2022. We recruited female patients above 18 years at time of diagnosis with histologically confirmed as breast cancer with no clinical or radiological evidence of metastasis at the time of diagnosis. The inclusion criteria for the current study were as follows:(1) histologically confirmed early stage breast cancer (2) available surgical records and pathology reports, and (3) available immune–histochemistry (IHC) staining results on ER, PR, and human epidermal growth factor receptor–2 (HER2). Patients with contralateral advanced stage breast cancer were excluded from the study.

Study procedures and assessment:

For statistical analysis a chart review of medical data was applied to identify patient and disease characteristics, and treatment features as well as relapse status, site and survival outcome (DFS and OS). Age at diagnosis, menopausal status, type of surgery, pathological tumour size, number of positive lymph nodes (LNs), tumour grade (G), lympho–vascular invasion (LVI), ER status (percentage and staining intensity), PR status (percentage and staining intensity).

Tumour staging was determined using the 6th American Joint Committee on Cancer Criteria, and the staging work–up, treatment protocols, and follow–up were determined using NCCN recommendations. In addition, treatment data such as type of adjuvant hormonal therapy and chemotherapy protocols were recorded. We also looked at the time and location of any relapses.

Statistical Analysis:

Categorical data was presented as percentages and were compared between the two ER– staining groups using Chi–Square test. Survival data was presented by Kaplan Meier method and differences in survival according to ER status (ER 1–10%, ER >10%) were evaluated using log rank test. Patients were adjusted according to traditional clinicopathological factors including pathological T–stage,

pathological nodal stage, tumour grade, age and PR status using Cox proportional hazard regression model. The model was used to adjust for a possible confounding effect due to any encountered imbalance with regards to the mentioned clinicopathological factors. An alpha value of 0.05 was set a priori for all two tailed comparisons. Statistical analysis was performed using SPSS version 17.

Results:

Patient and tumour characteristics

This study included 419 patients with non–metastatic ER–positive, HER2–negative breast cancer patients at the time of diagnosis. Approximately 46.6% of the patients (n=195) had N1 lymph node status, while 21 patients were considered as Nx (due to insufficient documentation of LN status at initial assessment or for patients referred to our institutions from the periphery after surgery there.

Neoadjuvant chemotherapy was documented in 47.5% (199 patients). Others did not receive neoadjuvant chemotherapy because they initially rejected it and chosen for surgery instead (32 patients), or for logistical reasons (86 patients), or because they were initially diagnosed at a hospital with limited oncology resources and underwent initial surgery there. Seventy–five patients (17.79%) were PR–negative. All recruited patients received adjuvant radiotherapy and hormonal treatment according to the standard guidelines.

Patient and tumour characteristics in different ER–staining groups:

Tables 1 and 2 compare the baseline patients and tumour characteristics of ER–Low (1–10%) versus ER–High (>10%) patients. Patients with ER–Low were more likely to have grade 3 tumour (64.3% vs. 21.0%, p=0.0001) and to be PR–negative (64.3% vs. 16.3%, p=0.0001). Furthermore, ER–Low group were more likely to be premenopausal than ER–High group (85.7% vs. 52.8%), but this was not statistically significant (p=0.116). Furthermore, younger age (50 years) was more common in the ER–Low group compared to the ER–High group (71.4% vs. 42.5%, p=0.032). Pathological T assessment with T0 stage was significantly more common in ER–low patients (21.4% vs 3%, p=0.014), with lower nodal stage compared to the ER–high group but without statistical significance (p= 0.293). Furthermore, patients with ER–high levels were more likely to have high ER–staining intensity (74.1% vs. 0.0%, p=0.0001) and high PR–staining intensity (44.2% vs.7.1%%, p=0.0001). (Table– 2).

Parameters		ER–Low (1–10%),N=14 .,(3.3%)	ER–High (>10%) N=405 (96.7%)	Total N=419 (100.0%)	P–Value
Age	≤50	10	172	182	0.032
		71.4%	42.5%	43.4%	
	>50	4	233	237	
		28.6%	57.5%	56.6%	
Menopause	Premenopausal	12	214	226	0.116
		85.7%	52.8%	53.9%	
	Perimenopausal	0	4	4	
		0.0%	1.0%	1.0%	
	Postmenopausal	2	185	187	
		14.3%	45.7%	44.6%	
	Male	0	2	2	
		0.0%	0.5%	0.5%	
Site	Left	5	199	204	0. 534
		35.7%	49.1%	48.7%	
	Right	9	201	210	
		64.3%	49.6%	50.1%	
	Bilateral	0	5	5	
		0.0%	1.2%	1.2%	

Table 01: Baseline Clinical parameters of patients with ER–Low (1–10%) Vs. ER–High (>10%).

Parameters		ER–Low (1–10%) N=14 (3.3%)	ER–High (>10%) N=405 (96.7%)	Total N=419 (100.0%)	P–Value
Pathological type	Invasive ductal	13	349	362	0.714
		92.9%	86.2%	86.4%	
	Invasive lobular	1	43	44	
		7.1%	10.6%	10.5%	
	Others	0	13	13	
		0.0%	3.2%	3.1%	
Pathological T–stage	Tx	0	5	5	0.014
		0.0%	1.2%	1.2%	
	T0	3	12	15	
		21.4%	3.0%	3.6%	
	T1	4	112	116	
		28.6%	27.7%	27.7%	
	T2	6	202	208	
		42.9%	49.9%	49.6%	
	T3	1	65	66	
		7.1%	16.0%	15.8%	
	T4	0	9	9	
		0.0%	2.2%	2.1%	
Multicentricity	Yes	0	58	58	0.234
		0.0%	14.3%	13.8%	
	No	14	347	361	
		100.0%	85.7%	86.2%	
Lymphovascular invasion	No	4	131	135	0.766
		28.6%	32.3%	32.2%	
	Yes	10	274	284	
		71.4%	67.7%	67.8%	
Tumour grade	Grade 1	2	51	53	<0.0001
		14.3%	12.6%	12.6%	
	Grade II	1	244	245	
		7.1%	60.2%	58.5%	
	Grade III	9	85	94	
		64.3%	21.0%	22.4%	
	Unknown	2	25	27	
		14.3%	6.2%	6.4%	

Continued on next page

Table (continued)

Parameters		ER–Low (1–10%) N=14 (3.3%)	ER–High (>10%) N=405 (96.7%)	Total N=419 (100.0%)	P–Value
N– stage*	N0	0	4	4	0.293
		0.0%	0.9%	0.9%	
	N1	11	184	195	
		78.6%	45.5%	46.6%	
	N2	2	123	125	
		14.3%	30.4%	29.8%	
	N3	1	73	74	
		7.1%	18.0%	17.7%	
PR status	Negative	9	66	75	<0.0001
		64.3%	16.3%	17.9%	
	Positive	5	339	344	
		35.7%	83.7%	82.1%	
ER intensity	Mild	11	36	47	<0.0001
		78.6%	8.9%	11.2%	
	Moderate	3	69	72	
		21.4%	17.0%	17.2%	
	High	0	300	300	
		0.0%	74.1%	71.6%	
PR intensity	Negative	9	65	74	<0.0001
		64.4%	26.0%	27.6%	
	Mild	3	66	69	
		21.4%	16.3%	16.5%	
	Moderate	1	95	96	
		7.1%	23.5%	22.9%	
	High	1	179	180	
		7.1%	44.2%	43.0%	

Table 02: Baseline Pathological parameters of patients with ER 1–10% Vs. ER >10%.

* 21 patients stated as Nx .

Treatment received (Surgery, Chemotherapy and Hormone Therapy) (Table–3).

In both neoadjuvant and adjuvant settings, the same chemotherapy protocols are administered to the patient (p=0.49). For node–positive patients, a total of 6 cycles of Anthracycline and Taxanes–based regimens in the form of three cycles of CAF protocol (Cyclophosphamide, Doxorubicin, and Fluorouracil) or FEC protocol (Fluorouracil, Epirubicin, and Cyclophosphamide) followed by three cycles of Taxanes (either Docetaxel or Paclitaxel). Node–negative patients, on the other hand, receive four cycles of either the AC regimen (Doxorubicin and Cyclophosphamide) or the EC therapy (Epirubicin and Cyclophosphamide), followed by four cycles of Taxens. All these patients' baseline echocardiograms or MUGAs were normal.

There is evidence that the ER–Low group has experienced a better initial clinical response to neoadjuvant treatment but no significant difference.

Patients received hormone therapy according to their menopausal status (Tamoxifen for premenopausal and

Parameters	ER–Low (ER 1–10%),N= 14	ER– High (>10%)., N= 405	Total 419(%)	P–value
Surgery n (%)				
MRM	5 (35.7)	194 (47.9)	199(47.5)	0.66
Mastectomy	2 (14.3)	151 (37.3)	153 (36.5)	
BCS	7 (50.0)	60 (14.8)	67 (16.0)	
Type of chemotherapy n (%)				
Neoadjuvant	4 (28.5)	195 (48.1)	199(47.4)	0.49
Adjuvant	10 (71.5)	210(51.9)	220(52.5)	
Hormonal Therapy n (%)				
Tamoxifen	3(21.4)	166(40.9)	169(40.4)	0.393
Aromatase inhibitor (AI)	1(7.14)	181(44.8)	182(43.4)	
Tamoxifen+AI	10(71.4)	13(3.2)	23(5.5)	
LHRH+Tamoxifen	0 (0.0)	21(5.2)	21(5.0)	
LHRH+AI	0(0.0)	24(5.9)	24(5.7)	

Table 03: Comparison of different treatment modalities in ER 1–10% Vs. ER>10% patients

postmenopausal women while Aromatase Inhibitors for postmenopausal patients only). Tamoxifen was prescribed to male patients. There was no significant difference between the two patient groups regarding the reported adverse effects of hormonal therapy. The most frequent adverse effect of aromatase inhibitors was bone pain, which was mild to moderate in most patients but severe in 13 patients (7.18%), necessitating a transition to Tamoxifen. On the other hand, 18 patients (9.47%) who received tamoxifen reported vaginal bleeding associated with endometrial thickening, and 11 patients (5.6%) developed deep vein thrombosis.

Survival outcome in different ER–staining groups:

The median duration of follow–up in our study was 35.27 mon. (range: 21–37 mon.). Within our research, 68 patients (16.2%) relapsed. Local/regional recurrence occurred in 15 patients (22%, the majority of whom underwent BCS), while systemic recurrence occurred in approximately 53 patients (78%, with visceral recurrence being the most common type). When comparing two groups independently, there was no statistically significant difference (P=0.2, with relapse rates of approximately 28.6% in the ER–low group and 15.6% in the ER–high group).

There was a significant correlation (p=0.001) between the ER–low group mortality (in 35.7% of patients) Vs the ER–high group mortality (in 7.2% of patients) in which the disease–related mortality was documented in 46 patients (10.9%) (Table–4).

Patients with ER–high (>10%) had numerically improve DFS compared to the ER–Low (1–10%) group, however, it did not reach statistical significance in univariate analysis for age (HR 0.86, 95% confidence interval 0.53–1.38, p=0.53) or PR status (HR 0.73, 95% confidence interval 0.37–1.43, p=0.36) and ER intensity (HR 2.06, 95% confidence interval 0.75–5.67, p=0.16) (Figure–1 , Table –5).

The median OS for the ER–low group was 36.5 mon. compared to 37 mon. for the ER–high group, which was statistically insignificant (p=0.337). In univariate analysis, it did not approach statistical significance for tumour grade or age (HR 0.79, CI: 0.4–1.54, p=0.48), but it is statistically significant for tumour grade (II), PR status, and ER intensity (p values of 0.05, 0.02, and 0.001 respectively). The only variable with a statistically significant result in the multivariate analysis is ER intensity (HR 4.84, 95% CI :1.72–13.65, p=0.003) (Figure–2, Table –6).

Discussion

Breast cancer is the most prevalent cancer among women and the second most prevalent cancer globally. Fundamentally, the expression of oestrogen receptor alpha (ER) classifies patients as having either ER–positive (ER+) or ER–negative (ER–) disease, with approximately 70% of patients having ER–positive disease [11].

In breast cancer, Estrogen receptor expression plays a crucial role for carcinogenesis and disease progression. Tumours with low levels of ER expression (1%–10%)

Parameters	ER–Low (ER 1–10%),N= 14	ER– High (>10%)., N= 405	Total 419	P–value
Relapse n (%)	4 (28.6)	64 (15.8)	68 (16.2)	0.2
Mortality n (%)	5 (35.7)	41 (7.7)	46 (10.9)	<0.001
Survival (Months)				
▪ **Mean**	32.79 ±0.403			
▪ **Median**	34.00±5.072			
▪ **Range**	20–37			
DFS (months) mean (95% CI)	34.005 (±0.457)	35.213(±0.673)	35.134(±0.463)	0.024
OS (months) mean (95% CI)	36.532 (±0.382)	37.000(±0.236)	36.380(±0.524)	0.337

Table 4: Correlation between ER Level and Survival

have recently been classified as ER low positive (ER–low). It has been proposed that ER–low cancers may differ physically and behaviourally from tumours with high ER expression (ER–high) [2].

The benefit of hormonal therapy is heterogeneous among those patients and is largely dependent on the level of ER/PR expression [12]. Currently, ER is stared positive if it is expressed on 1% of tumour cells by IHC, and according to many guidelines, adjuvant hormonal therapy is recommended. In clinical practice, the threshold for prescribing adjuvant hormonal therapy is commonly set at 10%. However, data supporting the optimal cut–off for hormonal receptors–positivity is limited in the literature [6].

In our study, 3.3% of ER+ group were classified as having ER 1–10%. This is consistent with data from a recent study by Kyung–Hwak Yoon et al. in 2022 [2], in which the ER–low group was 2.5%, which was lower than prior reports highlighted by Takayuki Iwamoto. et al. in 2012 [13]: ER–low group was 6.7%.

In our investigation, most ER–low patients also had low –staining intensity, no patients had strong ER staining, and the majority were PR–negative. Similarly, according to a prior study, patients with 1–10% ER expression have predominantly basal–like signatures [5].

Estrogen Resistance and Breast Cancer are diseases that are linked to ESR1.Even though the ER gene (ESR1) is expressed in different ways, there are big differences in how other genes are expressed between ER–positive and ER–negative tumours. ESR1 (which is a protein–coding gene) expression is much lower than what is seen in people with ER expression of 10% or more [13].

These tumours tend to be ER–negative by ESR1 mRNA (76%) and have predominantly non–luminal signature (92%) [14]. Given the above data, about one quarter of the 1% to 10% ER–positive tumours show ESR1 mRNA levels and gene signatures that are consistent with ER–positive, endocrine–sensitive tumours. A RNA–based ER assessment may help identify these *ESR1* mRNA–positive patients who are more likely to benefit from adjuvant hormonal therapy [15–17].

Overall, this research gives a physiologic explanation for the observed limited efficacy of hormone therapy in this group of low ER–positive patient. Similarly, data from the Oxford Overview backed up the same idea. Patients with low ER–expression below 10 fmol/ mg benefited little from adjuvant hormonal therapy in that meta–analysis [18]. Several studies have found that higher ER expression correlates with improved effectiveness from adjuvant hormonal therapy [18, 19]. This may highlight the crucial necessity to weigh the expected benefit of adjuvant hormone therapy in individuals with low ER expression against potential side effects and treatment costs [20].

In our study ER–1–10%/HER2 negative, were more likely to have features of aggressive tumours compared to ER>10% tumours, such as high pathological grade, younger age at diagnosis and premenopausal status in addition to worse DFS. This data same with data from Kyung–Hwak Yoon et al 2022 [2] for the pathological grade ($p<0.0001$ in our study and $p= 0.017$ for their study) but not the same for DFS ($p=0.024$ in our study and P= in their study). This discrepancy may be because of different in study number and groups (total 419 patients in our study with two groups only: ER low and ER high groups while in their study the total number was 2,162 patients with 3 groups: two groups like our study and 3rd group with ER negative which was about total pf 454 patients (21.0%)

Meanwhile, the lower pathological T–stage in ER 1–10% group in our study may reflect better pathological response to neoadjuvant chemotherapy which was given

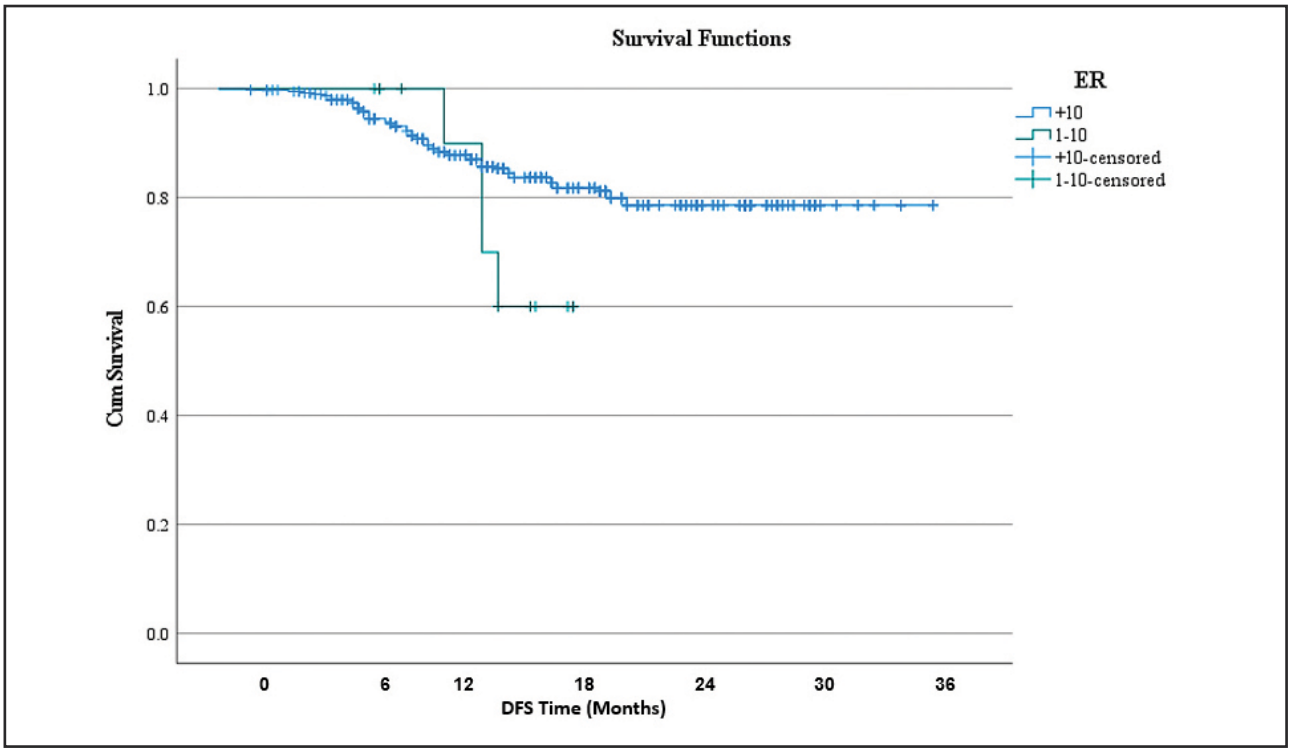


Figure 1. DFS Survival Curves for ER–Low and ER– High

	Univariate analysis			Multivariate analysis		
	HR	95%CI	p value	HR	95%CI	p value
Age	0.86	0.53–1.38	0.53	–	–	–
Tumor grade						
▪ **I**	Ref.					
▪ **II**	1.15	0.47–2.85	0.76	–	–	–
▪ **III**	1.48	0.45–4.87	0.52	–	–	–
PR status	0.73	0.37–1.43	0.36	–	–	–
ER intensity	2.06	0.75–5.67	0.16	–	–	–

Table–5: Predictors of DFS in the studied patients

to more than half of those patients. These features are more likely to be similar to triple negative breast cancer patients. Our results are consistent with previous reports such as the study of Yi et al in 2014 [6] as they reported that the survival outcome of patients with ER 1–9% was worse to those with ER≥ 10% with and without adjustment for clinical stage and grade and they have younger age and more advanced stage at diagnosis.

The relapse rate was found to be non–significant in both our study and the data from Kyung–Hwak Yoon et al 2022 [2], with p = 0.2 and 0.357, respectively.

For the OS by multivariant analysis, there is significant correlation with ER intensity but no significant correlation with tumour grade although the results from publication by Yunhai Li, et al 2020 [1] showed significant relationship.

There are several restrictions in our study. First, the study was limited by its retrospective design. Second, although the current investigation was conducted on a large number, the ER–low group sample size was relatively small. It is known that the popularity of breast cancers is either ER–negative or ER–positive, and tumours with low ER expression are uncommon. Future studies with larger populations may be able to circumvent this limitation and provide more data on ER–low tumours.

In the meantime, in our study, we reported different clinicopathological parameters and treatment factors

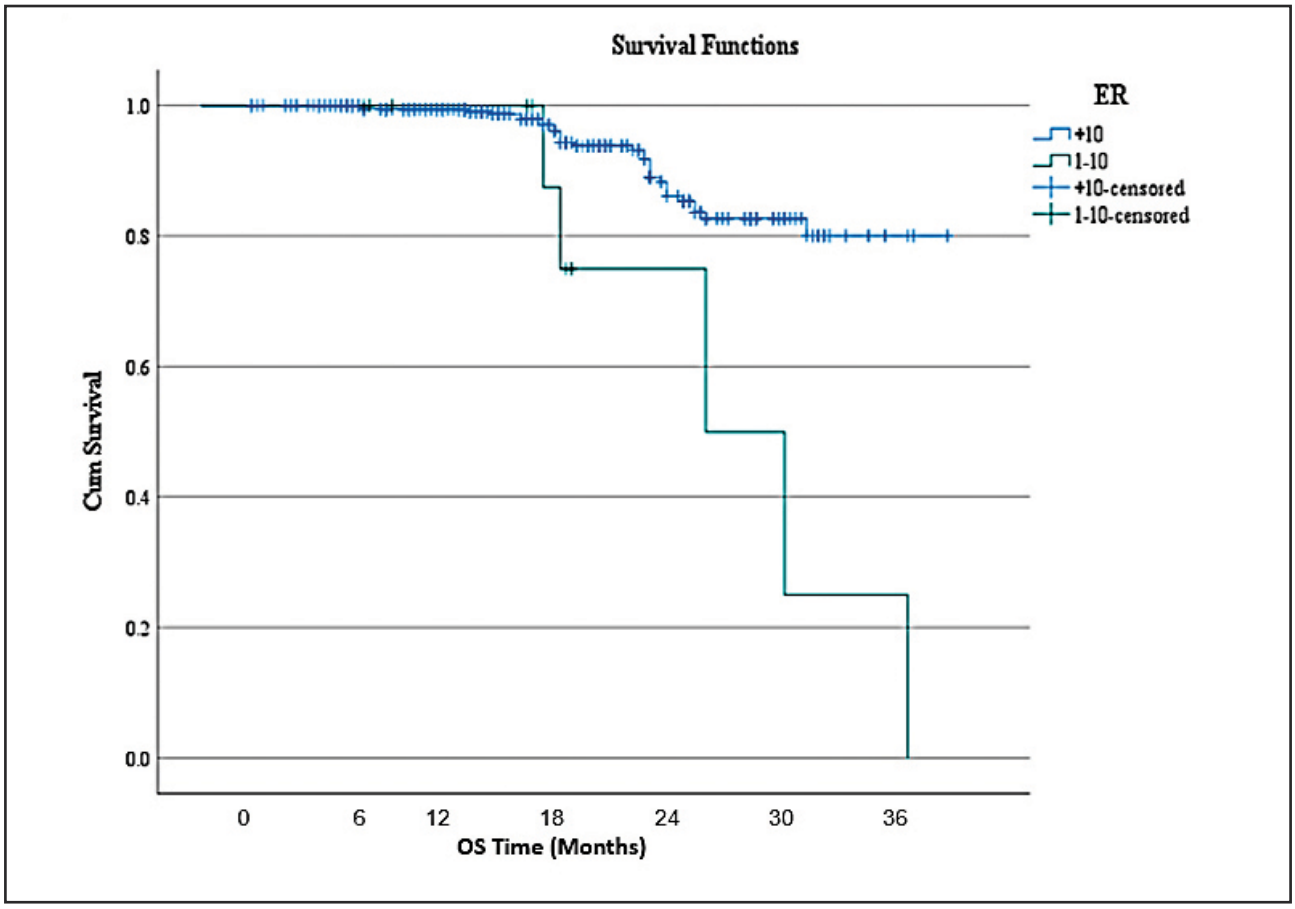


Figure 2. OS Survival Curves for ER–Low and ER– High

	Univariate analysis			Multivariate analysis		
	HR	95%CI	p value	HR	95%CI	p value
Age	0.79	0.4–1.54	0.48	–	–	–
Tumor grade						
▪ **I**	Ref.					
▪ **II**	0.33	0.1–1.02	0.055	0.74	0.44–1.24	0.26
▪ **III**	0.24	0.03–2.18	0.2	–	–	–
PR status	0.39	0.18–0.87	0.02	0.51	0.22–1.17	0.26
ER intensity	5.0	1.9–12.88	0.001	4.84	1.72–13.65	0.003

Table 6: Predictors of OS in the studied patients

and their relations with ER–staining groups. In addition, we highlighted the independent prognostic value of ER–staining groups for DFS, when adjusted for other routine clinicopathological parameters, including age, menopausal status, pathological T, N stages, tumour grade.

In conclusion, Low ER expression (1–10%) is an uncommon condition associated with more aggressive disease characteristics at diagnosis. This group may have a lower DFS compared to those with a higher level of ER expression, but there is no significant difference in OS.

Compliance With Ethical Standards

CONFLICT OF INTEREST: No

FUNDING: No

ETHICAL APPROVAL: This retrospective study gets IRB approval(H1RI–01–Feb21–01) accordance with the ethical standards of the responsible committee.

INFORMED CONSENT: with approved waiver

Abbreviations

ASCO: **American Society of Clinical Oncology**

CAP: **College of American Pathologists**

DFS: **Disease free survival**

ER: **Estrogen Receptors**

ESR1: **EStrogen Receptor 1**

FISH: **Fluorescence In Situ Hybridisation**

HER2: **human epidermal growth factor receptor 2**

HR :**Hormone Receptor**

IHC :**Immunohistochemistry**

LNs : **Lymph Nodes**

LVI : **Lympho–Vascular Invasion,**

mRNA: **Messenger RNA**

PR: **Progesterone Receptors**

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