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Clinical Implications of Low Estrogen Receptor Expression in Early Breast Cancer: A Systematic Review and Meta-Analysis

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Abstract

Breast cancers have traditionally been considered estrogen receptor (ER)-positive when at least 1% of tumor cells express ER. Recent ASCO/CAP guidelines, however, introduce a distinct category—ER-low-positive—for tumors with 1%–10% ER expression, reflecting the limited evidence on how low ER levels influence prognosis and treatment response. This study investigates whether ER-low tumors differ from ER-positive and ER-negative tumors in terms of outcomes and examines their predictive value for response to neoadjuvant chemotherapy (NeoCT). Following the MOOSE (Meta-analyses Of Observational Studies in Epidemiology) guidelines, we systematically searched ISI Web of Science and PubMed to identify eligible studies for meta-analysis. The investigation focused primarily on pathologic complete response (pCR), with overall survival (OS) and disease-free survival (DFS) as secondary outcomes. A total of twelve retrospective cohort studies were included. The results indicated that patients with ER-low tumors achieved higher pCR rates after neoadjuvant chemotherapy than those with ER-positive tumors, and their response was comparable to patients with ER-negative tumors. In terms of survival, ER-low breast cancers were linked to significantly poorer OS and DFS compared with ER-positive cancers, while no survival differences were observed when ER-low tumors were compared with ER-negative cases. Available evidence indicates that ER-low breast cancers resemble ER-negative tumors more closely than ER-positive ones in terms of disease-free survival (DFS) and overall survival (OS). Additionally, low ER expression appears to have predictive value for response to neoadjuvant chemotherapy (NeoCT). Given that the current evidence is rated as low to moderate in certainty, our findings highlight the urgent need for rigorously designed prospective studies to explore the molecular characteristics and optimal therapeutic approaches for ER-low breast cancers.

Keywords: Meta-analysis, Neoadjuvant chemotherapy, ER-low, Prognosis, Breast cancer, Adjuvant

Introduction

Breast cancer remains the most commonly diagnosed malignancy in women, with an incidence of 148.8 per 100,000 in Sweden in 2020 and 142.8 per 100,000 in the European Union.[1] Among its subtypes, estrogen receptor (ER)-positive breast cancer is the most prevalent, representing nearly 70% of cases.[2]

Traditionally, tumors with more than 1% of nuclei expressing ER have been classified as ER-positive.[3] However, the latest CAP/ASCO guidelines recommend a distinct category for tumors exhibiting 1%–10% ER expression, termed ER-low-positive. This classification acknowledges the limited clinical data on the prognostic and predictive value of low ER levels and underscores the need for further evidence.[4] The ABC5 international consensus guidelines for advanced breast cancer have adopted a similar approach. [5]

Treatment strategies in breast cancer are largely guided by ER status. For instance, neoadjuvant chemotherapy

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(NeoCT) is the standard approach for triple-negative breast cancer (TNBC),[6] whereas adjuvant endocrine therapy is indicated for all luminal-like tumors.[7] In this context, it is crucial to evaluate whether ER-low expression influences response to NeoCT and to clarify the prognostic outcomes of ER-low tumors compared with ER-negative (<1%) or ER-positive (>10%) breast cancers.

This meta-analysis and systematic review aims to summarize the available evidence on ER-low-positive breast cancer in two clinical scenarios: (i) response to NeoCT in comparison with ER-positive or ER-negative tumors; and (ii) survival outcomes following adjuvant therapy—including endocrine therapy, chemotherapy, or combination regimens—relative to ER-positive and ER-negative breast cancers.

Materials and Methods

Study design

We performed a systematic review following the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines. Study eligibility and exclusion criteria were established a priori using the PICO (intervention, patient, outcome, control) framework.

Patients of interest were individuals with breast cancer whose quantitative ER status was reported and who had received endocrine therapy or chemotherapy in either the adjuvant or neoadjuvant setting. The interventions examined included neoadjuvant chemotherapy (NeoCT) or endocrine therapy in tumors with ER expression between 10% and 1%. Comparators were patients treated with NeoCT whose tumors exhibited ER >10% or ER <1%, or those receiving endocrine therapy for tumors with ER >10%.

Outcomes evaluated were pathologic complete response (pCR) for neoadjuvant studies, defined according to each study's criteria, as well as disease-free survival (DFS) and overall survival (OS). DFS was defined as the period from diagnosis to recurrence or death from any cause, while OS was measured from diagnosis to death from any cause. To minimize confounding, only multivariate-adjusted estimates were included for survival analyses.

Search strategy

A comprehensive literature search was conducted in PubMed and ISI Web of Science databases, with no limitations on publication year, employing the following search strategies: (neoadjuvant OR primary OR preoperative OR induction) AND (low OR poor OR low positiv∗) AND (estrogen OR progesterone OR hormone) AND (prognosis OR survival OR efficacy OR response OR remission) AND breast cancer OR (adjuvant OR postoperative) AND (low OR poor OR low positiv∗) AND (estrogen OR progesterone OR hormone) AND (prognosis OR survival OR efficacy OR response OR remission) AND breast cancer. The most recent search was performed on August 8, 2021.

Abstracts and full-text articles were reviewed independently by two researchers (NP and AV). Agreement on study inclusion was reached through discussion. Trials were excluded from the meta-analysis if they lacked a comparator arm (such as ER >10% or ER <1%), did not provide isolated data for the low ER expression subgroup, focused on endpoints other than pathologic complete response (pCR), disease-free survival (DFS), or overall survival (OS), or omitted multivariate analyses for DFS or OS.

Quality assessment

The quality of the studies included in this meta-analysis and systematic review was evaluated using the Newcastle-Ottawa Scale (NOS) for cohort studies. Two investigators (AV, NP) independently assessed each study, and any discrepancies were resolved through discussion to reach a consensus on the final quality ratings.

Data collection

Data extraction was performed independently by two investigators (AV, NP), with any discrepancies resolved through discussion to reach consensus. For each eligible study, the following information was collected: first author, year of publication, journal, whether the study was multicenter, number of patients within each ER category, country of origin, total patient number, inclusion period, ER status, type of therapy, and key outcomes including pathologic complete response (pCR, as defined in each study), hazard ratios (HRs) for disease-free survival (DFS) with corresponding 95% confidence intervals, covariates included in multivariate analyses for DFS, HRs for overall survival (OS) with 95% confidence intervals, and covariates used in multivariate analyses for OS. The extracted data were subsequently stratified into two subgroups based on whether patients received neoadjuvant or adjuvant treatment.

Data synthesis

For the neoadjuvant subgroup, pooled estimates of pathologic complete response (pCR) were calculated using a random-effects model, generating 95% confidence intervals (CIs) for each ER subgroup (ER-low, ER-positive, ER-negative). Overall comparisons across the three groups were expressed as odds ratios (ORs) with 95% CIs using the DerSimonian and Laird approach.

To evaluate disease-free survival (DFS) and overall survival (OS) in both neoadjuvant and adjuvant cohorts, reported hazard ratios (HRs) and their associated standard errors were first converted to logarithmic form. Pooled HRs were then computed using the inverse variance method and subsequently back-transformed to the original scale. In cases where DFS or OS estimates were not directly reported, data were extracted following the methodology proposed by Tierney *et al* [8]

Between-study heterogeneity was assessed with the Q statistic, and its extent quantified using the I^2 statistic. Heterogeneity was considered significant if $P < 0.10$ or I^2 exceeded 50%, and the choice between fixed- or random-effects models was based on these results.

The certainty of the evidence was evaluated using the GRADE framework, focusing on three key questions: (i) the predictive value of ER-low expression for response to NeoCT compared with ER-positive and ER-negative tumors, (ii) the prognostic impact of ER-low expression on DFS, and (iii) the prognostic impact on OS.

Results and Discussion

Literature search

The systematic search yielded a total of 6,970 records. Following title and abstract screening, 91 articles were identified as potentially eligible. Full-text versions of these studies were obtained and independently reviewed by two investigators (NP, AV), with all discrepancies resolved through discussion. After excluding 79 studies for reasons outlined in **Figure 1**, 12 studies met the inclusion criteria for the meta-analysis. Among these, six provided data on neoadjuvant chemotherapy (NeoCT) [9-14], five reported outcomes for adjuvant therapy [15-19], and one study included results for both treatment settings. [20]

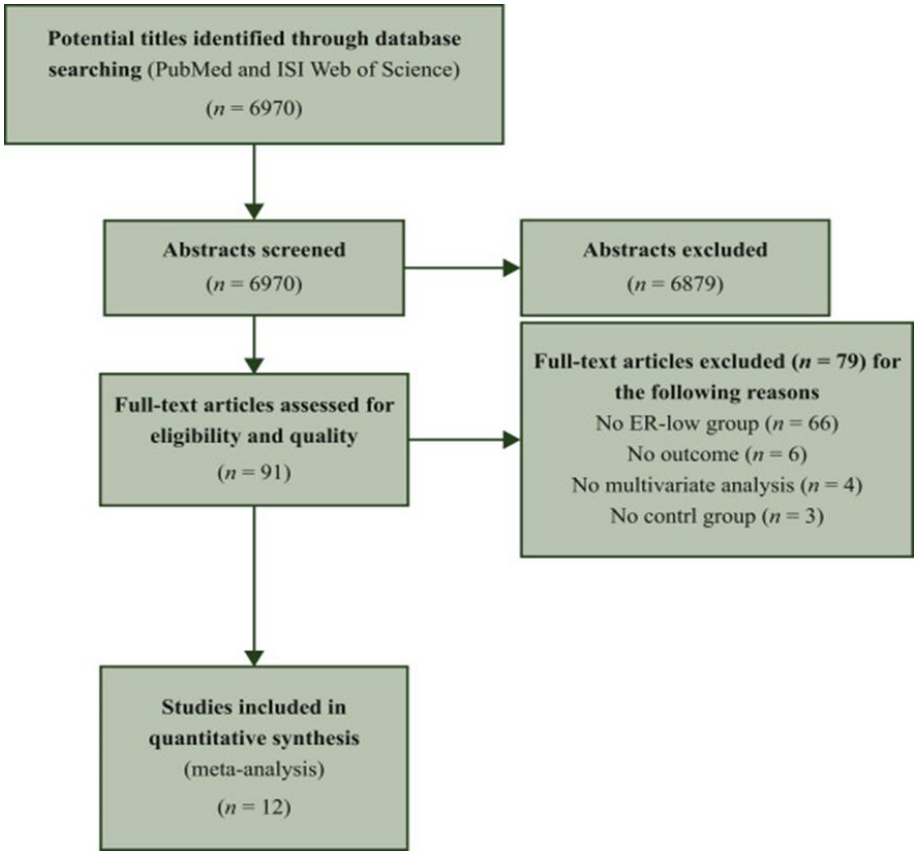

Figure 1. Flowchart for study selection process.

Study characteristics

The key features of the included studies are outlined in **Table 1**. Study populations ranged from 156 to 9,639 participants, with the majority employing a retrospective cohort design. Follow-up durations varied between 29 and 89.3 months, and three studies reported median follow-up periods exceeding five years.[14, 15, 18]

Table 1. Characteristics of eligible studies

First Author (Publication Year)	Nation of Origin	Type of Study Analysis	Years of Patient Enrollment	Use of Neoadjuvant Chemotherapy	Regimens Used for Neoadjuvant or Adjuvant Chemotherapy	Overall Patient Cohort Size	Patient Distribution by ER Expression Levels	Proportion Receiving Adjuvant Endocrine Therapy (HT) and Chemotherapy (CT) by ER Category
Balduzzi (2012)	Italy	Review of prospectively gathered data (retrospective)	1995–2009	None	Anthracyclines alone; anthracyclines + CMF; taxanes alone; CMF alone; miscellaneous	1424	<1%: 1300 1–10%: 124	<1%: HT 5%; CT 89% 1–10%: HT 41%; CT 59%
Colleoni (2004)	Italy	Review of prospectively gathered data (retrospective)	1994–2002	Administered	Anthracyclines; anthracyclines + taxanes; miscellaneous	399	<1%: 129 1–9%: 94 ≥10%: 171	Not specified
Dieci (2021)	Italy	Retrospective review	2000–2019	Administered in 41% of participants	Anthracyclines ± taxanes; miscellaneous	406	<1%: 364 ER 1–9%: 42	<1%: HT 4%; CT 100% 1–9%: HT 14%; CT 100%
Ding (2019)	China	Retrospective review	2007–2017	Administered	Anthracycline + cyclophosphamide + paclitaxel (sequential or combined)	570	<1%: 209 1–10%: 60 >10%: 301	Not specified

Villegas (2021)	**Raghav (2012)**	**Prabhu (2014)**	**Ohara (2019)**	**Landmann (2018)**	**Fujii (2017)**
Germany	United States	India	Japan	United States	United States
Secondary analysis of randomized trial data	Retrospective review	Prospective cohort	Retrospective review	Retrospective review	Retrospective review
Not reported	1990–2009	2008–2013	2004–2013	2010–2014	1982–2013
Administered	None	None	Administered	Administered	Administered
Anthracycline- and taxane-containing regimens	Anthracycline-containing; taxane-containing; both; miscellaneous	Anthracyclines + taxanes; anthracyclines + other agents; miscellaneous	Paclitaxel followed by fluorouracil + epirubicin + cyclophosphamide	Doxorubicin + cyclophosphamide + taxane; other/unspecified	Anthracyclines alone; taxanes alone; anthracyclines + taxanes
2765	1257	235	156	327	3055
<1%: 902 1–9%: 94 ≥10%: 1769	<1%: 897 1–5%: 241 6–10%: 119	<1%: 74 1–10%: 21 >10%: 140	<1%: 32 1–9%: 16 ≥10%: 108	<1%: 141 1–10%: 41 >10%: 145	<1%: 932 1–9%: 171 ≥10%: 1952
Not specified	<1%: HT 4%; CT 74% 1–5%: HT 14%; CT 70% 6–10%: HT 40%; CT 72%	<1%: HT 0%; CT 84% 1–10%: HT 71%; CT 76% >10%: HT 91%; CT 59%	Not specified	Not specified	<1%: HT 9%; CT 17% 1–9%: HT 25%; CT 9% ≥10%: HT 98%; CT 15%

Yi (2014)	United States	Retrospective review	1990–2011	Administered (combined data only)	Not specified	9639	<1%: 1625 1–9%: 250 ≥10%: 7764	<1%: HT 12.9%; CT 49.7% 1–9%: HT 20.4%; CT 49.2% ≥10%: HT 83.6%; CT 35.5%
Zhang (2014)	United States	Retrospective review	2000–2011	None	Not specified	1700	<1%: 401 1–10%: 32 >10%: 1267	<1%: HT 11%; CT 78% 1–10%: HT 87%; CT 81% >10%: HT 99%; CT 86%

HT, hormone therapy; CT, chemotherapy; NR, not reported; CMF, cyclophosphamide, methotrexate, fluorouracil; FEC, fluorouracil, epirubicin, cyclophosphamide; ER, estrogen receptor; ET, endocrine therapy.

Quality assessment

Table 2 provides an overview of the quality assessment for the included studies. The median score was 7, with individual study scores ranging from 5 to 9

Table 2. Appraisal of the quality of the studies included, utilizing the Newcastle-Ottawa Scale

Included studies	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at the start of study	For main factor (lymph node status)	For additional factor (tumor size)	Assessment of outcome	Sufficient follow-up (8 years)	Adequacy of follow-up	Total quality score
Ohara, 2019	*	*	*	*			*			5
Balduzzi, 2014	*	*	*	*	*	*	*			7
Fujii, 2017	*	*	*	*	*	*	*			7
Colleoni, 2004	*	*	*	*			*			5

Dieci, 2021	*	*	*	*	*	*	*		*	8
Landmann, 2018	*	*	*	*			*			5
Ding, 2019	*	*	*	*	*	*	*		*	8
Raghav, 2012	*	*	*	*	*	*	*			7
Prabhu, 2014	*	*	*	*			*		*	6
Villegas, 2021	*	*	*	*	*	*	*	*	*	9
Zhang , 2014	*	*	*	*	*	*	*			7
Yi, 2014	*	*	*	*	*	*	*			7

Pooled pCR rates after neoadjuvant chemotherapy by ER status

Seven studies reported pCR outcomes stratified by ER expression. [8-11, 15, 20] When analyzed collectively, patients with ER-low breast cancer achieved a pooled pCR rate of 24.8% following neoadjuvant chemotherapy, which was substantially higher than the 8.3% observed in ER-positive tumors, with a pooled odds ratio (OR) of 3.25 (95% CI, 1.85–5.71). In comparison, ER-negative tumors had a pooled pCR rate of 30.8%, which was not significantly different from the ER-low group (OR, 1.37; 95% CI, 0.83–2.22; **(Table 3).**

Table 3. Pooled pCR rates and corresponding ORs after neoadjuvant chemotherapy for ER-low breast cancer

Category	Number of Patients	Pooled pCR Rate (95% CI)	Odds Ratio (95% CI)	Heterogeneity I^2 (%)	P-value
ER-negative breast cancer	2486	30.8% (25.9–35.7%)	1.37 vs ER-low (0.83–2.22) 4.71 vs ER-positive (3.69–6.02)	74 49	<0.001 0.08
ER-low breast cancer	499	24.8% (16.0–34.7%)	3.25 vs ER-positive (1.85–5.71)	74	0.002
ER-positive breast cancer	4446	8.3% (6.9–9.9%)	–	–	–

ER, estrogen receptor; CI, confidence interval; pCR, pathologic complete response; OR, odds ratio

DFS based on ER expression

Seven studies provided data on disease-free survival (DFS) for ER-low versus ER-positive breast cancer, including four neoadjuvant [10, 11, 12, 14] and three adjuvant [16, 18, 19] studies. Fujii *et al* [11] reported time to recurrence (TTR), and Yi *et al* [18] reported recurrence-free survival (RFS); both were incorporated into the pooled DFS analysis, as these outcomes are encompassed within the DFS definition. [19] The pooled results indicated that patients with ER-low tumors experienced significantly shorter DFS compared with those with ER-positive tumors (HR, 1.85; 95% CI, 1.35–2.54); **(Figure 2).**

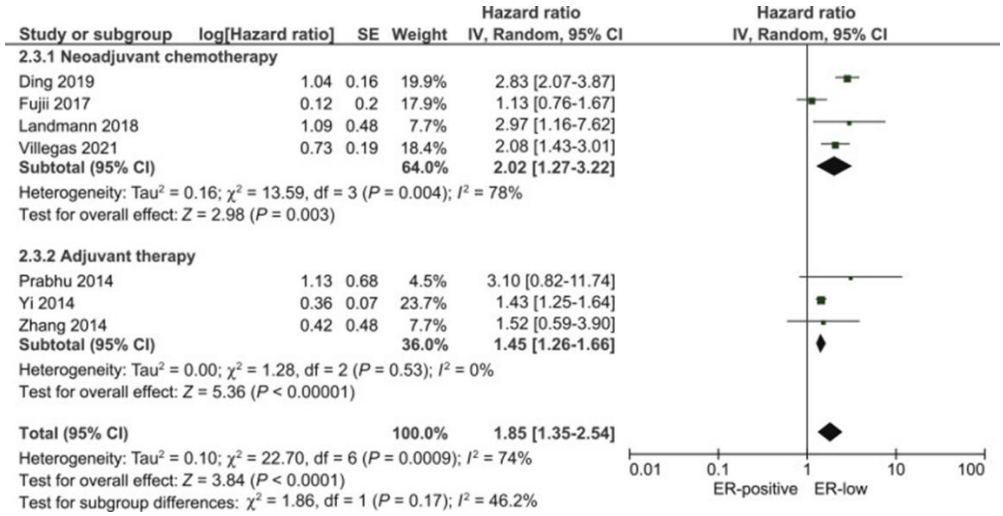

Figure 2. Pooled hazard ratio for disease-free survival in patients with ER-positive breast and ER-low versus cancer.

Df, degrees of freedom; CI, confidence interval; SE, standard error; ER, estrogen receptor

Five studies [14, 15, 17,18, 20] were included to assess DFS outcomes for ER-low compared with ER-negative breast cancer, with three reporting recurrence-free survival (RFS)17,18,20 which were incorporated into the analysis. The combined results indicated no significant difference in DFS between ER-negative and ER-low groups (pooled HR, 1.09; 95% CI, 0.93–1.26); **(Figure 3).**

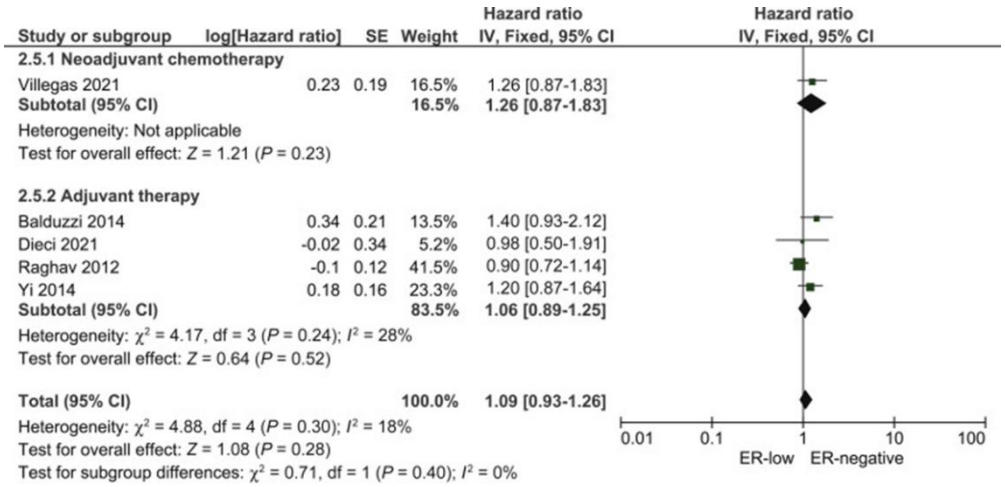

Figure 3. Pooled hazard ratio for disease-free survival comparing ER-negative and ER-low breast cancer.

ER, estrogen receptor; df, degrees of freedom; SE, standard error; CI, confidence interval.

For this pooled DFS analysis, we used data from Raghav *et al* [17] comparing ER expression 0% with ER 1%–5%. Although the study also reported outcomes for the ER 1%–5% group, the ER 6%–10% subgroupwas selected for the primary analysis because it included a larger number of patients. A sensitivity analysis incorporating the ER 0% versus ER 6%–10% comparison from the same study[17] yielded a similar pooled hazard ratio (95% CI, 0.97–1.35; HR, 1.17), consistent with the main analysis.

Regarding overall survival (OS), six studies[10-12, 14, 19, 21] provided data comparing ER-low and ER-positive breast cancer. The pooled analysis demonstrated that ER-low tumors were associated with significantly worse OS than ER-positive tumors (HR, 2.36; 95% CI, 1.35–3.86); **(Figure 4).**

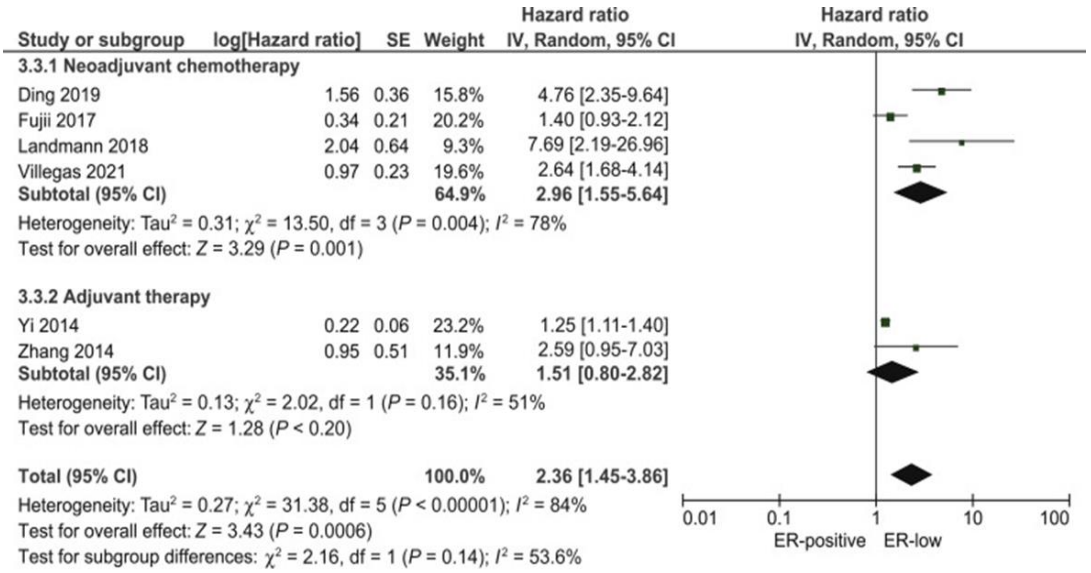

Figure 4. Pooled hazard ratio for overall survival in patients with ER-positive compared with ER-low breast cancer. df, degrees of freedom; CI, confidence interval; SE, standard error; ER, estrogen receptor.

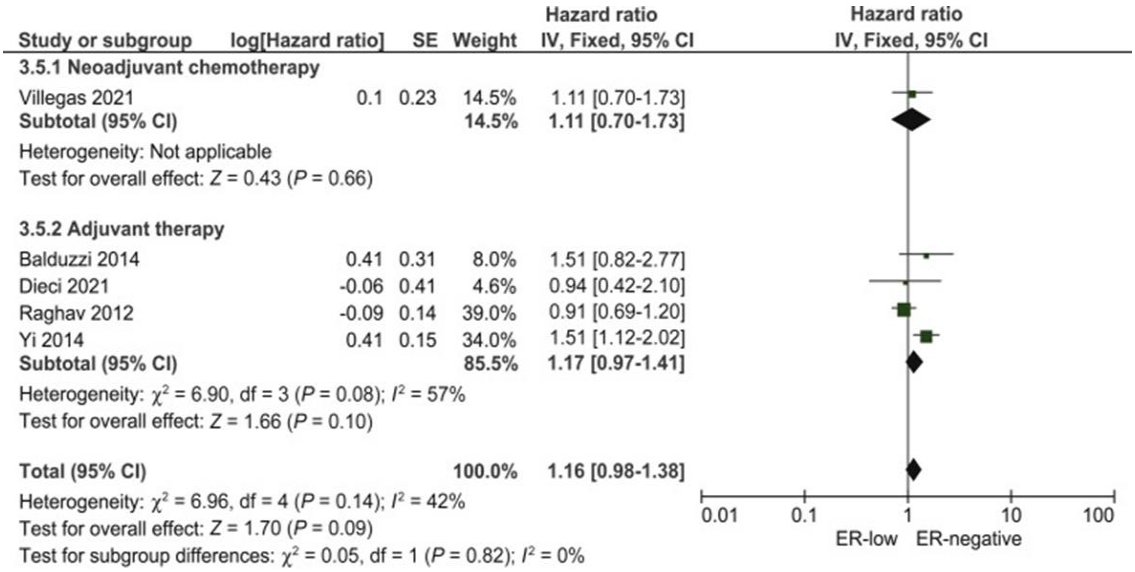

Figure 5. Pooled hazard ratio for overall survival comparing ER-negative and ER-low breast cancer. df, degrees of freedom; CI, confidence interval; SE, standard error; ER, estrogen receptor

Overall survival data for ER-negative versus ER-low breast cancer were available from five studies[14, 15, 17, 18, 20]. The combined analysis revealed no significant difference in OS between the two groups (pooled HR, 1.16; 95% CI, 0.98–1.38;) **(Figures 4 and 5).**

Data from Raghav *et al* [17] were treated in the same manner as in previous analyses. A sensitivity check including the ER 0% versus ER 6%–10% comparison produced results consistent with the main analysis (pooled HR, 1.21; 95% CI, 0.98–1.46).

Evidence certainty assessed using GRADE

The quality of the evidence from this meta-analysis was evaluated with the GRADE approach, covering three main research questions across six specific comparisons **(Table 4).**

Table 4. Assessment of evidence quality based on the GRADE framework

Outcome Comparison	Number of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Relative Effect (95% CI)	Certainty of Evidence
Pathologic complete response (pCR): ER-low vs ER-negative	7	Observational studies	Serious	Serious	Not serious	Not serious	None	OR 1.37 (0.83–2.22)	⊕⊕◯◯ LOW
Pathologic complete response (pCR): ER-low vs ER-positive	6	Observational studies	Serious	Not serious	Not serious	Not serious	None	OR 3.25 (1.85–5.71)	⊕⊕⊕◯ MODERATE
Disease-free survival: ER-low vs ER-negative	5	Observational studies	Serious	Serious	Not serious	Not serious	None	HR 1.09 (0.93–1.26)	⊕⊕◯◯ LOW
Overall survival: ER-low vs ER-negative	5	Observational studies	Serious	Serious	Not serious	Not serious	None	HR 1.16 (0.98–1.38)	⊕⊕◯◯ LOW

Overall survival: ER-low vs ER-positive	6	Observational studies	Serious	Not serious	Not serious	Not serious	None	HR 2.36 (1.35–3.86)	⊕⊕⊕◯ MODERATE
Disease-free survival: ER-low vs ER-positive	7	Observational studies	Serious	Not serious	Not serious	Not serious	None	HR 1.85 (1.35–2.54)	⊕⊕⊕◯ MODERATE

PCR, pathologic complete response; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ER, estrogen receptor

All analyses comparing ER-positive with ER-low breast cancer were rated as moderate certainty according to the GRADE framework, while comparisons between ER-negative and ER-low tumors were rated as low certainty, primarily due to inconsistencies among the results of the included studies.

When synthesizing the currently available evidence, low estrogen receptor (ER) expression emerges as a marker of chemosensitivity rather than endocrine responsiveness. Across pooled analyses, tumors with ER expression in the low range demonstrated response rates to neoadjuvant chemotherapy (NeoCT) that closely approximated those seen in ER-negative breast cancer, particularly with respect to pathologic complete response (pCR). In contrast, ER-low tumors consistently underperformed compared with ER-positive disease in long-term outcomes, exhibiting inferior disease-free survival (DFS) and overall survival (OS). Notably, survival outcomes for ER-low and ER-negative breast cancer were largely overlapping, suggesting a shared clinical behavior. However, the certainty supporting these observations varied, ranging from moderate when ER-low tumors were compared with ER-positive disease to low when comparisons involved ER-negative tumors, reflecting heterogeneity across studies and limitations in study design.

The clinical resemblance between ER-low and ER-negative breast cancer is further reinforced by molecular profiling studies. Analyses conducted by Iwamoto *et al* [22] and Deyarmin *et al* [23] demonstrated that ER-low tumors predominantly fall within non-luminal intrinsic subtypes, most commonly basal-like and, to a lesser extent, HER2-enriched. Only a minority of cases—16% and 12%, respectively—exhibited luminal molecular characteristics. These findings were corroborated by Villegas *et al*.,14 who reported that nearly nine out of ten ER-low tumors carried a basal-like gene expression profile, with no tumors classified as luminal. Collectively, these data provide a biological rationale for the observed similarities in chemotherapy responsiveness and prognosis between ER-low and ER-negative breast cancer.

Earlier evidence addressing this topic includes a meta-analysis by Chen *et al* [24] published in 2016, which characterized ER-low breast cancer as having an intermediate prognosis between ER-positive and ER-negative disease. While informative, that analysis differs from the present study in several key respects. Most importantly, we restricted inclusion to studies reporting multivariate-adjusted survival estimates, thereby reducing the impact of confounding—an inherent limitation of observational research. The prior meta-analysis incorporated both unadjusted and adjusted estimates, potentially inflating bias. Given that randomized trials are unavailable for this clinical question, reliance on multivariate-adjusted results represents a more methodologically rigorous approach.

In addition, our work addressed a clinically relevant question not explored in the earlier meta-analysis: the predictive role of ER-low expression for response to NeoCT. As NeoCT is a standard treatment strategy for ER-negative breast cancer, evaluating its efficacy in ER-low tumors aligns directly with current therapeutic decision-making. Methodological differences also extend to outcome measurement; we employed hazard ratios for DFS and OS, which are better suited for time-to-event analyses than odds ratios. Finally, the application of the GRADE framework allowed us to formally assess evidence certainty, facilitating interpretation of the findings within an evidence-based medicine framework and enhancing their relevance for clinical practice and policy development.

Several limitations warrant consideration. First, data addressing the benefit of adjuvant endocrine therapy in ER-low breast cancer were insufficient to permit quantitative synthesis. Nevertheless, available observational studies suggest minimal or no survival benefit from endocrine therapy in this subgroup. [15, 17, 25] This observation is supported by randomized data from the Early Breast Cancer Trialists' Collaborative Group, which demonstrated negligible benefit of adjuvant tamoxifen in tumors with low ER expression. [26] Second, follow-up duration was limited in most included studies, with median follow-up often below five years. While adequate for ER-negative disease, this duration is insufficient to capture late recurrences typical of ER-positive breast cancer, which often require follow-up extending beyond eight years. [27, 28]

Another important limitation relates to variability in ER assessment across institutions, time periods, and laboratory techniques. This variability is known to be more pronounced in tumors with low or intermediate ER expression [29] although it remains less substantial than that observed for other biomarkers such as HER2 or Ki-67. [30, 31] Finally, the absence of randomized trials necessitated reliance on observational evidence, inherently lowering confidence in causal inference, as reflected in the GRADE ratings.

Conclusion

In conclusion, the current body of evidence indicates that ER-low breast cancer behaves more like ER-negative than ER-positive disease in both treatment response and prognosis. ER-low tumors appear to derive meaningful benefit from NeoCT, achieving pCR rates similar to ER-negative tumors, while long-term outcomes mirror those of ER-negative rather than ER-positive breast cancer. These findings lend strong support to recent ASCO/CAP and ABC5 guideline recommendations[4,5] advocating for ER-low tumors to be recognized as a distinct biological and clinical subgroup. Moreover, they raise important clinical considerations regarding the potential extension of emerging therapeutic strategies for triple-negative breast cancer—such as immunotherapy and antibody–drug conjugates—to patients with low ER expression. Given the low to moderate certainty of existing evidence, there remains a clear and pressing need for well-designed prospective studies to clarify the molecular underpinnings and optimal management strategies for ER-low breast cancer.

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Ethics Statement: None

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