ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN CANCER HORIZONS

ORIGINAL RESEARCH

The prognostic and predictive impact of low estrogen receptor expression in early breast cancer: a systematic review and meta-analysis

N.-M. Paakkola[1†], A. Karakatsanis[2†], D. Mauri[3], T. Foukakis[4] & A. Valachis[5*]

[1]School of Medical Sciences, Faculty of Medicine and Health, Örebro University, Örebro; [2]Department of Surgical Sciences, Uppsala University, Uppsala, Sweden; [3]Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece; [4]Department of Oncology-Pathology, Karolinska Institutet Stockholm, Stockholm; [5]Department of Oncology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

Available online xxx

Introduction: Traditionally, estrogen receptor (ER)-positive breast cancer has been defined as tumors with ≥1% positive for ER. The updated American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines recommend that tumors with ER expression of 1%-10% should be classified as ER-low-positive, recognizing the limited clinical evidence on the prognostic and predictive role of low ER expression. We aimed to investigate the predictive role of ER-low expression to neoadjuvant chemotherapy (NeoCT) and the prognostic significance of ER-low expressing breast tumors compared with ER-positive or ER-negative breast tumors.

Methods: A meta-analysis was conducted using the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines and eligible articles were identified on PubMed and ISI Web of Science databases. The primary outcome was pathologic complete response and secondary outcomes were disease-free survival (DFS) and overall survival (OS). Twelve retrospective cohort studies were included in the meta-analysis. NeoCT resulted in higher pathologic complete response among patients with ER-low expression compared with ER-positive and comparable to ER-negative. Patients with ER-low breast cancer had a statistically significant worse DFS and OS compared with patients with ER-positive breast cancer, whereas no difference in DFS or OS was observed between ER-low and ER-negative subgroups.

Discussion: The current evidence suggests that ER-low breast cancer has a more similar outcome to ER-negative than to ER-positive breast cancer in terms of DFS and OS. ER-low expression seems also to have a predictive role regarding NeoCT. Considering the certainty of current evidence categorized as low to moderate, our results urge the need for well-designed prospective studies investigating the molecular background and the most appropriate treatment strategy for ER-low expressing breast cancer.

Key words: ER-low, neoadjuvant chemotherapy, adjuvant, prognosis, breast cancer, meta-analysis

INTRODUCTION

Breast cancer is the most common type of cancer in females with an incidence of 142.8 per 100 000 in the European Union and 148.8 per 100 000 in Sweden in 2020.[1] Estrogen receptor (ER)-positive breast cancer is the most common breast cancer subtype, with nearly 70% of the cases considered ER-positive.[2]

Traditionally, ER-positive breast cancer has been defined as tumors with >1% of tumor nuclei positive for ER.[3] The updated American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines recommend that tumors with ER expression of 1%-10% should be classified as ER-low-positive, recognizing the limited clinical evidence on the prognostic and predictive role of low ER expression and highlighting the need for more robust evidence.[4] A similar approach has been adopted by the ABC5 international consensus guidelines for advanced breast cancer.[5]

Considering the different treatment strategies depending on ER status, where neoadjuvant chemotherapy (NeoCT) is the recommended treatment approach for triple negative breast cancer (TNBC)[6] and adjuvant endocrine therapy is recommended in all luminal-like cancers,[7] it is essential to investigate the predictive role of ER-low expression to NeoCT and the prognostic significance of ER-low expressing breast tumors compared with ER-positive (>10%) or ER-negative (<1%) breast tumors.

In the present systematic review and meta-analysis, we aimed to summarize the current evidence on

*Correspondence to: Assoc Prof. Antonis Valachis, Department of Oncology, Faculty of Medicine and Health, Örebro University, 701 82 Örebro, Sweden. Tel: +46-735617691

E-mail: antonios.valachis@oru.se (A. Valachis).

†These authors contributed equally to this work.

ER-low-positive breast cancer in two clinical scenarios: (i) when NeoCT is given (compared with ER-negative or ER-positive breast cancer); (ii) in patients treated with adjuvant therapy including chemotherapy, endocrine therapy, or a combination (compared with ER-negative or ER-positive breast cancer).

MATERIALS AND METHODS

Study design

A systematic search in accordance with the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines was conducted.

Eligibility and exclusion criteria were prespecified according to the patient, intervention, control, and outcome (PICO) format.

Patient characteristics: breast cancer patients with information about quantitative ER status who received chemotherapy or endocrine therapy as neoadjuvant or adjuvant treatment; intervention: NeoCT or endocrine therapy for breast cancer with ER status 1%-10%; control: NeoCT for breast cancer with ER status $<$1% or ER $>$10%. Endocrine treatment of breast cancer with ER status $>$10%. Outcome: pathologic complete response (pCR) for neoadjuvant studies based on the definition of each study, disease-free survival (DFS) defined as the time from diagnosis until disease recurrence or death due to any cause, and overall survival (OS) defined as the time from diagnosis until death due to any cause. For DFS and OS, only results derived from multivariate analyses were used to limit the risk for confounding bias.

Search strategy

The electronic literature search was carried out using PubMed and ISI Web of Science without any year restrictions with the following algorithms: (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 last search date was on 8 August 2021.

The resulting abstracts and full texts were screened independently by two investigators (NP, AV). Consensus by discussion was achieved regarding eligible trials. Studies without a comparison group (ER $>$10% or ER $<$1%), studies without separate results on low ER expression group, studies that reported outcomes other than pCR, DFS, or OS, and studies without multivariate analyses for DFS or OS were excluded from the meta-analysis.

Quality assessment

The Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort studies was used to judge the quality of the studies included in the systematic review and meta-analysis. Two investigators (NP, AV) assessed the quality of each trial independently and a consensus through discussion was reached regarding all eligible trials.

Data collection

Data were extracted independently by two investigators (NP, AV). Consensus by discussion was achieved in all extracted data. From each eligible trial, the following data were extracted: first author, journal, year of publication, country of origin, multicenter study, inclusion period, total number of patients, type of therapy, ER status, number of patients for each ER status, relevant outcomes as pCR (based on the definition of each study), hazard ratio (HR) for DFS, 95% low HR for DFS, 95% high HR for DFS, covariates in multivariate analysis for DFS, HR for OS, 95% low HR for OS, 95% high HR for OS, and covariates in multivariate analysis for OS. The results were divided into two subgroups according to neoadjuvant and adjuvant treatment.

Data synthesis

To carry out the meta-analysis for the neoadjuvant subgroup with pCR, a random-effects model was used to produce a pooled pCR and corresponding 95% confidence interval (CI) for each group (ER-low, ER-positive, ER-negative). An overall effect estimate among three comparisons was calculated using odds ratio (OR) with 95% CI through the DerSimonian and Laird method.

For the comparisons of DFS and OS for both neoadjuvant and adjuvant subgroups, a meta-analysis was carried out first by transforming the HRs and their errors into their log counterparts, and then using the inverse variance method for transforming back into the HR scale. If DFS or OS data were unavailable for direct extraction from the primary studies, data were extracted according to the method described by Tierney et al.[8]

The presence of statistical heterogeneity among the studies was addressed by using the Q statistics, and the magnitude of heterogeneity by using the I^2 statistic. A P value $<$0.10 or an I^2 value $>$50% was considered as substantial heterogeneity. All meta-analyses were carried out using the fixed- or random-effects model depending on the results of the statistical heterogeneity.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was applied to rate the certainty of current evidence in three research questions: the predictive role of ER-low to NeoCT (compared with ER-positive and ER-negative), the prognostic role of ER-low in terms of DFS, and the prognostic role in terms of OS.

RESULTS

Literature search

The search algorithm identified 6970 records. After reading the titles and abstracts, 91 studies were considered potentially eligible. The full texts of the potentially eligible articles were obtained and reviewed independently by two

investigators (NP, AV) in further detail, and a consensus was reached on all studies. After excluding 79 studies due to various reasons (Figure 1), a total of 12 studies, 6 with data on NeoCT,[9-14] 5 with adjuvant treatment,[15-19] and 1 with data on both treatment settings,[20] were considered eligible and included in the meta-analysis.

Study characteristics

Table 1 presents the key characteristics of the eligible studies. The number of study participants ranged from 156 to 9639 and the majority of the studies were retrospective cohort studies. The median follow-up ranged between 29 and 89.3 months with three studies exceeding a median follow-up of >5 years.[14,15,18]

Quality assessment

The quality assessment of eligible studies is summarized in Table 2. The median quality score was 7 (range: 5-9).

Pooled pCR rates after neoadjuvant chemotherapy based on ER expression

Seven studies provided data on pCR in relation to ER status.[8-11,15,20] Overall, ER-low breast cancer reached a higher pooled pCR rate (24.8%) with neoadjuvant chemotherapy in comparison to ER-positive breast cancer (8.3%) with a pooled OR of 3.25 (95% CI 1.85-5.71). The pooled pCR for ER-negative breast cancer was 30.8% without a statistically significant difference compared with the pooled pCR rate for the ER-low patient group (OR: 1.37; 95% CI 0.83-2.22; Table 3).

DFS based on ER expression

For comparison between ER-low and ER-positive breast cancer, four neoadjuvant[10-12,14] and three adjuvant studies[16,18,19] provided data on DFS. Fujii et al.[11] provided data on time to recurrence (TTR) and Yi et al.[18] on recurrence-free survival (RFS), but both studies were included in the pooled DFS analysis since TTR and RFS are part of the DFS definition.[19] ER-low breast cancer was associated with worse DFS compared with ER-positive breast cancer (pooled HR: 1.85; 95% CI 1.35-2.54; Figure 2).

When ER-low breast cancer was compared with ER-negative breast cancer in terms of DFS, five studies[14,15,17,18,20] were eligible, three of which presented data on RFS.[17,18,20] We found no statistically significant difference between ER-low and ER-negative breast cancer in terms of DFS (pooled HR: 1.09; 95% CI 0.93-1.26; Figure 3).

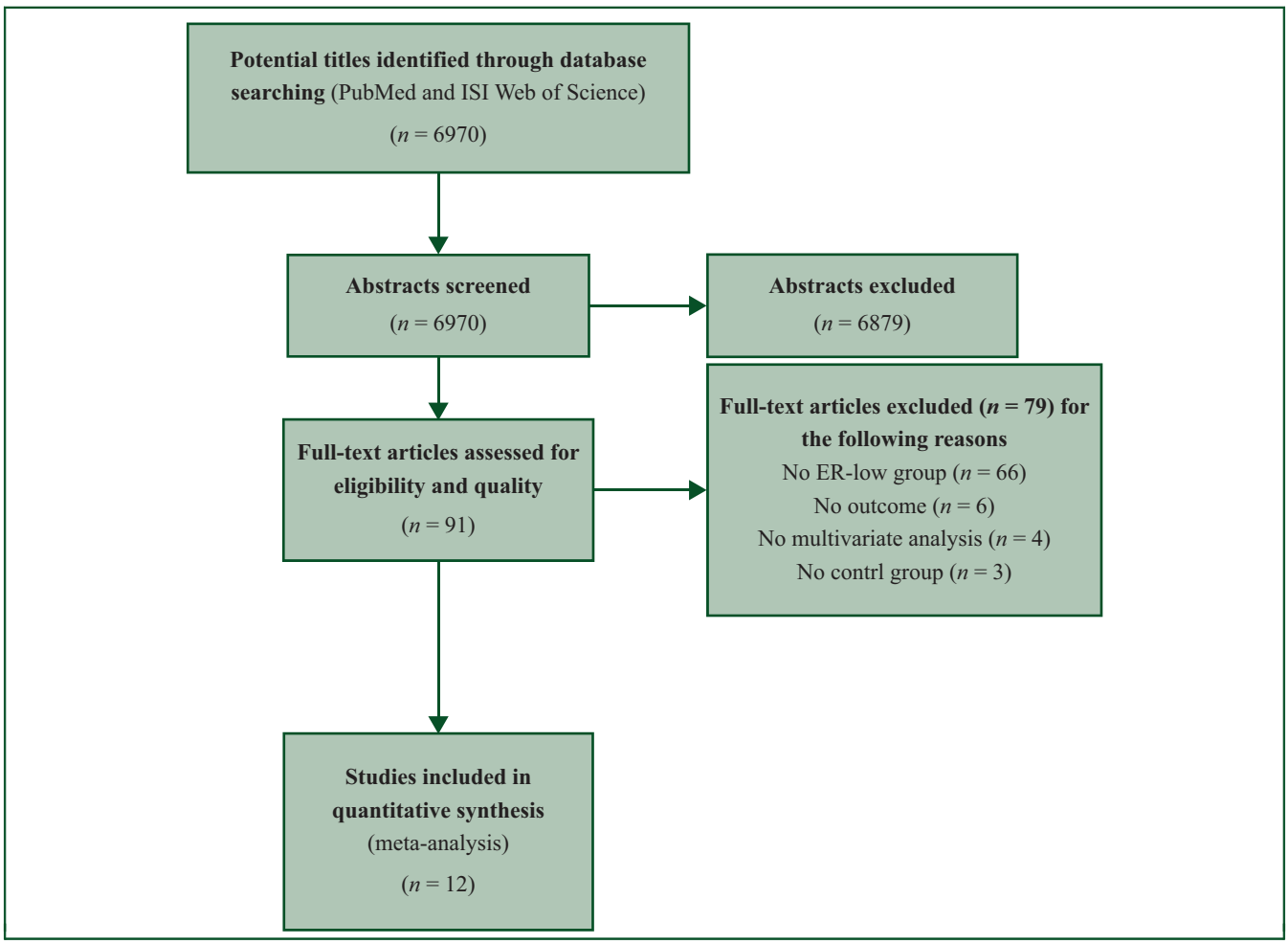

Figure 1. Flowchart for study selection process.

Table 1. Characteristics of eligible studies

Author, year	Country	Study design	Inclusion Period	Neoadjuvant CT	Type of neoadjuvant/adjuvant CT	Total number of patients	Number of patients according to ER status	% CT and HT as adjuvant
Balduzzi, 2012	Italy	Retrospective analysis of prospectively collected data	1995-2009	No	Anthracycline only, anthracycline and CMF, taxane only, CMF only, others	1424	<1%: 1300 1%-10%: 124	HT 5; CT 89 HT 41; CT 59
Colleoni, 2004	Italy	Retrospective analysis of prospectively collected data	1994-2002	Yes	Anthracycline Anthracycline and taxane Other	399	<1%: 129 1%-9%: 94 ≥10%: 171	NR
Dieci, 2021	Italy	Retrospective	2000-2019	Yes (41% of study cohort)	Anthracyclines and/or taxanes Other	406	<1%: 364 1%-9%: 42	HT 4; CT 100 HT 14; CT 100
Ding, 2019	China	Retrospective	2007-2017	Yes	Anthracycline, cyclophosphamide, and paclitaxel sequentially or concomitant	570	<1%: 209 1%-10%: 60 >10%: 301	NR
Fujii, 2017	USA	Retrospective	1982-2013	Yes	Anthracyclines alone Taxanes alone Anthracycline and taxane	3055	<1%: 932 1%-9%: 171 ≥10%: 1952	HT 9; CT 17 HT 25; CT 9 HT 98; CT 15
Landmann, 2018	USA	Retrospective	2010-2014	Yes	Adriamycin-cyclophosphamide-taxane Other/unknown	327	<1%: 141 1%-10%: 41 >10%: 145	NR
Ohara, 2019	Japan	Retrospective	2004-2013	Yes	Paclitaxel, followed by FEC	156	<1%: 32 1%-9%: 16 ≥10%: 108	NR
Prabhu, 2014	India	Prospective	2008-2013	No	Anthracycline and taxane Anthracycline plus other Other	235	<1%: 74 1%-10%: 21 >10%: 140	HT 0; CT 84 HT 71; CT 76 HT 91; CT 59
Raghav, 2012	USA	Retrospective	1990-2009	No	Anthracycline-based, taxane-based, anthracycline and taxane, other	1257	<1%: 897 1%-5%: 241 6%-10%: 119	HT 4; CT 74 HT 14; CT 70 HT 40; CT 72
Villegas, 2021	Germany	*Post hoc* analysis of randomized data	NR	Yes	Anthacycline- and taxane-based	2765	<1%: 902 1%-9%: 94 ≥10%: 1769	NR
Yi, 2014	USA	Retrospective	1990-2011	Yes (no separate data)	NR	9639	<1%: 1625 1%-9%: 250 ≥10%: 7764	HT 12.9; CT 49.7 HT 20.4; CT 49.2 HT 83.6; CT 35.5
Zhang, 2014	USA	Retrospective	2000-2011	No	NR	1700	<1%: 401 1%-10%: 32 >10%: 1267	HT 11; CT 78 HT 87; CT 81 HT 99; CT 86

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

Table 2. Quality assessment of eligible studies according to Newcastle-Ottawa Scale

Included studies	Selection				Comparability		Outcome			Total quality score
	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	
Balduzzi, 2014	*	*	*	*	*	*	*			7
Colleoni, 2004	*	*	*	*			*			5
Dieci, 2021	*	*	*	*	*	*	*		*	8
Ding, 2019	*	*	*	*	*	*	*		*	8
Fujii, 2017	*	*	*	*	*	*	*			7
Landmann, 2018	*	*	*	*			*			5
Ohara, 2019	*	*	*	*			*			5
Prabhu, 2014	*	*	*	*			*		*	6
Raghav, 2012	*	*	*	*	*	*	*			7
Villegas, 2021	*	*	*	*	*	*	*	*	*	9
Yi, 2014	*	*	*	*	*	*	*			7
Zhang, 2014	*	*	*	*	*	*	*			7

Table 3. pCR pooled rates and corresponding OR after neoadjuvant chemotherapy in ER-low breast cancer

	N patients	Pooled pCR (95% CI)	Odds ratio	95% CI	Heterogeneity	
					I^2	P
ER-positive breast cancer	4446	8.3 (6.9-9.9)	—	—	—	—
ER-low breast cancer	499	24.8 (16.0-34.7)	3.25 (versus ER-positive)	1.85-5.71	74	0.002
ER-negative breast cancer	2486	30.8 (25.9-35.7)	1.37 (versus ER-low)	0.83-2.22	74	<0.001
			4.71 (versus ER-positive)	3.69-6.02	49	0.08

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

For the latter pooled analysis, we used data from the comparison between ER expression 0% and ER 1%-5% from Raghav et al.[17] The authors also presented data on the ER 6%-10% group but we chose the ER 1%-5% group for the main analysis since it included more patients. When we carried out a sensitivity analysis by including the results from the ER expression 0% versus ER 6%-10% comparison from Raghav et al.,[17] we found a similar pooled HR as in the main analysis (pooled HR: 1.17; 95% CI 0.97-1.35).

OS based on ER expression

Six studies[10-12,14,19,21] presented data on OS between ER-low and ER-positive breast cancer. ER-low breast cancer was associated with worse OS compared with ER-positive (pooled HR: 2.36; 95% CI 1.35-3.86; Figure 4).

Five studies[14,15,17,18,20] presented data on OS for the comparison between ER-low and ER-negative breast cancer. No statistically significant difference was observed between the two breast cancer patient groups in terms of OS (pooled HR: 1.16; 95% CI 0.98-1.38; Figures 4 and 5).

OS data from Raghav et al.[17] were addressed in the same way as described above and our sensitivity analysis when we included the comparison ER expression 0% and ER 6%-10% in the pooled analysis, we found similar results to the main analysis (pooled HR: 1.21; 95% CI 0.98-1.46).

Quality of evidence according to GRADE approach

The quality of evidence from the present meta-analysis was assessed by the GRADE approach for three research questions and six comparisons (Table 4).

All comparisons between ER-low and ER-positive breast cancer were categorized as moderate certainty of evidence, whereas the comparisons between ER-low and ER-negative were categorized as low certainty of evidence due to the observed inconsistency of the results from eligible studies.

DISCUSSION

According to the pooled analyses based on current evidence, ER-low expression seems to be a predictive factor for NeoCT, with pCR rates similar to ER-negative breast cancer. Regarding the impact of ER-low expression on breast cancer prognosis, we found a worse prognosis in terms of DFS and OS compared with ER-positive breast cancer, whereas the prognoses of ER-low and ER-negative breast cancer were comparable. The quality of evidence for both the predictive and prognostic role of ER-low expression on breast cancer ranged between low (for the comparisons between ER-low and ER-negative breast cancer) and moderate (for the comparisons between ER-low and ER-positive breast cancer), highlighting the need for high-quality evidence on this topic.

Our findings on the similar efficacy of NeoCT and prognosis in patients with ER-low and ER-negative breast cancer are supported by prior studies on the molecular background of ER-low breast cancer. Iwamoto et al.[22] and Deyarmin et al.[23] analyzed the intrinsic subtype of ER-low expressing breast cancer and found that most ER-low breast cancers were molecularly primarily basal-like or secondarily human epidermal growth factor receptor 2 (HER2)-enriched, whereas only a small minority, 16% and 12%, respectively,

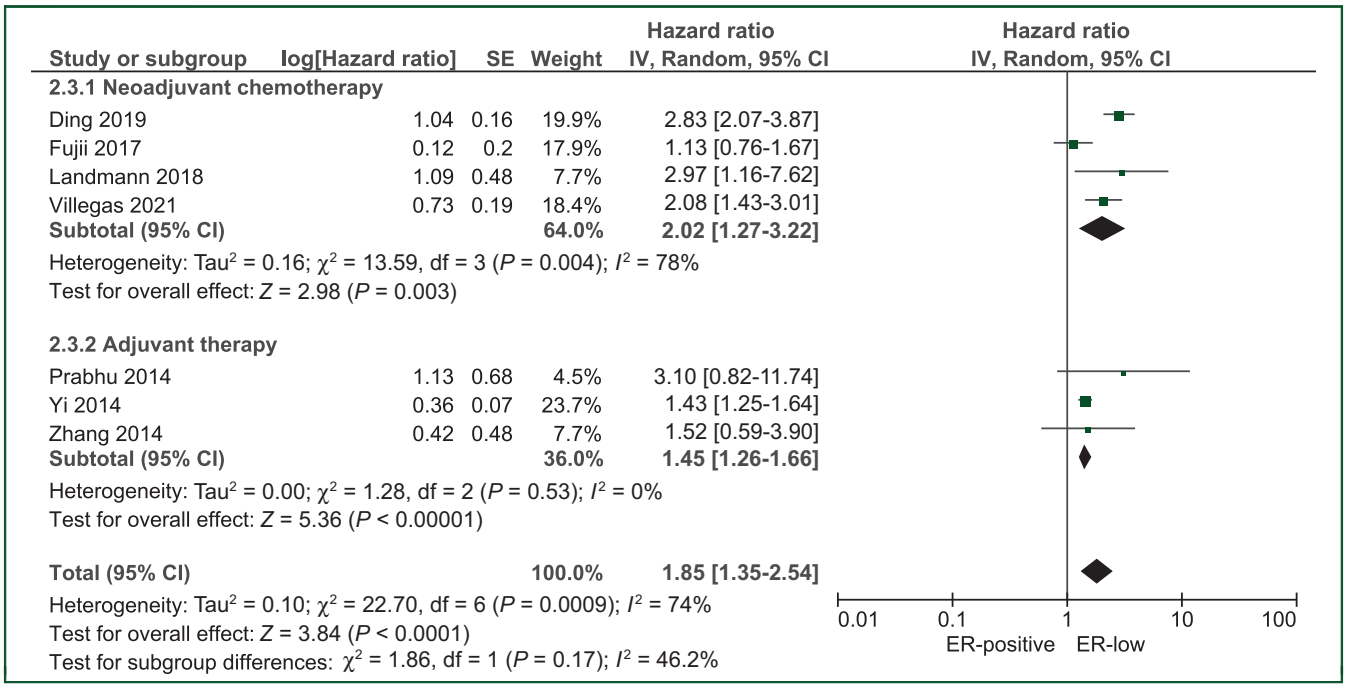

Figure 2. Pooled hazard ratio for disease-free survival between patients with ER-low and ER-positive breast cancer.
CI, confidence interval; df, degrees of freedom; ER, estrogen receptor; SE, standard error.

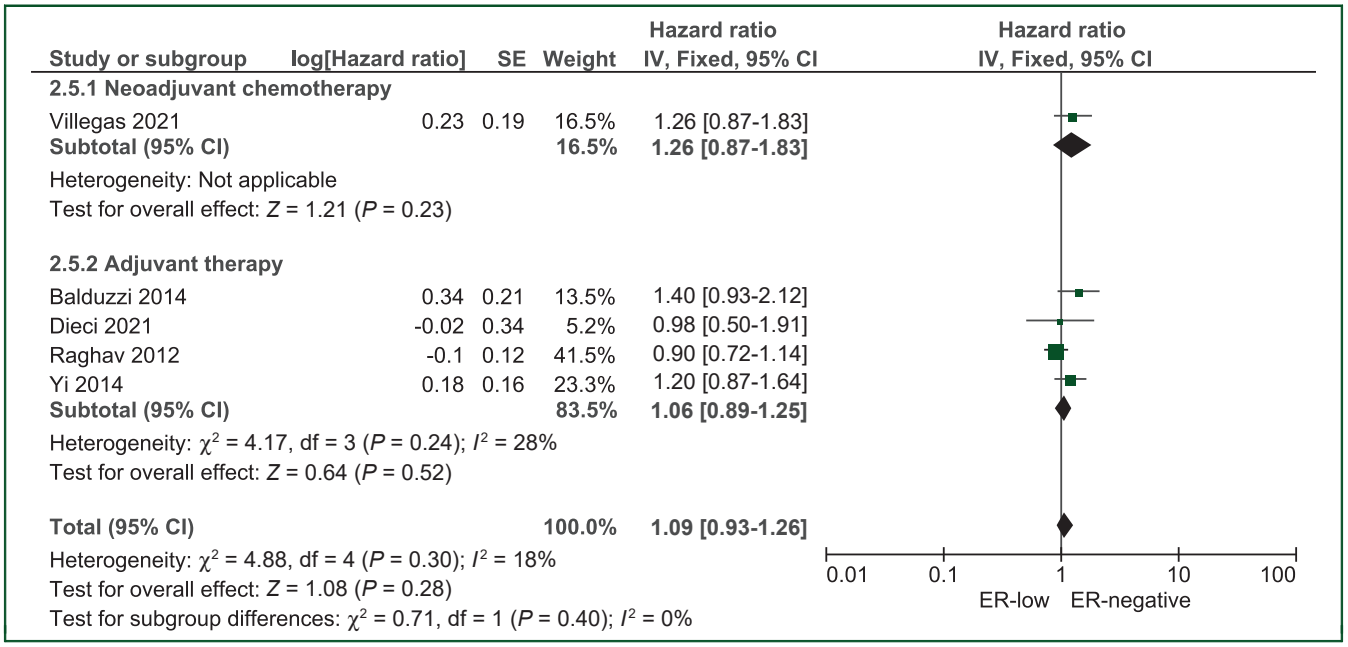

Figure 3. Pooled Hazard Ratio for disease-free survival between patients with ER-low and ER-negative breast cancer.
CI, confidence interval; df, degrees of freedom; ER, estrogen receptor; SE, standard error.

had luminal-like molecular features. Similarly, Villegas et al.[14] found that nearly 87% of ER-low breast cancer had a basal-like gene expression signature, whereas none was classified as luminal.

A meta-analysis by Chen et al.[24] was published in 2016 and suggested an intermediate prognosis for ER-low breast cancer, with patients in this subgroup faring worse than the ER-positive subgroup but better than the ER-negative subgroup in DFS and OS. There are, however, some important methodological differences between the two meta-analyses that deserve attention. First, we included only studies with results on prognosis derived from multivariate analyses to mitigate the risk for confounding bias, whereas the prior meta-analysis included results from bivariate analyses as well. As confounding bias is a major source of bias in observational studies that can jeopardize the validity of the results and multivariate analysis is an analytic approach that can mitigate this risk, a meta-analysis based only on results

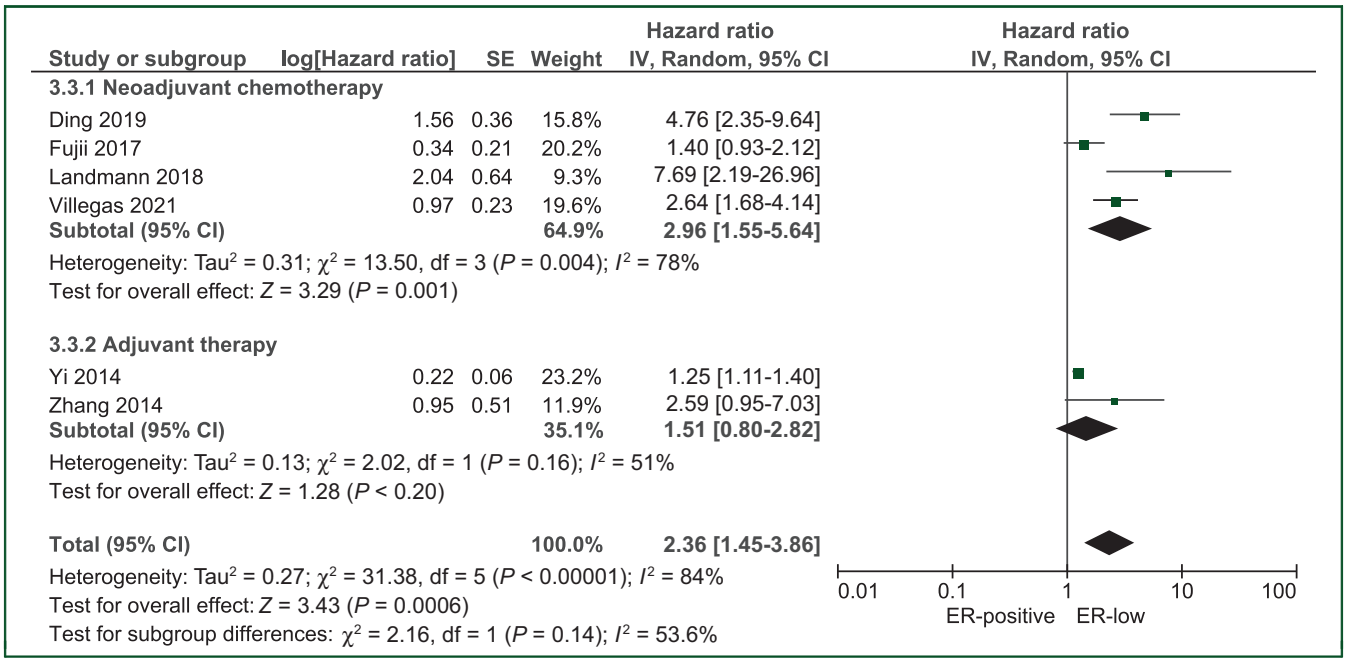

Figure 4. Pooled Hazard Ratio for overall survival between patients with ER-low and ER-positive breast cancer.
CI, confidence interval; df, degrees of freedom; ER, estrogen receptor; SE, standard error.

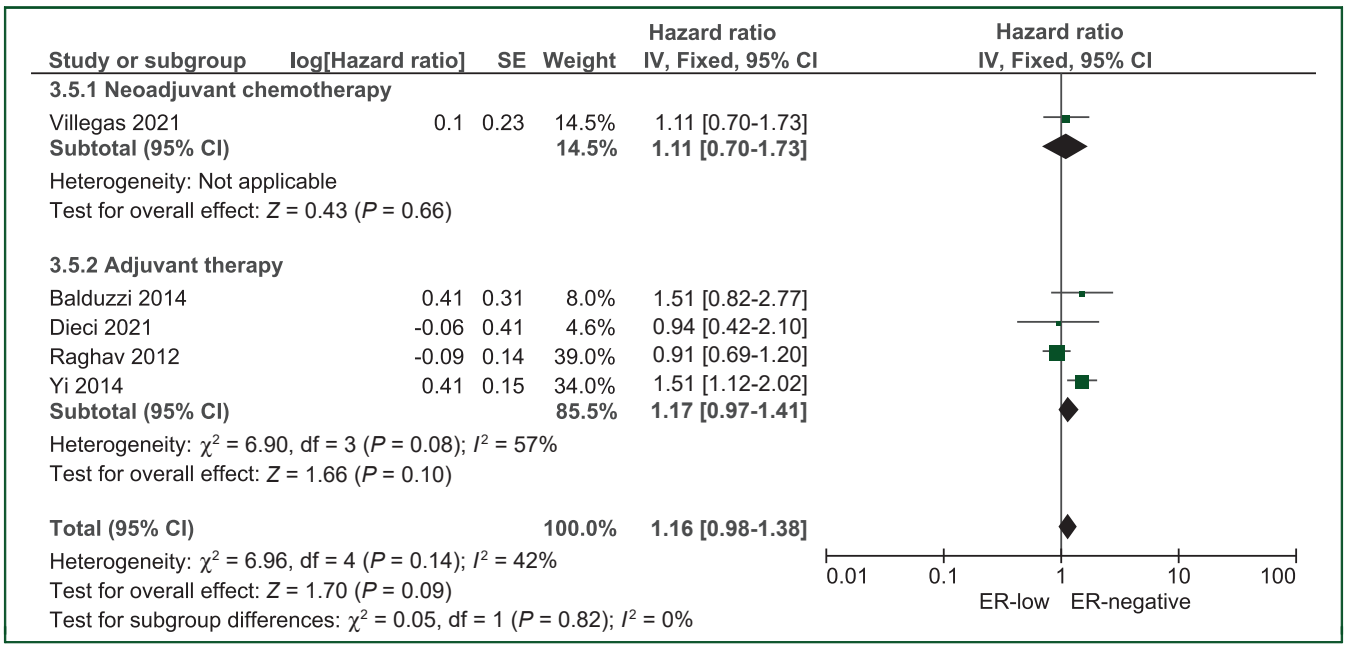

Figure 5. Pooled Hazard Ratio for overall survival between patients with ER-low and ER-negative breast cancer.
CI, confidence interval; df, degrees of freedom; ER, estrogen receptor; SE, standard error.

from multivariate analyses is a more suitable approach when only observational studies are available. Second, our meta-analysis investigated an additional research question on the predictive role of NeoCT in patients with ER-low breast cancer. Since NeoCT is currently the recommended treatment strategy for ER-negative breast cancer, our meta-analysis provides evidence on a research question which is in line with current clinical practice. In addition, we used HR as a pooled effect measure for DFS and OS which is a more robust measure for time-to-event outcomes compared with OR, which was used in the prior meta-analysis. Finally, the pooled analyses from the present meta-analysis are accompanied by the level of evidence according to the GRADE approach, enabling the clinicians and policymakers to interpret the results following the principles of evidence-based medicine.

This meta-analysis has several limitations that need to be discussed. First, the eligible studies lack adequate analyses on the effectiveness of adjuvant endocrine therapy in patients with ER-low breast cancer, which made us unable to

Table 4. Quality of evidence according to GRADE approach

No. of studies	Certainty assessment						Relative effect (95% confidence interval)	Certainty
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
pCR in patients with ER-low compared with ER-positive breast cancer (assessed with: odds ratio)								
6	Observational studies	Serious	Not serious	Not serious	Not serious	None	3.25 (1.85-5.71)	⊕⊕⊕◯ MODERATE
pCR in patients with ER-low compared with ER-negative breast cancer (assessed with: odds ratio)								
7	Observational studies	Serious	Serious	Not serious	Not serious	None	1.37 (0.83-2.22)	⊕⊕◯◯ LOW
Disease-free survival ER-low versus ER-positive (assessed with: hazard ratio)								
7	Observational studies	Serious	Not serious	Not serious	Not serious	None	1.85 (1.35-2.54)	⊕⊕⊕◯ MODERATE
Disease-free survival ER-low versus ER-negative (assessed with: hazard ratio)								
5	Observational studies	Serious	Serious	Not serious	Not serious	None	1.09 (0.93-1.26)	⊕⊕◯◯ LOW
Overall survival ER-low versus ER-positive (assessed with: hazard ratio)								
6	Observational studies	Serious	Not serious	Not serious	Not serious	None	2.36 (1.35-3.86)	⊕⊕⊕◯ MODERATE
Overall survival ER-low versus ER-negative (assessed with: hazard ratio)								
5	Observational studies	Serious	Serious	Not serious	Not serious	None	1.16 (0.98-1.38)	⊕⊕◯◯ LOW

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

carry out a meta-analysis on this issue. Some evidence from observational studies, however, suggests that adjuvant endocrine therapy does not seem to improve DFS or OS in patients with ER-low breast cancer.[15,17,25] This observation is also supported by randomized evidence from the latest Early Breast Cancer Trialists' Collaborative Group meta-analysis on the benefit of adjuvant tamoxifen, where low ER expression was associated with nearly zero benefit.[26] Second, most of the eligible studies had a median follow-up of <5 years which can be considered adequate for ER-negative but not for ER-positive breast cancer where there is a greater tendency for late recurrence not able to be captured with follow-up shorter than 8 years.[27,28] Another potential limitation is the risk for variability in the immunohistochemical assessment of ER status throughout the years and among different laboratories and countries. This risk has been shown to be higher in low or medium ER expressions[29] but considerably lower compared with other breast cancer biomarkers such as HER2 and Ki-67.[30,31] Finally, this meta-analysis included only observational studies which negatively impact the certainty of evidence, as reflected by the grading of evidence according to the GRADE approach.

Based on current evidence, our findings suggest that ER-low expression in breast cancer is predictive for response to NeoCT with anticipated pCR comparable to ER-negative breast cancer. Furthermore, ER-low breast cancer appears to resemble ER-negative more than ER-positive breast cancer in terms of prognosis. Our results support the updated ASCO/CAP and ABC5 guidelines[4,5] recommending that tumors with ER-low expression should be classified as ER-low-positive, namely separately from ER-positive tumors. Our results also raise reasonable clinical thoughts on whether new treatment strategies for TNBC such as immunotherapy and antibody—drug conjugates might be suitable for patients with low ER expression as well and emphasize the complexity of biological subtyping for breast cancer. Considering the low to moderate level of evidence for both the predictive and prognostic role of ER-low expression on breast cancer, our findings urge the need for high-quality, prospective studies investigating the molecular background and the most appropriate treatment strategy for this subgroup.

FUNDING

None declared.

DISCLOSURE

The authors have declared no conflicts of interest.

DATA SHARING

The data presented in this study are available on request from the corresponding author.

REFERENCES

1. European Cancer Information System. Available at https://ecis.jrc.ec.europa.eu/explorer.php?$0-0. Accessed August 12, 2020.
2. Rosenberg PS, Barker KA, Anderson WF. Estrogen receptor status and the future burden of invasive and in situ breast cancers in the United States. *J Natl Cancer Inst*. 2015;107:djv159.
3. Hammond MEH, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol*. 2010;28:2784-2795.
4. Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. *J Clin Oncol*. 2020;38(12):1346-1366.
5. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol*. 2020;31(12):1623-1649.
6. Korde LA, Somerfield MR, Carey LA, et al. Neoadjuvant chemotherapy, endocrine therapy, and targeted therapy for breast cancer: ASCO guideline. *J Clin Oncol*. 2021;39:1485-1505.

7. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2019;30:1194-1220.
8. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials*. 2007;8:16.
9. Colleoni M, Viale G, Zahrieh D, et al. Chemotherapy is more effective in patients with breast cancer not expressing steroid hormone receptors: a study of preoperative treatment. *Clin Cancer Res*. 2004;10:6622-6628.
10. Ding Y, Ding K, Yu K, et al. Prognosis and endocrine therapy selection for patients with low hormone receptor-positive breast cancer following neoadjuvant chemotherapy: a retrospective study of 570 patients in China. *Oncol Lett*. 2019;18:6690-6696.
11. Fujii T, Kogawa T, Dong W, et al. Revisiting the definition of estrogen receptor positivity in HER2-negative primary breast cancer. *Ann Oncol*. 2017;28:2420-2428.
12. Landmann A, Farrugia DJ, Zhu L, et al. Low estrogen receptor (ER)-positive breast cancer and neoadjuvant systemic chemotherapy: is response similar to typical ER-positive or ER-negative disease? *Am J Clin Pathol*. 2018;150:34-42.
13. Ohara AM, Naoi Y, Shimazu K, et al. PAM50 for prediction of response to neoadjuvant chemotherapy for ER-positive breast cancer. *Breast Cancer Res Treat*. 2019;173:533-543.
14. Villegas SL, Nekljudova V, Pfarr N, et al. Therapy response and prognosis of patients with early breast cancer with low positivity for hormone receptors — an analysis of 2765 patients from neoadjuvant clinical trials. *Eur J Cancer*. 2021;148:159-170.
15. Balduzzi A, Bagnardi V, Rotmensz N, et al. Survival outcomes in breast cancer patients with low estrogen/progesterone receptor expression. *Clin Breast Cancer*. 2014;14:258-264.
16. Prabhu JS, Korlimarla A, Desai K, et al. A majority of low (1-10%) ER positive breast cancers behave like hormone receptor negative tumors. *J Cancer*. 2014;5:156-165.
17. Raghav KPS, Hernandez-Aya LF, Lei X, et al. Impact of low estrogen/progesterone receptor expression on survival outcomes in breast cancers previously classified as triple negative breast cancers. *Cancer*. 2012;118:1498-1506.
18. Yi M, Huo L, Koenig KB, et al. Which threshold for ER positivity? A retrospective study based on 9639 patients. *Ann Oncol*. 2014;25:1004-1011.
19. Zhang Z, Wang J, Skinner KA, et al. Pathological features and clinical outcomes of breast cancer according to levels of oestrogen receptor expression. *Histopathology*. 2014;65:508-516.
20. Dieci MV, Griguolo G, Bottosso M, et al. Impact of estrogen receptor levels on outcome in non-metastatic triple negative breast cancer patients treated with neoadjuvant/adjuvant chemotherapy. *NPJ Breast Cancer*. 2021;7:101.
21. Gourgou-Bourgade S, Cameron D, Poortmans P, et al. Guidelines for time-to-event end point definitions in breast cancer trials: results of the DATECAN initiative (Definition for the Assessment of Time-to-event Endpoints in CANcer trials). *Ann Oncol*. 2015;26:873-879.
22. Iwamoto T, Booser D, Valero V, et al. Estrogen receptor (ER) mRNA and ER-related gene expression in breast cancers that are 1% to 10% ER-positive by immunohistochemistry. *J Clin Oncol*. 2012;30:729-734.
23. Deyarmin B, Kane JL, Valente AL, et al. Effect of ASCO/CAP guidelines for determining ER status on molecular subtype. *Ann Surg Oncol*. 2013;20:87-93.
24. Chen T, Zhang N, Moran MS, Su P, Haffty BG, Yang Q. Borderline ER-positive primary breast cancer gains no significant survival benefit from endocrine therapy: a systematic review and meta-analysis. *Clin Breast Cancer*. 2018;18:1-8.
25. Bouchard-Fortier A, Provencher L, Blanchette C, Diorio C. Prognostic and predictive value of low estrogen receptor expression in breast cancer. *Curr Oncol*. 2017;24:e106-e114.
26. Early Breast Cancer Trialists' Collaborative Group (EBCTCG)Davies C, Godwin J, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet*. 2011;378:771-784.
27. Colleoni M, Sun Z, Price KN, et al. Annual hazard rates of recurrence for breast cancer during 24 years of follow-up: results from the international breast cancer study group trials I to V. *J Clin Oncol*. 2016;34:927-935.
28. van Maaren MC, de Munck L, Strobbe LJA, et al. Ten-year recurrence rates for breast cancer subtypes in the Netherlands: a large population-based study. *Int J Cancer*. 2019;144:263-272.
29. Rhodes A, Jasani B, Balaton AJ, Miller KD. Immunohistochemical demonstration of oestrogen and progesterone receptors: correlation of standards achieved on in house tumours with that achieved on external quality assessment material in over 150 laboratories from 26 countries. *J Clin Pathol*. 2000;53:292-301.
30. De Schutter H, Van Damme N, Colpaert C, et al. Quality of pathology reporting is crucial for cancer care and registration: a baseline assessment for breast cancers diagnosed in Belgium in 2008. *Breast*. 2015;24:143-152.
31. Acs B, Fredriksson I, Rönnlund C, et al. Variability in breast cancer biomarker assessment and the effect on oncological treatment decisions: a nationwide 5-year population-based study. *Cancers*. 2021;13:1166.