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Prognostic Significance of Platelet-Lymphocyte Ratio (PLR) in Breast Cancer Patients Treated with Neoadjuvant Chemotherapy: A Meta-analysis

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Abstract

Objective: PLR (platelet-lymphocyte ratio), known as a key systemic inflammatory parameter, have been proved to be associated with response to neoadjuvant therapy in breast cancer (BC); however, the results remain controversial. This meta-analysis was carried out to evaluate the prognostic values of PLR in breast cancer patients treated with neoadjuvant chemotherapy.

Design: Meta-analysis.

Data sources: Relevant literature published on the following databases: PubMed, Embase, Web of Science databases and the Cochrane Library.

Eligibility criteria: All studies involving patients with breast cancer treated with NACT and peripheral blood pretreatment PLR recorded were included.

Data extraction and synthesis: Two researchers independently extracted and evaluated hazard ratio (HR) /Odds Ratio (OR) and its 95% confidence (CI) of survival outcomes, pCR rate and clinicopathological parameters.

Results: A total of 22 studies with 5533 breast cancer patients treated with neoadjuvant chemotherapy were enrolled in the final meta-analysis. Our results demonstrate that elevated PLR value appears to correlate with low pCR rate (HR: 0.77, 95% CI: 0.67-0.88, $p < 0.001$, I^2=75.80%, $P_h < 0.001$) and poor prognosis, including OS (HR: 1.90, 95% CI: 1.39-2.59, $p < 0.001$; I^2= 7.40%, $P_h = 0.365$) and DFS (HR: 1.97, 95% CI: 1.56-2.50, $p < 0.001$; I^2= 0.0%, $P_h = 0.460$). Furthermore, PLR level was associated with age (OR: 0.86, 95% CI: 0.79-0.93, $p < 0.001$, I^2= 40.60%, $P_h = 0.096$), menopausal status (OR: 0.83, 95% CI: 0.76-0.90, $p < 0.001$, I^2= 50.80%, $P_h = 0.087$) and T stage (OR: 1.05, 95% CI: 1.00-1.11, $p = 0.035$; I^2= 70.30%, $P_h = 0.005$) of breast cancer patients.

Conclusions: This meta-analysis demonstrated that high PLR was significantly related to the low pCR rate, poor OS and PFS of breast cancer patients treated with neoadjuvant chemotherapy. Therefore, PLR can be used as a potential predictor biomarker for the efficacy of neoadjuvant chemotherapy in breast cancer.

Strengths and limitations of this study

1. This is the first meta-analysis to assess the role of platelet-lymphocyte ratio (PLR) in predicting pCR rate and survival in BC patients treated with NACT.
2. Scientific and reliable statistical methods were applied.
3. The results of this study showed that PLR could be a potential predictor biomarker for the efficacy of neoadjuvant chemotherapy and provided a strategy for further large-sample prospectively randomised controlled studies.
4. All the studies included in this meta-analysis were retrospective and lacked detailed clinicopathological information, which may lead to bias of our results.

Keywords

Platelet, Lymphocyte, PLR, Breast Cancer, Neoadjuvant Chemotherapy, Meta-Analysis

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Introduction

Breast cancer (BC) is the most frequently diagnosed malignant neoplasm in women worldwide [1]. BC patients in China account for 12.2% of the total number of newly diagnosed and 9.6% of all breast cancer related deaths in the world [2]. About 20-25% of patients are diagnosed with locally advanced breast cancer, which prone to recurrence and metastasis after surgery without any Preoperative treatment [3 4]. Survival rates for BC patients have increased dramatically due to the development of treatment strategies, such as individualized treatment plans made by multidisciplinary teams, including surgical, radiation and medical oncology [5]. At present, neoadjuvant chemotherapy (NACT) has become the standard and effective treatment for patients with locally advanced breast cancer [6]. The aim of NACT is mainly to reduce tumor size and the stage of tumors, improve tumor operability, and improve the success rates of breast conservative operation [7-9]. Additionally, the effects of NACT could provide information to assessing the efficacy of chemotherapy during the treatment [10]. However, not all patients receiving neoadjuvant therapy can achieve therapeutic effect, especially pathologic complete response (pCR). Previous studies showed that the pCR rate of NACT in HER2 (+) patients was about 30%, 30-50% in triple negative breast cancer and less than 10% in ER (+) and HER2 (-) breast cancer patients [11-13]. The reasons may be different pathological types, ER status, HER-2 status, disease stage, and other factors. Some gene mutations, such as PIK3CA, TP53, SIRT5 and CDKN2A, have been proved to be associated with poor response to NACT in breast cancer patients [14]. However, these above biomarkers are expensive and difficult to obtain. Hence, it's necessary to find a convenient, inexpensive and reliable marker, which can predict response after NACT.

It is well recognized that the systemic inflammatory response plays an essential role in breast cancer progression and development [15 16]. Numerous studies have shown that inflammatory biomarkers such as neutrophil-tolymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and systemic immune-inflflammation index (SII), are associated with chemosensitivity and prognosis for different malignancies [17-21].

PLR, as one of the most commonly used markers, was proved to be an convenient and cost-effective blood-derived prognostic marker to evaluate the prognosis of breast cancer. Elevated PLR has been linked with poor prognosis for breast cancer in previous studies [22-24]. Furthermore, some research found that a higher PLR may lead to a worse response to NACT for breast cancer patients [25 26]. However, some other studies showed that the BC patients with higher PLR may achieve more pCR rate after NACT [27 28]. Thus, the role of PLR as a predictor for outcomes in BC patients after NACT is still not clear. This meta-analysis is aimed to explore the predictive value of PLR in patients with breast cancer treated with NACT.

Materials and Methods

Literature search

A systematic literature search was conducted based on the following databases: PubMed, Embase, Web of Science databases and the Cochrane Library. The keywords for the search strategy are as follows: ("PLR" or "platelet lymphocyte ratio" or "platelet-to-lymphocyte ratio" or "platelet-lymphocyte ratio") and ("breast cancer", "breast tumor", "breast carcinoma", "breast neoplasms", "mammary cancer") and ("neoadjuvant chemotherapy", "preoperative chemotherapy", "preoperative systemic treatment", "pre-surgical treatment", "primary chemotherapy"). The last search was updated to Dec 31, 2022, and all the articles were limited to English-language. We also used a hand search for the reference list of the retrieved articles in order to identify additional studies. The selection process of the meta-analysis is shown in Figure 1. This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. No patient consent and ethical approval were required in this study.

Inclusion and exclusion criteria

The studies included in the analysis had to meet the following criteria: (1) breast cancer patients received neoadjuvant treatment and surgery; (2) studies with the peripheral blood pretreatment PLR values; (3) studies with pathologic response status or survival outcomes post neoadjuvant treatment, including pCR, disease-free survival

(DFS), overall survival (OS), OR and HR with 95% confidence intervals (CI). The exclusion criteria were as follows: (1) Abstracts, reviews, case studies, letters, non-human subject studies and not English-language studies; (2) breast cancer participants did not receive neoadjuvant treatment; (3) studies with no sufficient data.

Data extraction and quality assessment

Two researchers independently reviewed the available literature and extracted data as follows: (1) study details: first author, country, publication year, study design, study period, sample size, median age, outcomes, follow-up time; (2) clinicopathologic parameters: subtype of BC, cut-off value, cut-off method, numbers in high and low PLR groups stratified by age, histologic type, tumor grade, T stage, lymph node metastasis, ki-67 value, hormone receptor status, HER-2 status, molecular subtype, menopausal status; (3) treatment outcomes: numbers in pCR and non-pCR groups, HR with 95% CIs of DFS and OS.

We used the Newcastle Ottawa Scale (NOS) rating scale to assess the quality of the included studies. The studies was scored from 0 to 9 points, based on the object selection, comparability, outcome, and exposure. High-quality literature should have a score of ≥6. If the two researchers had disagreement, a third researcher was invited to achieve a consistent result.

Statistical analysis

All analyses were performed using Stata software version 12.0 (Stata Corporation, College Station, TX, USA), using two-sided P values. Odds ratio (OR) with corresponding 95% CI was used to evaluate the association between PLR and pCR rate, clinicopathological characteristics. Hazard ratios (HR) with corresponding 95% CI was used as an effect measure to assess the relationship between PLR and DFS, OS. Then the log OR, log HR, and corresponding standard error (SE) were used to compute pooled effect measures. Moreover, stratified analyses were also performed based on ethnicity, cut-off value, cut-off method and sub-type of breast cancer. Both the Cochran's Q statistic and the I^2 statistic were calculated to estimate heterogeneity among the included studies [29 30]. If the P value of the Q test was <0.10 or I^2 >50%, indicating significant heterogeneity across studies, the pooled OR and HR were

calculated by the random effects model (the DerSimonian and Laird method) [31]. Otherwise, fixed effects model (the Mantel–Haenszel method) was used [31]. Publication bias was evaluated using Funnel plots and Egger's linear regression test. Sensitivity analyses were performed by omitting each single study to show the influence of the individual data set to the pooled results. $P < 0.05$ was considered statistically significant.

Results

Study characteristics

As shown in the flow diagram (Figure S1), 176 research articles were identified in the preliminary search. After reviewing the titles, abstracts and full texts, 154 studies were excluded according to the search criteria and 22 studies were finally included in the meta-analysis [22 25-28 32-48]. The main characteristics of the included studies are summarized in Table 1. The 22 enrolled studies containing 5533 BC patients were published between 2016 and 2022 with the sample size ranging from 55 to 980. 11 studies were carried out in Asian countries (China and Japan) and the other 11 studies were conducted in Caucasian countries (Turkey, America, Spain, Italy, France and Morocco). All studies were retrospective, with study period ranging from 1996 – 2022. The follow-up time ranged from 3.4 to 124.8 months in these studies, with NOS scores of 6 – 8 points. Most of the study subjects embraced all breast cancer types, also including two inflammatory breast cancer studies, two triple negative breast cancer studies and one Luminal B breast cancer study. All patients received standardized neoadjuvant chemotherapy and surgery, with the median age ranged from 45 to 71 years old. Cut-off values for PLR were provided in 21 studies, 6 of which were derived from previous studies and another 15 were obtained from ROC curves.

Association between PLR and pCR of BC

19 studies with 4301 patients reported the correlation between the PLR and pCR [22 26 28 32-41 43 44 46-49]. Our results indicate that high PLR level was significantly associated with low pCR rate (HR: 0.77, 95% CI: 0.67-0.88, $p < 0.001$), and

significant heterogeneity was observed (I^2=75.80%, P_h < 0.001, Table 2, Figure 1). When stratified analyses were performed based on ethnicity, the results showed that Caucasian studies were still statistically significant (HR: 0.77, 95% CI: 0.68-0.88, p < 0.001; I^2=61.60%, P_h = 0.004). On the other hand, there was no statistically significance observed for PLR and pCR among the Asian studies (HR: 0.83, 95% CI: 0.58-1.17, p = 0.288; I^2= 85.00%, P_h < 0.001). Subgroup analysis were also performed to determine the effects of cut-off values and methods on the outcomes. Studies with cut-off value >=150 showed a significant association between the PLR and pCR (HR: 0.78, 95% CI: 0.67-0.91, p = 0.001; I^2= 68.20%, P_h = 0.001), while cut-off values <150 did not achieve statistical significance (HR: 0.80, 95% CI: 0.59-1.10, p = 0.172; I^2= 82.90%, P_h < 0.001). On the other hand, we observed statistically significant relationship between PLR and pCR, no matter the cut-off values obtained from ROC curves (HR: 0.72, 95% CI: 0.57-0.92, p = 0.008; I^2= 81.10%, P_h < 0.001) or previous studies (HR: 0.86, 95% CI: 0.78-0.94, p = 0.001; I^2= 39.30%, P_h = 0.144). Further subgroup analysis was also conducted by tumor subtypes. In the all types group (HR: 0.76, 95% CI: 0.64-0.89, p = 0.001; I^2= 74.00%, P_h < 0.001) and inflammatory breast cancer group (HR: 0.83, 95% CI: 0.70-0.97, p = 0.021; I^2= 0.00%, P_h = 0.368), statistical significance were noted between PLR and pCR. In comparison, studies in the triple negative breast cancer group did not show a significant association (HR: 0.91, 95% CI: 0.26-3.21, p = 0.885; I^2= 94.70%, P_h < 0.001).

Association between PLR and survival of BC

5 studies with 912 patients evaluated the relationship between OS and PLR [25 35 40-42]. The pooled results demonstrated that high PLR was significantly associated with poor OS in patients with breast cancer (HR: 1.90, 95% CI: 1.39-2.59, p < 0.001; I^2= 7.40%, P_h = 0.365) (Table 3, Figure S2). Subgroup analyses by ethnicity showed that PLR had significantly prognostic value for OS both in Asian and Caucasian populations (HR: 2.00, 95% CI: 1.19-3.38, p = 0.009, I^2= 56.70%, P_h = 0.128; HR: 1.85, 95% CI: 1.26-2.71, p = 0.002, I^2= 0.0%, P_h = 0.378). Moreover, when stratified by subtypes of breast cancer, the results indicated that the prognostic effect of PLR on OS was similarly significant among the all types group (HR: 1.92, 95% CI: 1.31-2.83,

p = 0.001; I^2= 15.30%, P_h = 0.307) and inflammatory breast cancer group (HR: 1.86, 95% CI: 1.11-3.11, p = 0.018; I^2= 48.60%, P_h = 0.163). Furthermore, when considering different cut-off value methods, high PLR significantly predicted shorter OS when cut-off values were conducted by ROC (HR: 2.15, 95% CI: 1.44-3.22, p < 0.001; I^2= 19.80%, P_h = 0.288), but did not show significantly prognostic efficiency in the group of cut-off value obtained from previous studies (HR: 1.58, 95% CI: 0.97-2.56, p = 0.065; I^2= 0.0%, P_h = 0.345).

7 studies with 1887 patients analyzed the relationship between the PLR and DFS [25 26 35 37 38 41 45]. The pooled results indicated that DFS was significantly shorter in high PLR group than in low PLR group (HR: 1.97, 95% CI: 1.56-2.50, p < 0.001; I^2= 0.0%, P_h = 0.460) (Table 3, Figure S3). We also performed further subgroup analysis based on ethnicity, subtypes of BC and cut-off value methods. Compared with the overall results, no significant changes were identified after stratification, and no significant heterogeneity was observed.

Association between PLR and clinicopathological parameters of BC

To analyze the impact of PLR on the clinicopathological characteristics in breast cancer patients, we pooled the results from included studies according to age, histologic type, tumor grade, T stage, lymph node metastasis, ki-67 value, hormone receptor status, HER-2 status, molecular subtype, menopausal status. As shown in Table S1, young patients and pre-menopausal status patients had significantly higher PLR value than old or post-menopausal status patients (OR: 0.86, 95% CI: 0.79-0.93, p < 0.001, I^2= 40.60%, P_h = 0.096; OR: 0.83, 95% CI: 0.76-0.90, p < 0.001, I^2= 50.80%, P_h = 0.087). In comparison to low PLR groups, the high PLR groups had a higher T stage (OR: 1.05, 95% CI: 1.00-1.11, p = 0.035; I^2= 70.30%, P_h = 0.005). Whereas the other results indicated no significant association of PLR with histologic type, tumor grade, lymph node metastasis, ki-67 value, hormone receptor status, HER-2 status and molecular subtype.

Sensitivity analysis

According to the sensitivity analysis, the pooled ORs were not altered materially when deleted a single study each time. All the included studies were near the central

line with no clear deviation, suggesting that our results were statistically robust (Figure 2A).

Publication bias

Begg's funnel plot and Egger's test were used to evaluate the publication bias of the literature. The funnel plots did not reveal obvious evidence of asymmetry (Figure 2B). Then, the Egger's test still did not show any significant statistical evidence of publication bias (P = 0.862).

Discussion

This meta-analysis assessed the association between pretreatment PLR with pCR and survival on 5533 breast cancer patients treated with neoadjuvant chemotherapy. Our results demonstrate that elevated PLR value appears to correlate with low pCR rate and poor prognosis, including OS and DFS. Consistent with previous studies, our findings suggest that PLR could be a significant prognostic marker for breast cancer patients who received NACT [26 35 37 40 41].

Neoadjuvant chemotherapy is increasingly used to treat locally advanced breast cancer, so as to reduce the size of tumors and increase the possibility of breast-conserving surgery [50]. However, there are no ready-made and reliable biomarkers to predict the response to NACT. In recent years, many studies have focused on the relationship between inflammation related biomarkers and tumors. These studies showed that tumor related inflammation, which may contribute to the tumor growth, invasion and metastasis, was associated with the occurrence, development, and prognosis of cancers [51 52]. Common components in peripheral blood, such as neutrophils, monocytes, platelets, and lymphocytes, are closely related to the biological behavior of tumor cells [53]. Numerous studies have shown that lymphocytes can inhibit tumor progression and metastasis, which play an important role in tumor immune monitoring [54 55]. Lymphopenia is commonly seen in immune system defects caused by tumor cells. The possible mechanism is that lymphocytes can control growth of tumor cells through cytotoxicity and induction tumor cell apoptosis [56]. Another research showed that lymphocytes could inhibit tumor cell

growth by secreting interferon-gamma and tumor necrosis factor-α [57]. Some studies have found that more tumor infiltrating lymphocyte is associated with better prognosis of breast cancer patients [58 59]. In addition, previous studies reported that tumor infiltrating lymphocyte could be a predictor for the response to neoadjuvant and adjuvant chemotherapy of breast cancer patients [60 61]. On the other hand, platelets, as key substances in the process of inflammation, plays an important role in tumor progression. Firstly, platelets could protect tumor cells in peripheral blood from high flow shear stress and immune attacks by aggregating and adhering to tumor cells [62]. Secondly, platelets could contribute tumor progression by secreting various cell growth factors, which could stimulate tumor angiogenesis and growth [63-65]. Thirdly, platelets could induce epithelial mesenchymal transition and impede cell-mediated immune clearance effects, leading to the tumor cell metastasis [66]. Therefore, high platelet count may be associated with poor prognosis of breast cancer patients.

Platelet-to-lymphocyte ratio (PLR) , as a commonly used indicator of inflammatory status, could predict the prognosis of variant tumors. Elevated value of PLR, with a high platelet count and/or low lymphocyte count, often lead to a low antitumor activity and poor prognosis. Previous studies showed that PLR is significantly related to the survival of colorectal cancer, gastric cancer and liver cancer [67-69]. Gunduz et al. showed that elevated PLR value was associated with poor DFS in breast cancer [70]. However, Ulas et al. reported that there is no association between PLR and DFS or OS in breast cancer [71]. What's more, when subgroup analysis by different molecular types of breast cancer, Koh et al. demonstrated that elevated PLR could result in an increased risk of mortality in ER+ and HER2+ group but not in ER− and HER2+ group [72]. Studies focused on the relationship between PLR and metastatic breast cancer could achieve positive results easily [73]. However, the predictive efficacy of PLR in early stage breast cancer was limited. The possible explanation is that inflammatory reaction may not be so obvious in early breast cancer. Recently, many studies have be devoted to explore whether PLR could be a predictor for locally advanced breast cancer treated with neoadjuvant chemotherapy. Tekyol et al. found that PLR value was associated with chemotherapy sensitivity and

could serve as a predictive marker of the therapeutic effect of NACT in breast cancer [34]. Similarly, Ouissam showed that PLR was associated with OS and DFS in breast cancer treated with NACT [41]. However, some other studies reported that the PLR value has no significant predictive effect on pCR rate, DFS or OS in breast cancer treated with NACT [25 42]. So far, the above studies indicated that the prognostic role and clinical value of PLR in locally advanced breast cancer with NACT is still controversial.

We conducted this meta-analysis to explore the predictive value of PLR in breast cancer patients treated with NACT. Our results indicate that high PLR level was significantly associated with low pCR rate (HR: 0.77, 95% CI: 0.67-0.88, $p < 0.001$). This finding is consistent with previous studies confirming that PLR may act as a significant marker for predicting the effective of NACT in BC patients [33 34 37]. In subgroup analysis, we found that PLR was only significantly associated with Caucasian patients but not Asian patients. The possible explanations were the differences in baseline PLR values due to different genetic backgrounds, different chemotherapy regimens and doses. What's more, the heterogeneity of the Asian group is also more obvious than that of the Caucasian group, which may lead to no significance in the Asian group. Previous studies reported that high PLR value may indicate a lower pCR rate and poor prognosis of TNBC patients [46]. Subgroup analysis by tumor subtypes in this meta-analysis including two studies showed no significant association between PLR and pCR in the triple negative breast cancer group. Further more research is needed to evaluate the predictive value of PLR in TNBC treated with NACT. How to identify the optimal critical value for the clinical application of PLR may be a major concern for doctors. Unfortunately, this value has not been determined for predicting the efficacy and prognosis of neoadjuvant therapy in breast cancer patients. Some studies reported that high PLR was associated with poor prognosis using a cut-off value of 292 and 200 [74 75], while other studies did not find significant association between PLR and prognosis of breast cancer patients with a cut-off value of 161, 107, and 160, respectively [22 37 76]. Different studies use variant cut-off values from different methods. Traditionally, we believe that the ROC curve is

the most suitable for getting the optimal cutoff value [33 41 46-48]. However, other studies have also achieved significant results using the cut-off values from previous studies [26 28 34]. We performed subgroup analysis to determine the effects of cut-off values and methods on the outcomes. The results showed statistically significant relationship between PLR and pCR, no matter the cut-off values obtained from ROC curves or previous studies. This result indicated that the source and method of optimal cut-off values are not the key influence factors for PLR acting as a predictive factor for breast cancer. On the other hand, our results also showed that studies with cut-off value >=150 showed a significant association between the PLR and pCR, while cut-off values <150 did not achieve statistical significance. Therefore, a higher cut-off value for PLR may increase its predictive value for breast cancer patients. However, a higher cut-off value may lead to the omission of a large number of patient and reduce its predictive sensitivity in clinical practice [77]. Therefore, further researches are needed to determine the optimal cut-off value of PLR for future individualized treatment.

We also evaluated the association between PLR and prognosis of breast cancer patients treated with NACT. Zhang et al. conducted a meta-analysis which including 5542 breast cancer patients with different stages and indicated that high PLR level is significantly associated with poor OS and DFS of breast cancer patients [78]. However, the results were inconsistent when evaluated the prognosis value for NACT. Christophe et al. and Jiang et al. reported that the PLR value has no significant effect on DFS or OS in breast cancer treated with NACT [25 42]. Contradictory results made by Ileana and Ouissam showed that PLR was associated with OS and DFS in breast cancer treated with NACT [35 41]. In our study, the pooled results demonstrated that high PLR was significantly associated with poor OS and PFS in patients with breast cancer. Subgroup analyses by ethnicity, method and subtype showed the same results with no significant heterogeneity. The consistency of this result may be due to the fact that the included patients are all local advanced stage patients who have received NACT. Therefore, further studies are needed to evaluate the prognostic value of PLR in different clinical stages and molecular subtypes of breast cancer. What's more, this

meta-analysis also explored the association between PLR and clinicopathological characteristics. Our results indicated that high PLR level was more common in young women and patients with premenopausal status. One possible explanation is that young people may have more lymphocyte and platelet reserves and a more sensitive inflammatory state. On the other hand, we also found that elevated PLR is associated with high T stage, which indicated that PLR may involve in the occurrence and progression of breast cancer. Some exploration experiments are needed to prove the mechanisms between PLR and breast cancer.

There are still several limitations to be considered in this meta-analysis. First, All of the studies included were retrospective, and some studies have incomplete data, which may have some impact on the final results. Second, the cut-off values of PLR were inconsistent among the studies, some of them determined the optimum PLR value according to the previous studies instead of using ROC curve, which may lead to the introduction of selection bias in the meta-analysis. Third, variant molecular subtypes of breast cancer respond differently to neoadjuvant therapy, and the heterogeneity of the results may be affected for the lacking of relevant information about molecular typing in most studies. Finally, PLR may be influenced by some factors, including bacterial and viral infections, nutritional state and history of medication. These intrinsic factors were not statistically available and uncontrollable, which were unavoidable sources of heterogeneity in this meta-analysis.

Conclusions

This study indicated that PLR level was associated with age, menopausal status and T stage of breast cancer patients. In addition, high PLR was significantly related to the low pCR rate, poor OS and PFS of breast cancer patients treated with neoadjuvant chemotherapy. Therefore, PLR can be used as a potential predictor biomarker for the efficacy of neoadjuvant chemotherapy. However, further high quality and well-designed studies with larger samples are needed to identify the optimal cut-off value of PLR and explore the mechanism of PLR with breast cancer.

Abbreviations

HR: hazard ratio; OR: odds ratio; 95% CI: 95% confidence interval; Ph: p values of Q test for heterogeneity test; OS: overall survival; DFS: disease-free survival. PLR: platelet-lymphocyte ratio; BC: breast cancer; NACT: neoadjuvant chemotherapy; ROC: receiver operating characteristic curve; NOS: Newcastle-Ottawa Scale;

Declarations

Ethics approval and consent to participate

All the data supporting our findings in this paper were freely downloaded from the PubMed, EMBASE, Web of Science databases and the Cochrane Library. No ethical approval or written informed consent for participation was required.

Consent for publication

Not applicable.

Availability of data and materials

All data for this study are publicly available and are ready for the public to download at no cost from the official websites of the PubMed, EMBASE, Web of Science databases and the Cochrane Library. There is no need to have the formal permission to use data for this study. The sources and data robustness have been described in the section of "Methods".

Competing interests

The authors declare that they have no competing interests.

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Author Contributions

XQ, JC and XZ were involved in drafting the manuscript. SW and JN made contributions to the concepts, acquisition and analysis of the data. LS was involved in acquisition of data and preparing the Figs. LY and CJ designed and revised the manuscript. All authors have read and approved the final manuscript.

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Table 1. Characteristics of included studies in meta-analysis.

NO.	Author	Year	Country	Ethnicity	Study design	Study period	Subtype	Patients (n)	Median age (years)	Follow-up (month)	Cut-off value	Method	Outcomes	NOS score
1	Asano	2016	Japan	Asian	retrospective	2007-2013	All	177	NA	3.4 (0.6-6.0)	150	Previous study	pCR/DFS	8
2	Vincenzo	2018	Italy	Caucasian	retrospective	1999-2018	All	373	50 (26-82)	NA	104.47	ROC	pCR	6
3	Losada	2018	Spain	Caucasian	retrospective	2004-2018	All	104	71 (65-89)	48 (6-149）	150	Previous study	pCR/DFS	8
4	Javier	2018	America	Caucasian	retrospective	2013-2016	All	272	51 (27-85)	NA	150	Previous study	pCR	6
5	Peng	2019	China	Asian	retrospective	2013-2017	All	808	50 (20-72)	NA	151.3	ROC	pCR+PR	6
6	Ileana	2020	France	Caucasian	retrospective	2005-2013	All	206	50.3 (25.3-76.6)	80.4 (2.4-135.6)	150	Previous study	pCR/OS/DFS	8
7	Tulay	2020	Turkey	Caucasian	retrospective	2009-2018	All	131	49 (23-74)	NA	119	ROC	pCR	6
8	Hu	2020	China	Asian	retrospective	2012-2016	Luminal B	980	NA	37 (5-77)	NA	NA	pCR/DFS	8
9	Alan	2020	Turkey	Caucasian	retrospective	2015-2017	All	55	48.5 (27-80)	41 (15-49)	225.3	ROC	pCR	7
10	Jiang	2020	China	Asian	retrospective	2014-2018	All	249	51	4-72	88.23	ROC	pCR/OS	8
11	Christophe	2021	France	Caucasian	retrospective	1996-2016	IBC	75	NA	124.8 (68.5-166.8)	150	Previous study	pCR/OS/DFS	8
12	Ahmet	2021	Turkey	Caucasian	retrospective	2008-2019	All	743	48 (22.0-83.5)	67.5 (10.5-194.4)	131.8	ROC	pCR	7
13	Kübra	2021	Turkey	Caucasian	retrospective	2016-2020	All	150	45.6	NA	150	Previous study	pCR	6
14	Ma	2021	China	Asian	retrospective	2017-2018	All	203	NA	31 (1-39)	135	ROC	pCR/DFS	8
15	Ouissam	2021	Morocco	Caucasian	retrospective	2010-2014	IBC	102	49 (29-88)	NA	178	ROC	pCR/OS/DFS	7
16	Cong	2022	China	Asian	retrospective	2012-2016	All	280	49	NA	155	ROC	pCR/OS	7
17	Chung	2022	China	Asian	retrospective	2012-2019	TNBC	88	51	NA	148.14	ROC	pCR	6
18	Jin	2022	China	Asian	retrospective	2014-2019	All	67	51 (27-81)	NA	106.3	ROC	pCR	6
19	Song	2022	China	Asian	retrospective	2016-2018	All	144	50.4	32 (1-40)	158.365	ROC	DFS	8
20	Lou	2022	China	Asian	retrospective	2015-2018	TNBC	92	52.3 (29-67)	NA	141.36	ROC	pCR	6
21	Yang	2022	China	Asian	retrospective	2020-2022	All	95	NA	NA	118.78	ROC	pCR	6
22	Acikgoz	2022	Turkey	Caucasian	retrospective	2014-2019	All	139	45 (25-75)	39.5 (7.5-93)	181.7	ROC	pCR	7

Abbreviations: NA: not available; OS: overall survival; DFS: disease-free survival; pCR: pathologic complete response; ROC: receiver operating characteristic curve; NOS: Newcastle-Ottawa Scale.

Table 2. Meta-analysis of the association between PLR and pCR of BC with NACT.

Factors	No. of studies	No. of patients	Effects model	OR (95% CI)	p	Heterogeneity	
						I^2	P_H
Overall	19	4301	Random	0.77(0.67-0.88)	<0.001	75.80%	<0.001
Ethnicity							
Caucasian	11	2350	Random	0.77(0.68-0.88)	<0.001	61.60%	0.004
Asian	8	1951	Random	0.83(0.58-1.17)	0.288	85.00%	<0.001
Method							
Previous study	6	984	Fixed	0.86(0.78-0.94)	0.001	39.30%	0.144
ROC	12	2337	Random	0.72(0.57-0.92)	0.008	81.10%	<0.001
Subtype							
All	14	2964	Random	0.76(0.64-0.89)	0.001	74.00%	<0.001
IBC	2	177	Fixed	0.83(0.70-0.97)	0.021	0.00%	0.368
TNBC	2	180	Random	0.91(0.26-3.21)	0.885	94.70%	<0.001
Luminal B	1	980	Fixed	0.76(0.61-0.94)	0.013	—	—
Cut-off							
<150	9	2041	Random	0.80(0.59-1.10)	0.172	82.90%	<0.001
>=150	9	1280	Random	0.78(0.67-0.91)	0.001	68.20%	0.001

Abbreviations: ROC: receiver operating characteristic curve; IBC: inflammatory breast cancer; TNBC: triple negative breast cancer; OR: odds ratio; 95% CI: 95% confidence interval; P_h: *p* values of Q test for heterogeneity test.

Table 3. Meta-analysis of the association between PLR and OS, DFS of BC with NACT.

	Factors	No. of studies	No. of patients	Effects model	HR (95% CI)	p	Heterogeneity I^2	Heterogeneity P_H
OS	**Overall**	5	912	Fixed	1.898(1.394-2.586)	<0.001	7.40%	0.365
	Ethnicity							
	Caucasian	3	383	Fixed	1.845(1.258-2.706)	0.002	0.00%	0.378
	Asian	2	529	Fixed	2.002(1.187-3.377)	0.009	56.70%	0.128
	Method							
	Previous study	2	281	Fixed	1.579(0.973-2.564)	0.065	0.00%	0.345
	ROC	3	631	Fixed	2.153(1.442-3.216)	<0.001	19.80%	0.288
	Subtype							
	All	3	735	Fixed	1.922(1.306-2.828)	0.001	15.30%	0.307
	IBC	2	177	Fixed	1.857(1.110-3.109)	<0.018	48.60%	0.163
DFS	**Overall**	7	1887	Fixed	1.972(1.557-2.499)	<0.001	0.00%	0.460
	Ethnicity							
	Caucasian	3	383	Fixed	2.001(1.415-2.831)	<0.001	0.00%	0.568
	Asian	4	1504	Fixed	1.948(1.409-2.692)	<0.001	33.90%	0.209
	Method							
	Previous study	3	458	Fixed	1.990(1.374-2.884)	<0.001	0.00%	0.513
	ROC	3	449	Fixed	2.544(1.614-4.010)	<0.001	1.50%	0.362
	Subtype							
	All	4	730	Fixed	2.260(1.576-3.240)	<0.001	0.00%	0.407
	IBC	2	177	Fixed	2.086(1.295-3.361)	0.003	6.50%	0.301
	Luminal B	1	980	Fixed	1.576(1.039-2.390)	0.032	—	—

Abbreviations: ROC: receiver operating characteristic curve; IBC: inflammatory breast cancer; HR: hazard ratio; 95% CI: 95% confidence interval; P_h: p values of Q test for heterogeneity test.

Figure legends

Figure 1: The forest plot between elevated PLR and pCR in BC with NACT.

Figure 2: Sensitivity analysis and Begg's funnel plot of publication bias test of PLR for pCR in BC with NACT.

Supplemental files

Table S1. Meta-analysis of the association between PLR and clinicopathological parameters of BC with NACT.

Figure S1: The flow diagram of publications selection.

Figure S2: The forest plot between elevated PLR and OS in BC with NACT.

Figure S3: The forest plot between elevated PLR and DFS in BC with NACT.

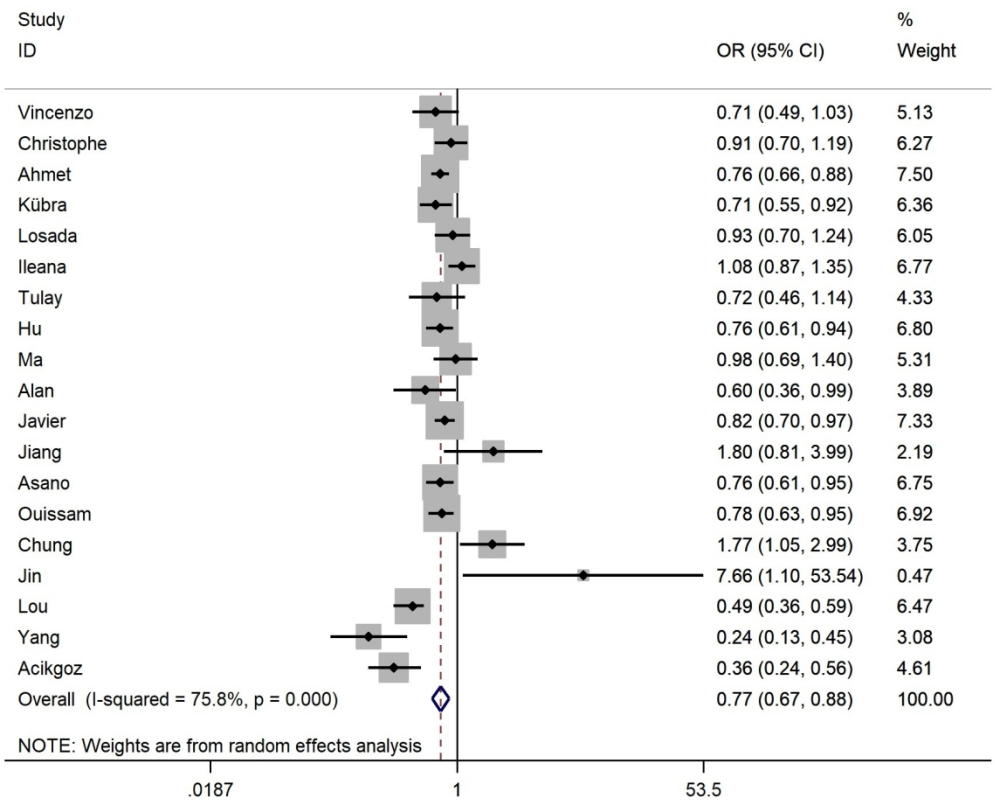

Figure 1

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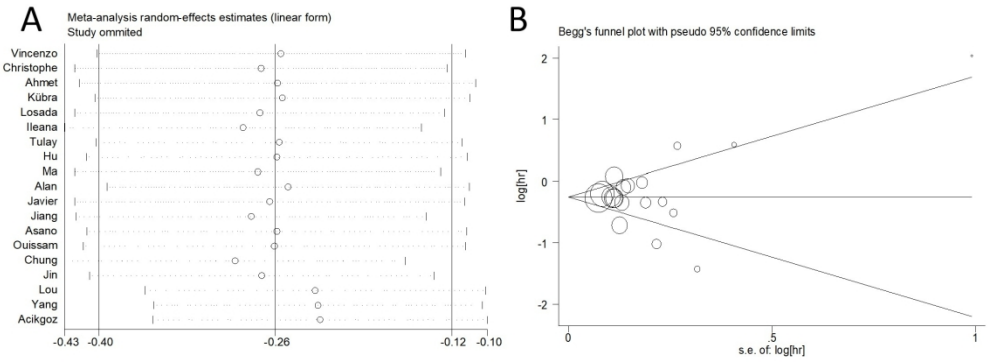

Figure 2

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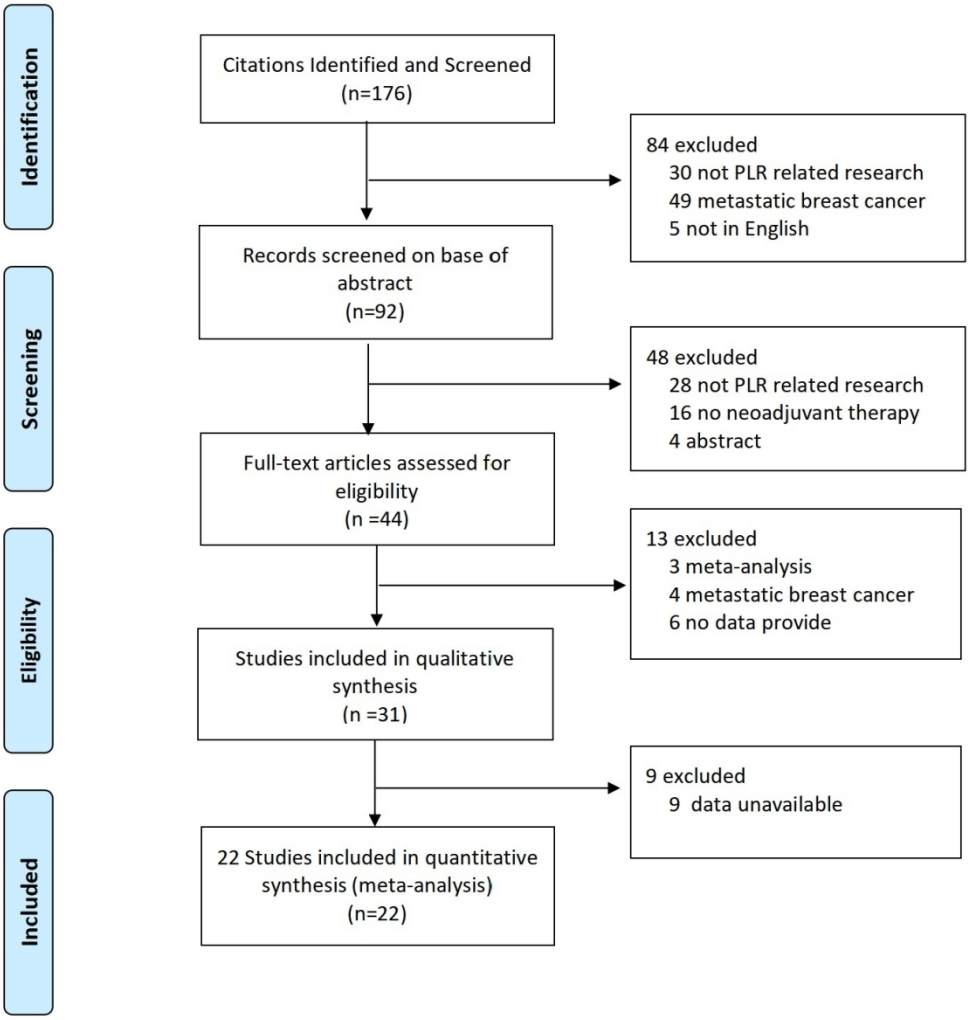
Table S1. Meta-analysis of the association between PLR and clinicopathological parameters of BC with NACT.

Variable	No. of studies	No. of patients	Effects model	OR (95% CI)	p	Heterogeneity	
						I^2	P_H
Age (Yong vs. Old)	9	3273	Fixed	0.86(0.79-0.93)	<0.001	40.60%	0.096
Histologic type (Ductal vs. Others)	4	1520	Fixed	0.97(0.94-1.01)	0.147	7.20%	0.357
Grade (G1+G2 vs. G3+unknown)	4	1692	Fixed	0.96(0.91-1.02)	0.203	0.00%	0.439
T stage (T1–T2 vs. T3–T4)	6	2178	Random	1.05(1.00-1.11)	0.035	70.30%	0.005
Lymph node metastasis (No vs. Yes)	5	2341	Fixed	0.97(0.88-1.06)	0.440	0.00%	0.952
ki-67 (<14 vs. >=14)	7	2783	Fixed	0.99(0.90-1.09)	0.771	0.00%	0.458
Hormone Receptor (－ vs. ＋)	6	2049	Fixed	0.94(0.84-1.06)	0.309	0.00%	0.526
HER-2 (－ vs. ＋)	7	2023	Random	0.91(0.76-1.09)	0.293	69.20%	0.003
Molecular subtype (Luminal vs. TriNeg + HER-2+)	8	2143	Fixed	0.99(0.92-1.07)	0.845	15.20%	0.310
Menopausal status (Pre vs. Post)	5	1604	Fixed	0.83(0.76-0.90)	<0.001	50.80%	0.087

Abbreviations: OR: odds ratio; 95% CI: 95% confidence interval; P_h: p values of Q test for heterogeneity test.



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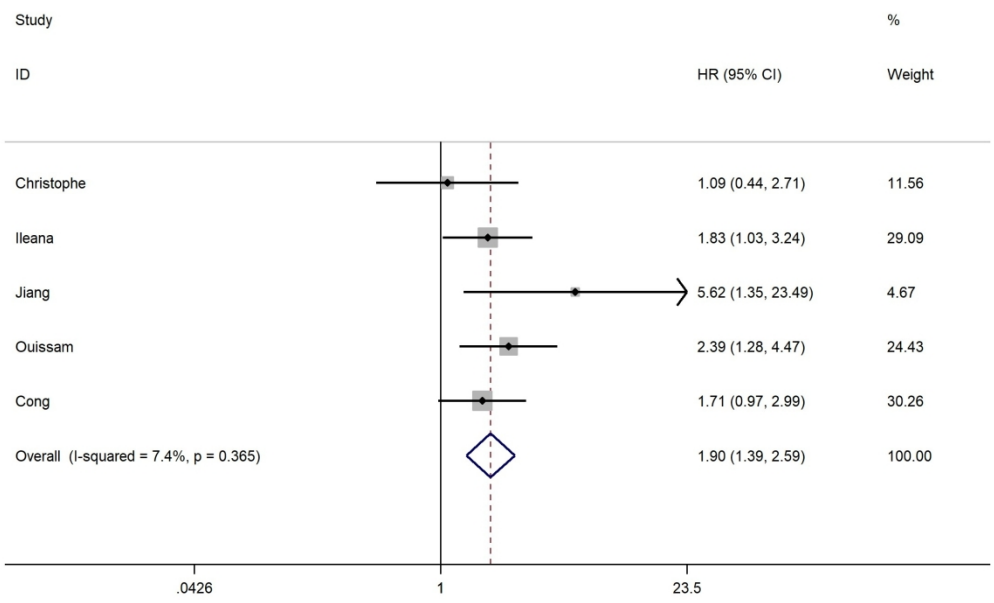

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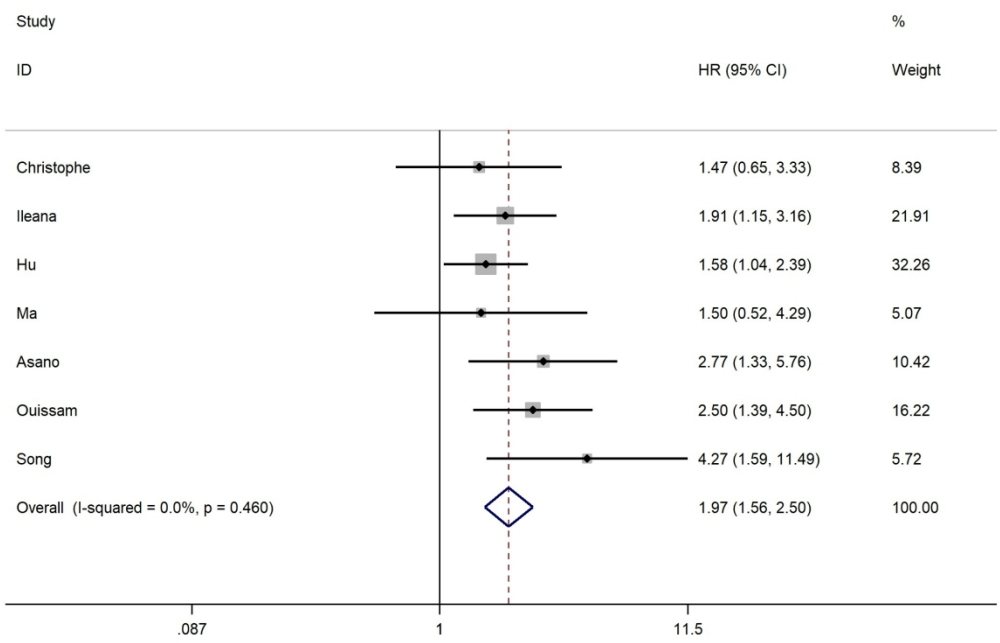

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Standards for Reporting Qualitative Research (SRQR)

O'Brien B.C., Harris, I.B., Beckman, T.J., Reed, D.A., & Cook, D.A. (2014). Standards for reporting qualitative research: a synthesis of recommendations. *Academic Medicine, 89(9)*, 1245-1251.

No. Topic	Item	Page Number
Title and abstract		
S1 Title	Concise description of the nature and topic of the study identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	Page 1
S2 Abstract	Summary of key elements of the study using the abstract format of the intended publication; typically includes objective, methods, results, and conclusions	Page 2
Introduction		
S3 Problem formulation	Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	Page 4, Page 5, line 1-7
S4 Purpose or research question	Purpose of the study and specific objectives or questions	Page 5, line 8-9
Methods		
S5 Qualitative approach and research paradigm	Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., positivist, constructivist/interpretivist) is also recommended	Page 5, line 11-21
S6 Researcher characteristics and reflexivity	Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, or transferability	Page 6, line 6
S7 Context	Setting/site and salient contextual factors; rationale[a]	Page 6, line 7-8
S8 Sampling strategy	How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale[a]	Page 5, line 26-29
S9 Ethical issues pertaining to human subjects	Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	Page 5, line 23-24

S10 Data collection methods	Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale[a]	Page 6, line 6-13
S11 Data collection instruments and technologies	Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	Page 5, line 13-18
S12 Units of study	Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	Page 7, line 13
S13 Data processing	Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/deidentification of excerpts	Page 6, line 6-13
S14 Data analysis	Process by which inferences, themes, etc., were identified and developed, including researchers involved in data analysis; usually references a specific paradigm or approach; rationale[a]	Page 6, line 20-30 Page 7, line 1-6
S15 Techniques to enhance trustworthiness	Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale[a]	Page 6, line 14-18
Results/Findings		
S16 Synthesis and interpretation	Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	Page 9, line 9-14
S17 Links to empirical data	Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	Page 12, line 11-30 Page 13
Discussion		
S18 Integration with prior work, implications, transferability, and contribution(s) to the field	Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	Page 10, line 15-30 Page 11 Page 12, line 1-7
S19 Limitations	Trustworthiness and limitations of findings	Page 14, line 9-20
Other		
S20 Conflicts of interest	Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	Page 15, line 13-14
S21 Funding	Sources of funding and other support; role of funders in data collection, interpretation, and reporting	Page 15, line 27-29

[a]The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

BMJ Open

Prognostic Significance of Platelet-Lymphocyte Ratio (PLR) in Breast Cancer Patients Treated with Neoadjuvant Chemotherapy: A Meta-analysis

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Prognostic Significance of Platelet-Lymphocyte Ratio (PLR) in Breast Cancer Patients Treated with Neoadjuvant Chemotherapy: A Meta-analysis

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Abstract

Objective: PLR (platelet-lymphocyte ratio), known as a key systemic inflammatory parameter, have been proved to be associated with response to neoadjuvant therapy in breast cancer (BC); however, the results remain controversial. This meta-analysis was carried out to evaluate the prognostic values of PLR in breast cancer patients treated with neoadjuvant chemotherapy.

Design: Meta-analysis.

Data sources: Relevant literature published on the following databases: PubMed, Embase, Web of Science databases and the Cochrane Library.

Eligibility criteria: All studies involving patients with breast cancer treated with NACT and peripheral blood pretreatment PLR recorded were included.

Data extraction and synthesis: Two researchers independently extracted and evaluated hazard ratio (HR) /Odds Ratio (OR) and its 95% confidence (CI) of survival outcomes, pathologic complete response (pCR) rate and clinicopathological parameters.

Results: The last search was updated to Dec 31, 2022. A total of 22 studies with 5533 breast cancer patients treated with neoadjuvant chemotherapy were enrolled in the final meta-analysis. Our results demonstrate that elevated PLR value appears to correlate with low pCR rate (HR: 0.77, 95% CI: 0.67-0.88, $p < 0.001$, I^2=75.80%, $P_h < 0.001$) and poor prognosis, including OS (HR: 1.90, 95% CI: 1.39-2.59, $p < 0.001$; I^2= 7.40%, P_h = 0.365) and DFS (HR: 1.97, 95% CI: 1.56-2.50, $p < 0.001$; I^2= 0.0%, P_h = 0.460). Furthermore, PLR level was associated with age (OR: 0.86, 95% CI: 0.79-0.93, $p < 0.001$, I^2= 40.60%, P_h = 0.096), menopausal status (OR: 0.83, 95% CI: 0.76-0.90, $p < 0.001$, I^2= 50.80%, P_h = 0.087) and T stage (OR: 1.05, 95% CI: 1.00-1.11, p = 0.035; I^2= 70.30%, P_h = 0.005) of breast cancer patients.

Conclusions: This meta-analysis demonstrated that high PLR was significantly related to the low pCR rate, poor OS and PFS of breast cancer patients treated with neoadjuvant chemotherapy. Therefore, PLR can be used as a potential predictor biomarker for the efficacy of neoadjuvant chemotherapy in breast cancer.

Strengths and limitations of this study

1. This is the first meta-analysis to assess the role of platelet-lymphocyte ratio (PLR) in predicting pCR rate and survival in BC patients treated with NACT.

2. Scientific and reliable statistical methods were applied.

3. The association between PLR and clinicopathological parameters of BC with NACT were explored in the stratified analysis.

4. All the studies included in this meta-analysis were retrospective and lacked detailed clinicopathological information, which may lead to bias of our results.

Keywords

Platelet, Lymphocyte, PLR, Breast Cancer, Neoadjuvant Chemotherapy, Meta-Analysis

Word count: 8455

Introduction

Breast cancer (BC) is the most frequently diagnosed malignant neoplasm in women worldwide.[1] BC patients in China account for 12.2% of the total number of newly diagnosed and 9.6% of all breast cancer related deaths in the world.[2] About 20-25% of patients are diagnosed with locally advanced breast cancer, which prone to recurrence and metastasis after surgery without any Preoperative treatment.[3] [4] Survival rates for BC patients have increased dramatically due to the development of treatment strategies, such as individualized treatment plans made by multidisciplinary teams, including surgical, radiation and medical oncology.[5] At present, neoadjuvant chemotherapy (NACT) has become the standard and effective treatment for patients with locally advanced breast cancer.[6] The aim of NACT is mainly to reduce tumor size and the stage of tumors, improve tumor operability, and improve the success rates of breast conservative operation.[7-9] Additionally, the effects of NACT could provide information to assess the efficacy of chemotherapy during the treatment.[10] However, not all patients receiving neoadjuvant therapy can achieve therapeutic benefit, especially pathologic complete response (pCR). Previous studies showed that the pCR rate of NACT is about 30% in human epidermal growth factor receptor 2 (HER2) (+) patients, 30-50% in triple negative breast cancer and less than 10% in estrogen receptor (ER) (+) and HER2 (-) breast cancer patients.[11-13] The situation may be related to different pathological types, ER status, HER-2 status, disease stage, and other factors. Some gene mutations, such as PIK3CA, TP53, SIRT5 and CDKN2A, have been proved to be associated with poor response to NACT in breast cancer patients.[14] However, these above biomarkers are expensive and difficult to obtain. Hence, it's necessary to find a convenient, inexpensive and reliable marker, which can predict response after NACT.

It is well recognized that the systemic inflammatory response plays an essential role in breast cancer progression and development.[15] [16] Numerous studies have shown that inflammatory biomarkers such as neutrophil-tolymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and systemic immune-inflflammation index (SII),

are associated with chemosensitivity and prognosis for different malignancies.[17-21] PLR, as one of the most commonly used markers, was proved to be an convenient and cost-effective blood-derived prognostic marker to evaluate the prognosis of breast cancer. Elevated PLR has been linked with poor prognosis for breast cancer in previous studies.[22-24] Furthermore, some research found that a higher PLR may lead to a worse response to NACT for breast cancer patients.[25] [26] However, some other studies showed that the BC patients with higher PLR may achieve more pCR rate after NACT.[27] [28] Thus, the role of PLR as a predictor for outcomes in BC patients after NACT is still not clear. This meta-analysis is aimed to explore the predictive value of PLR in patients with breast cancer treated with NACT.

Materials and Methods

Literature search

A systematic literature search was conducted based on the following databases: PubMed, Embase, Web of Science databases and the Cochrane Library. The keywords for the search strategy are as follows: ("PLR" or "platelet lymphocyte ratio" or "platelet-to-lymphocyte ratio" or "platelet-lymphocyte ratio") and ("breast cancer", "breast tumor", "breast carcinoma", "breast neoplasms", "mammary cancer") and ("neoadjuvant chemotherapy", "preoperative chemotherapy", "preoperative systemic treatment", "pre-surgical treatment", "primary chemotherapy"). The last search was updated to Dec 31, 2022, and all the articles were limited to English-language. We also used a hand search for the reference list of the retrieved articles in order to identify additional studies. The selection process of the meta-analysis is shown in Figure S1. This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. No patient consent and ethical approval were required in this study.

Inclusion and exclusion criteria

The included studies in this analysis had to meet the following criteria: (1) patients with breast cancer received neoadjuvant treatment and surgery; (2) studies with the peripheral blood pretreatment PLR values; (3) studies with pathologic

response status or survival outcomes after neoadjuvant treatment, including pCR, disease-free survival (DFS), overall survival (OS), OR and HR with 95% confidence intervals (CI). The exclusion criteria were as follows: (1) Abstracts, reviews, case studies, letters, non-human subject studies and non-English language studies; (2) breast cancer participants did not receive neoadjuvant treatment; (3) Research with insufficient data.

Data extraction and quality assessment

Two researchers independently reviewed the available literature and extracted data as follows: (1) study details: first author, country, publication year, study design, study period, sample size, median age, outcomes, follow-up time; (2) clinicopathologic parameters: subtype of BC, cut-off value, cut-off method, numbers in high and low PLR groups stratified by age, histologic type, tumor grade, T stage, lymph node metastasis, ki-67 value, hormone receptor status, HER-2 status, molecular subtype, menopausal status; (3) treatment outcomes: numbers in pCR and non-pCR groups, HR with 95% CIs of DFS and OS.

We used the Newcastle Ottawa Scale (NOS) rating scale to assess the quality of the included studies. The studies was scored from 0 to 9 points, based on the object selection, comparability, outcome, and exposure. High-quality literature should have a score of ≥6. If the two researchers had disagreement, a third researcher was invited to achieve a consistent result.

Statistical analysis

All analyses were performed using Stata software version 12.0 (Stata Corporation, College Station, TX, USA), using two-sided P values. Odds ratio (OR) with corresponding 95% CI was used to evaluate the association between PLR and pCR rate, clinicopathological characteristics. Hazard ratios (HR) with corresponding 95% CI was used as an effect measure to assess the relationship between PLR and DFS, OS. Then the log OR, log HR, and corresponding standard error (SE) were used to compute pooled effect measures. Moreover, stratified analyses were also performed based on ethnicity, cut-off value, cut-off method and sub-type of breast cancer. Both

the Cochran's Q statistic and the I^2 statistic were calculated to estimate heterogeneity among the included studies.[29 30] If the P value of the Q test was <0.10 or I^2 >50%, indicating significant heterogeneity across studies, the pooled OR and HR were calculated by the random effects model (the DerSimonian and Laird method).[31] Otherwise, fixed effects model (the Mantel–Haenszel method) was used.[31] Publication bias was evaluated using Funnel plots and Egger's linear regression test. Sensitivity analyses were performed by omitting each single study to show the influence of the individual data set to the pooled results. $P < 0.05$ was considered statistically significant.

Results

Study characteristics

As shown in the flow diagram (Figure S1), 176 research articles were identified in the preliminary search. After reviewing the titles, abstracts and full texts, 154 studies were excluded according to the search criteria and 22 studies were finally included in the meta-analysis.[22 25 26 28 32-41] The main characteristics of the included studies are summarized in Table S1. The 22 enrolled studies containing 5533 BC patients were published between 2016 and 2022 with the sample size ranging from 55 to 980. 11 studies were carried out in Asian countries (China and Japan) and the other 11 studies were conducted in Caucasian countries (Turkey, America, Spain, Italy, France and Morocco). All studies were retrospective, with study period ranging from 1996 – 2022. The follow-up time ranged from 3.4 to 124.8 months in these studies, with NOS scores of 6 – 8 points. Most of the study subjects contained all breast cancer types, and included two studies of inflammatory breast cancer, two studies of triple negative breast cancer and one study of Luminal B breast cancer. All patients received standardized neoadjuvant chemotherapy and surgery, with the median age ranged from 45 to 71 years old. Cut-off values for PLR were provided in 21 studies, 6 of which were derived from previous studies and another 15 were obtained from ROC curves.

Association between PLR and pCR of BC

19 studies with 4301 patients reported the correlation between the PLR and pCR.[22 26 28 32-40 42-48] Our results indicate that high PLR level was significantly associated with low pCR rate (HR: 0.77, 95% CI: 0.67-0.88, p < 0.001), and significant heterogeneity was observed (I^2=75.80%, P_h < 0.001, Table 1, Figure 1). When stratified analyses were performed based on ethnicity, the results showed that Caucasian studies were still statistically significant (HR: 0.77, 95% CI: 0.68-0.88, p < 0.001; I^2=61.60%, P_h = 0.004). On the other hand, there was no statistically significance observed for PLR and pCR among the Asian studies (HR: 0.83, 95% CI: 0.58-1.17, p = 0.288; I^2= 85.00%, P_h < 0.001). Subgroup analysis were also performed to determine the effects of cut-off values and methods on the outcomes. Studies with cut-off value >=150 showed a significant association between the PLR and pCR (HR: 0.78, 95% CI: 0.67-0.91, p = 0.001; I^2= 68.20%, P_h = 0.001), while cut-off values <150 did not achieve statistical significance (HR: 0.80, 95% CI: 0.59-1.10, p = 0.172; I^2= 82.90%, P_h < 0.001). On the other hand, we observed statistically significant relationship between PLR and pCR, no matter the cut-off values obtained from ROC curves (HR: 0.72, 95% CI: 0.57-0.92, p = 0.008; I^2= 81.10%, P_h < 0.001) or previous studies (HR: 0.86, 95% CI: 0.78-0.94, p = 0.001; I^2= 39.30%, P_h = 0.144). Further subgroup analysis was also conducted by tumor subtypes. In the all types group (HR: 0.76, 95% CI: 0.64-0.89, p = 0.001; I^2= 74.00%, P_h < 0.001) and inflammatory breast cancer group (HR: 0.83, 95% CI: 0.70-0.97, p = 0.021; I^2= 0.00%, P_h = 0.368), statistical significance were noted between PLR and pCR. In comparison, studies in the triple negative breast cancer group did not show a significant association (HR: 0.91, 95% CI: 0.26-3.21, p = 0.885; I^2= 94.70%, P_h < 0.001).

Association between PLR and survival of BC

5 studies with 912 patients evaluated the relationship between OS and PLR.[25 35 40 43 49] The pooled results demonstrated that high PLR was significantly associated with poor OS in patients with breast cancer (HR: 1.90, 95% CI: 1.39-2.59, p < 0.001; I^2= 7.40%, P_h = 0.365) (Table 2, Figure S2). Subgroup analyses by ethnicity showed

that PLR had significantly prognostic value for OS both in Asian and Caucasian populations (HR: 2.00, 95% CI: 1.19-3.38, p = 0.009, I^2= 56.70%, P_h = 0.128; HR: 1.85, 95% CI: 1.26-2.71, p = 0.002, I^2= 0.0%, P_h = 0.378). Moreover, when stratified by subtypes of breast cancer, the results indicated that the prognostic effect of PLR on OS was similarly significant among the all types group (HR: 1.92, 95% CI: 1.31-2.83, p = 0.001; I^2= 15.30%, P_h = 0.307) and inflammatory breast cancer group (HR: 1.86, 95% CI: 1.11-3.11, p = 0.018; I^2= 48.60%, P_h = 0.163). Furthermore, when considering different cut-off value methods, high PLR significantly predicted shorter OS when cut-off values were conducted by ROC (HR: 2.15, 95% CI: 1.44-3.22, p < 0.001; I^2= 19.80%, P_h = 0.288), but did not show significantly prognostic efficiency in the group of cut-off value obtained from previous studies (HR: 1.58, 95% CI: 0.97-2.56, p = 0.065; I^2= 0.0%, P_h = 0.345).

7 studies with 1887 patients analyzed the relationship between the PLR and DFS.[25 26 35 37 38 43 50] The pooled results indicated that DFS was significantly shorter in high PLR group than in low PLR group (HR: 1.97, 95% CI: 1.56-2.50, p < 0.001; I^2= 0.0%, P_h = 0.460) (Table 2, Figure S3). We also performed further subgroup analysis based on ethnicity, subtypes of BC and cut-off value methods. Compared with the overall results, no significant changes were identified after stratification, and no significant heterogeneity was observed.

Association between PLR and clinicopathological parameters of BC

To analyze the impact of PLR on the clinicopathological characteristics in breast cancer patients, we pooled the results from included studies according to age, histologic type, tumor grade, T stage, lymph node metastasis, ki-67 value, hormone receptor status, HER-2 status, molecular subtype, menopausal status. As shown in Table S2, young patients and pre-menopausal status patients had significantly higher PLR value than old or post-menopausal status patients (OR: 0.86, 95% CI: 0.79-0.93, p < 0.001, I^2= 40.60%, P_h = 0.096; OR: 0.83, 95% CI: 0.76-0.90, p < 0.001, I^2= 50.80%, P_h = 0.087). In comparison to low PLR groups, the high PLR groups had a higher T stage (OR: 1.05, 95% CI: 1.00-1.11, p = 0.035; I^2= 70.30%, P_h = 0.005).

Whereas the other results indicated no significant association of PLR with histologic type, tumor grade, lymph node metastasis, ki-67 value, hormone receptor status, HER-2 status and molecular subtype.

Sensitivity analysis

Sensitivity analysis results showed that the pooled ORs are not altered materially when deleted a single study each time. The sensitivity analysis plot presented that all the included studies are near the central line with no clear deviation, suggesting that our results were statistically robust (Figure 2A).

Publication bias

Begg's funnel plot and Egger's test were used to evaluate the publication bias of the literature. The funnel plots did not reveal obvious evidence of asymmetry (Figure 2B). Then, the Egger's test still did not show any significant statistical evidence of publication bias (P = 0.862).

Discussion

This meta-analysis assessed the association between pretreatment PLR with pCR and survival on 5533 breast cancer patients treated with neoadjuvant chemotherapy. Our results demonstrate that elevated PLR value appears to correlate with low pCR rate and poor prognosis, including OS and DFS. Consistent with previous studies, our findings suggest that PLR could be a significant prognostic marker for breast cancer patients who received NACT.[26 35 37 40 43]

Neoadjuvant chemotherapy is increasingly used to treat locally advanced breast cancer, so as to reduce the size of tumors and increase the possibility of breast-conserving surgery.[51] However, there are no ready-made and reliable biomarkers to predict the response to NACT. In recent years, many studies have focused on the relationship between inflammation related biomarkers and tumors. These studies showed that tumor related inflammation, which may contribute to the tumor growth, invasion and metastasis, was associated with the occurrence, development, and prognosis of cancers.[52 53] Common components in peripheral blood, such as neutrophils, monocytes, platelets, and lymphocytes, are closely related to the

biological behavior of tumor cells.[54] Numerous studies have shown that lymphocytes can inhibit tumor progression and metastasis, which play an important role in tumor immune monitoring.[55 56] Lymphopenia is commonly seen in immune system defects caused by tumor cells. The possible mechanism is that lymphocytes can control growth of tumor cells through cytotoxicity and induction tumor cell apoptosis.[57] Another research showed that lymphocytes could inhibit tumor cell growth by secreting interferon-gamma and tumor necrosis factor-α.[58] Studies have found that the more infiltrating lymphocyte by tumor, the better prognosis of breast cancer patients.[59 60] In addition, previous studies have reported that tumor-infiltrating lymphocyte can be used as a predictor of the response to neoadjuvant and adjuvant chemotherapy in breast cancer patients.[61 62] On the other hand, platelets, as key actors in the process of inflammation, play important roles in tumor progression. Firstly, platelets can protect tumor cells in peripheral blood from high flow shear stress and immune attacks by aggregating and adhering to tumor cells.[63] Secondly, platelets could contribute tumor progression by secreting various cell growth factors, which could stimulate tumor angiogenesis and growth.[64-66] Thirdly, platelets could induce epithelial mesenchymal transition and impede cell-mediated immune clearance effects, leading to the tumor cell metastasis.[67] Therefore, high platelet count may be associated with poor prognosis of breast cancer patients.

Platelet-to-lymphocyte ratio (PLR), as a commonly used indicator of inflammatory status, could predict the prognosis of variant tumors. Elevated value of PLR, with a high platelet count and/or low lymphocyte count, often lead to a low antitumor activity and poor prognosis. Previous studies showed that PLR is significantly related to the survival of colorectal cancer, gastric cancer and liver cancer.[68-70] Gunduz et al. showed that elevated PLR value was associated with poor DFS in breast cancer.[71] However, Ulas et al. reported that there is no association between PLR and DFS or OS in breast cancer.[72] What's more, when subgroup analysis by different molecular types of breast cancer was performed, Koh et al. found that elevated PLR could result in an increased risk of mortality in ER+ and HER2+

group but not in ER− and HER2+ group.[73] Studies focused on the relationship between PLR and metastatic breast cancer could achieve positive results easily.[74] However, the predictive efficacy of PLR in early stage breast cancer was limited. The possible explanation is that inflammatory reaction may not be so obvious in early breast cancer. Recently, many studies have be devoted to explore whether PLR could be a predictor for locally advanced breast cancer treated with neoadjuvant chemotherapy. Tekyol et al. found that PLR value was associated with chemotherapy sensitivity and could serve as a predictive marker of the therapeutic effect of NACT in breast cancer.[34] Similarly, Ouissam and Ma showed that PLR was associated with OS and DFS in breast cancer treated with NACT.[43 75] However, some other studies reported that the PLR value has no significant predictive effect on pCR rate, DFS or OS in breast cancer treated with NACT.[25 49] So far, the above studies indicated that the prognostic role and clinical value of PLR in locally advanced breast cancer with NACT is still controversial.

We conducted this meta-analysis to explore the predictive value of PLR in breast cancer patients treated with NACT. Our results indicate that high PLR level was significantly associated with low pCR rate (HR: 0.77, 95% CI: 0.67-0.88, $p < 0.001$). This finding is consistent with previous studies confirming that PLR may act as a significant marker for predicting the effective of NACT in BC patients.[33 34 37] In subgroup analysis, we found that PLR was only significantly associated with Caucasian patients but not Asian patients. The possible explanations were the differences in baseline PLR values due to different genetic backgrounds, different chemotherapy regimens and doses. What's more, the heterogeneity of the Asian group is also more obvious than that of the Caucasian group, which may lead to no significance in the Asian group. Previous studies reported that high PLR value may indicate a lower pCR rate and poor prognosis of TNBC patients.[46] Subgroup analysis by tumor subtypes in this meta-analysis including two studies showed no significant association between PLR and pCR in the triple negative breast cancer group. One of the reasons for the negative statistical significance is the small number of included

studies. On the other hand, TNBC is a heterogeneous disease that includes several subtypes of tumors. There are differences in prognosis among the different subtypes of TNBC.[44] Further more research is needed to evaluate the predictive value of PLR in TNBC treated with NACT. How to identify the optimal critical value for the clinical application of PLR may be a major concern for doctors. Unfortunately, this value has not been determined for predicting the efficacy and prognosis of neoadjuvant therapy in breast cancer patients. Because of the different phase of evaluation of the blood sample or basic blood values of different populations, the cutoff values of PLR were varied. Some studies reported that high PLR was associated with poor prognosis using a cut-off value of 292 and 200,[76 77] while other studies did not find significant association between PLR and prognosis of breast cancer patients with a cut-off value of 161, 107, and 160, respectively.[22 37 78] Different studies use variant cut-off values from different methods. Traditionally, we believe that the ROC curve is the most suitable for getting the optimal cutoff value.[33 43 46-48] However, other studies have also achieved significant results using the cut-off values from previous studies.[26 28 34] We performed subgroup analysis to determine the effects of cut-off values and methods on the outcomes. The results showed statistically significant relationship between PLR and pCR, no matter the cut-off values obtained from ROC curves or previous studies. This result indicated that the source and method of optimal cut-off values are not the key influence factors for PLR acting as a predictive factor for breast cancer. On the other hand, our results also showed that studies with cut-off value >=150 showed a significant association between the PLR and pCR, while cut-off values <150 did not achieve statistical significance. Therefore, a higher cut-off value for PLR may increase its predictive value for breast cancer patients. However, a higher cut-off value may lead to the omission of a large number of patient and reduce its predictive sensitivity in clinical practice.[79] Therefore, further researches are needed to determine the optimal cut-off value of PLR for future individualized treatment.

We also evaluated the association between PLR and prognosis of breast cancer

patients treated with NACT. Zhang et al. conducted a meta-analysis which including 5542 breast cancer patients with different stages and indicated that high PLR level is significantly associated with poor OS and DFS of breast cancer patients.[80] However, the results were inconsistent when evaluated the prognosis value for NACT. Christophe et al. and Jiang et al. reported that the PLR value has no significant effect on DFS or OS in breast cancer treated with NACT.[25 49] Contradictory results made by Ileana and Ouissam showed that PLR was associated with OS and DFS in breast cancer treated with NACT.[35 43] In our study, the pooled results demonstrated that high PLR was significantly associated with poor OS and PFS in patients with breast cancer. Subgroup analyses by ethnicity, method and subtype showed the same results with no significant heterogeneity. The consistency of this result may be due to the fact that the included patients are all local advanced stage patients who have received NACT. Therefore, further studies are needed to evaluate the prognostic value of PLR in different clinical stages and molecular subtypes of breast cancer. What's more, this meta-analysis also explored the association between PLR and clinicopathological characteristics. Our results indicated that high PLR level was more common in young women and patients with premenopausal status. One possible explanation is that young people may have more lymphocyte and platelet reserves and a more sensitive inflammatory state. On the other hand, we also found that elevated PLR is associated with tumor stage, which indicated that PLR may be involved in the occurrence and progression of breast cancer. Some exploration experiments are needed to prove the mechanisms between PLR and breast cancer.

There are still several limitations to be considered in this meta-analysis. First, All of the studies included were retrospective, and some studies have incomplete data, which may have some impact on the final results. Second, the cut-off values of PLR were inconsistent among the studies, some of them determined the optimum PLR value according to the previous studies instead of using ROC curve. Even if using ROC curve, the different phase of evaluation of the blood sample or basic blood values of different populations may also result in different cutoff values, which may

lead to the introduction of selection bias in the meta-analysis. Third, breast cancer is a heterogeneous tumor with many subtypes. The biological behavior, malignant degree and immune response of different subtypes were varied. Variant molecular subtypes of breast cancer respond differently to neoadjuvant therapy, and the heterogeneity of the results may be affected for the lacking of relevant information about molecular typing in most studies. Finally, PLR may be influenced by some factors, including bacterial and viral infections, nutritional state and history of medication. These intrinsic factors were not statistically available and uncontrollable, which were unavoidable sources of heterogeneity in this meta-analysis. Further more studies were needed to accurately focus on the different subtype of breast cancer and provide more detailed clinicopathological information for stratified analysis, which may reduce heterogeneity to some extent.

Conclusions

This study indicated that PLR level was associated with age, menopausal status and T stage of breast cancer patients. In addition, high PLR was significantly related to the low pCR rate, poor OS and PFS of breast cancer patients treated with neoadjuvant chemotherapy. Therefore, PLR can be used as a potential predictor biomarker for the efficacy of neoadjuvant chemotherapy. However, further high quality and well-designed studies with larger samples are needed to identify the optimal cut-off value of PLR and explore the mechanism of PLR with breast cancer.

Abbreviations

HR: hazard ratio; OR: odds ratio; 95% CI: 95% confidence interval; Ph: p values of Q test for heterogeneity test; OS: overall survival; DFS: disease-free survival. PLR: platelet-lymphocyte ratio; BC: breast cancer; NACT: neoadjuvant chemotherapy; ROC: receiver operating characteristic curve; NOS: Newcastle-Ottawa Scale;

Declarations

Ethics approval and consent to participate

All the data supporting our findings in this paper were freely downloaded from the PubMed, EMBASE, Web of Science databases and the Cochrane Library. No ethical approval or written informed consent for participation was required.

Consent for publication

Not applicable.

Availability of data and materials

All data for this study are publicly available and are ready for the public to download at no cost from the official websites of the PubMed, EMBASE, Web of Science databases and the Cochrane Library. There is no need to have the formal permission to use data for this study. The sources and data robustness have been described in the section of “Methods”.

Competing interests

The authors declare that they have no competing interests.

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Author Contributions

XQ, JC and XZ were involved in drafting the manuscript. SW and JN made contributions to the concepts, acquisition and analysis of the data. LS was involved in acquisition of data and preparing the Figs. LY and CJ designed and revised the manuscript. All authors have read and approved the final manuscript.

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Patient and Public Involvement

None

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Table 1. Meta-analysis of the association between PLR and pCR of BC with NACT.

Factors	No. of studies	No. of patients	Effects model	OR (95% CI)	p	Heterogeneity	
						I^2	P_H
Overall	19	4301	Random	0.77(0.67-0.88)	<0.001	75.80%	<0.001
Ethnicity							
Caucasian	11	2350	Random	0.77(0.68-0.88)	<0.001	61.60%	0.004
Asian	8	1951	Random	0.83(0.58-1.17)	0.288	85.00%	<0.001
Method							
Previous study	6	984	Fixed	0.86(0.78-0.94)	0.001	39.30%	0.144
ROC	12	2337	Random	0.72(0.57-0.92)	0.008	81.10%	<0.001
Subtype							
All	14	2964	Random	0.76(0.64-0.89)	0.001	74.00%	<0.001
IBC	2	177	Fixed	0.83(0.70-0.97)	0.021	0.00%	0.368
TNBC	2	180	Random	0.91(0.26-3.21)	0.885	94.70%	<0.001
Luminal B	1	980	Fixed	0.76(0.61-0.94)	0.013	—	—
Cut-off							
<150	9	2041	Random	0.80(0.59-1.10)	0.172	82.90%	<0.001
>=150	9	1280	Random	0.78(0.67-0.91)	0.001	68.20%	0.001

Abbreviations: ROC: receiver operating characteristic curve; IBC: inflammatory breast cancer; TNBC: triple negative breast cancer; OR: odds ratio; 95% CI: 95% confidence interval; P_h: *p* values of Q test for heterogeneity test.

Table 2. Meta-analysis of the association between PLR and OS, DFS of BC with NACT.

	Factors	No. of studies	No. of patients	Effects model	HR (95% CI)	p	Heterogeneity I^2	Heterogeneity P_H
OS	**Overall**	5	912	Fixed	1.898(1.394-2.586)	<0.001	7.40%	0.365
	Ethnicity							
	Caucasian	3	383	Fixed	1.845(1.258-2.706)	0.002	0.00%	0.378
	Asian	2	529	Fixed	2.002(1.187-3.377)	0.009	56.70%	0.128
	Method							
	Previous study	2	281	Fixed	1.579(0.973-2.564)	0.065	0.00%	0.345
	ROC	3	631	Fixed	2.153(1.442-3.216)	<0.001	19.80%	0.288
	Subtype							
	All	3	735	Fixed	1.922(1.306-2.828)	0.001	15.30%	0.307
	IBC	2	177	Fixed	1.857(1.110-3.109)	<0.018	48.60%	0.163
DFS	**Overall**	7	1887	Fixed	1.972(1.557-2.499)	<0.001	0.00%	0.460
	Ethnicity							
	Caucasian	3	383	Fixed	2.001(1.415-2.831)	<0.001	0.00%	0.568
	Asian	4	1504	Fixed	1.948(1.409-2.692)	<0.001	33.90%	0.209
	Method							
	Previous study	3	458	Fixed	1.990(1.374-2.884)	<0.001	0.00%	0.513
	ROC	3	449	Fixed	2.544(1.614-4.010)	<0.001	1.50%	0.362
	Subtype							
	All	4	730	Fixed	2.260(1.576-3.240)	<0.001	0.00%	0.407
	IBC	2	177	Fixed	2.086(1.295-3.361)	0.003	6.50%	0.301
	Luminal B	1	980	Fixed	1.576(1.039-2.390)	0.032	—	—

Abbreviations: ROC: receiver operating characteristic curve; IBC: inflammatory breast cancer; HR: hazard ratio; 95% CI: 95% confidence interval; P_h: p values of Q test for heterogeneity test.

Figure legends

Figure 1: The forest plot between elevated PLR and pCR in BC with NACT. The results showed that high PLR is significantly related to the low pCR rate.

Figure 2: Sensitivity analysis and Begg's funnel plot of publication bias test of PLR for pCR in BC with NACT. (A): Sensitivity analysis plot showed that all the included studies are near the central line with no clear deviation, suggesting that the results are statistically robust. (B): The funnel plots did not reveal obvious evidence of asymmetry.

Supplemental files

Table S1. Characteristics of included studies in meta-analysis.

Table S2. Meta-analysis of the association between PLR and clinicopathological parameters of BC with NACT.

Figure S1: The flow diagram of publications selection.

Figure S2: The forest plot between elevated PLR and OS in BC with NACT.

Figure S3: The forest plot between elevated PLR and DFS in BC with NACT.

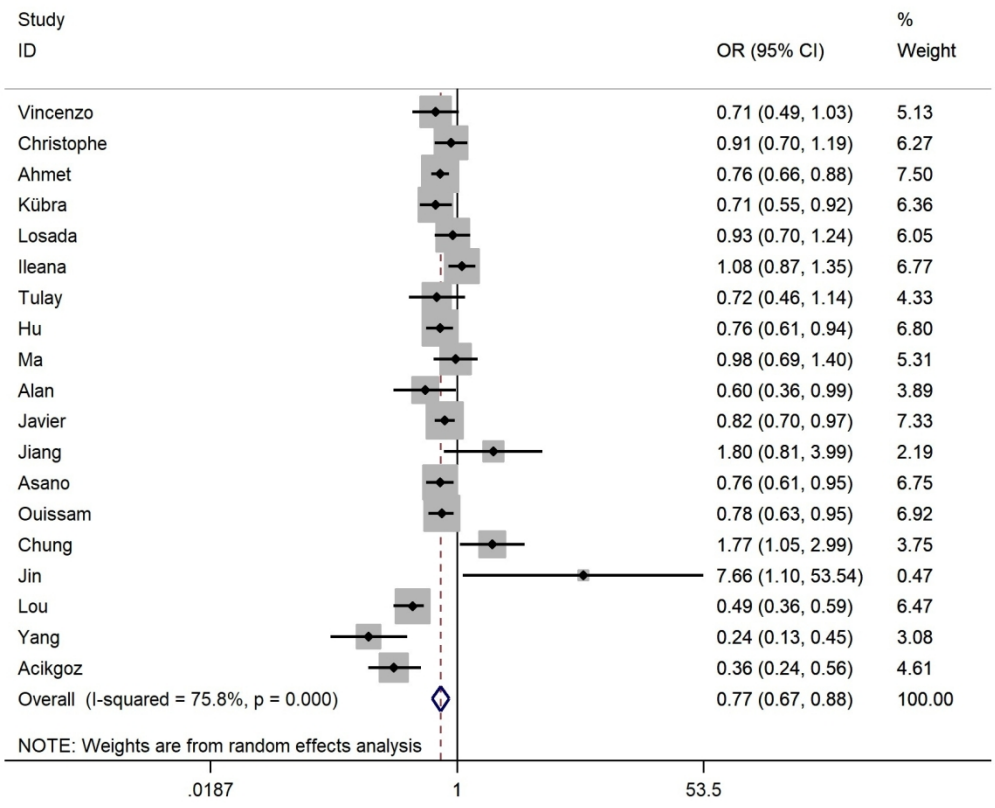

Figure 1

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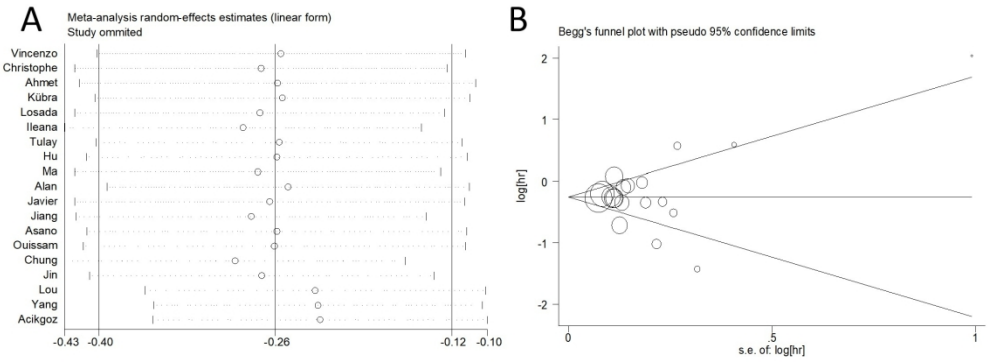

Figure 2

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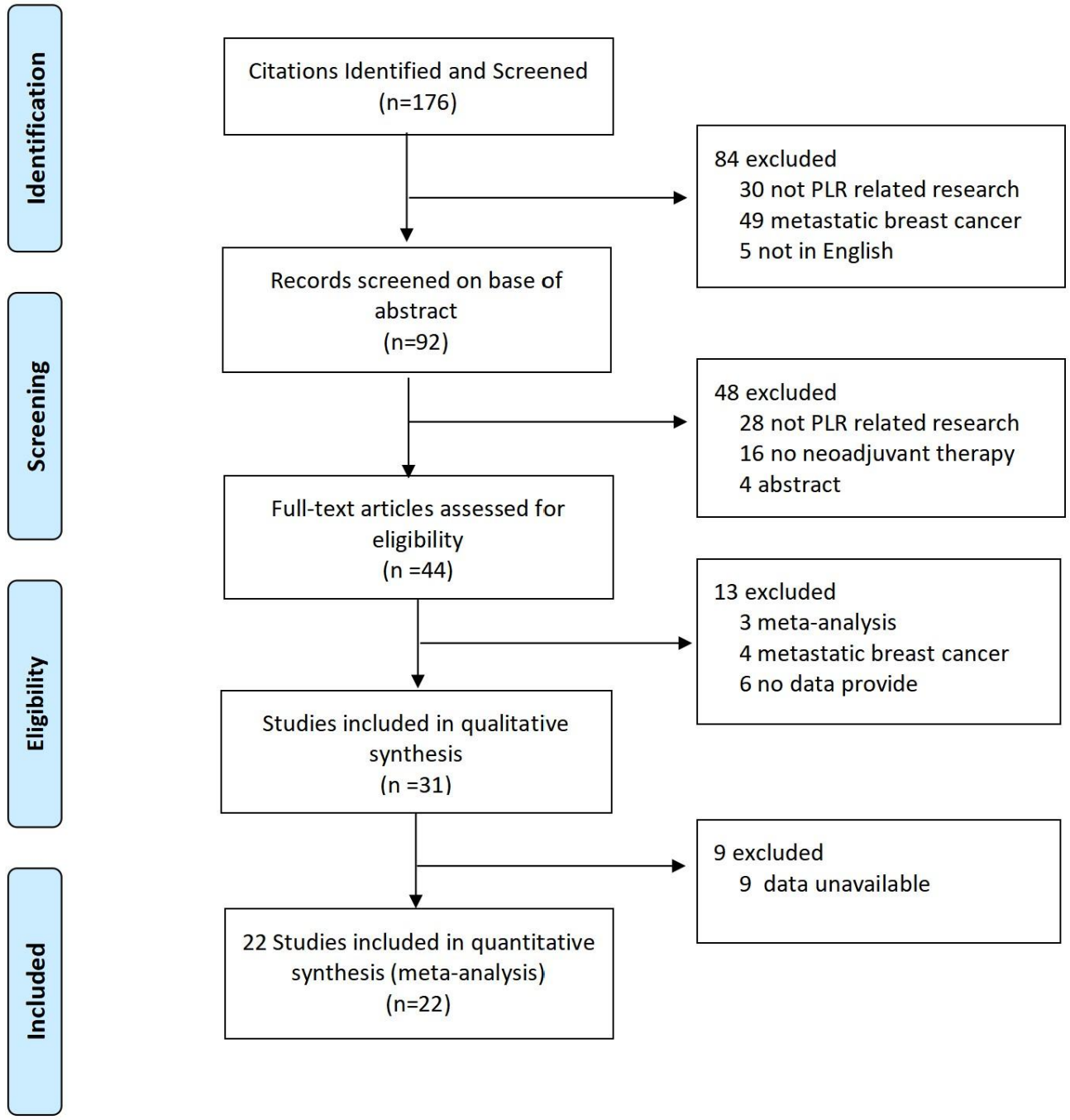
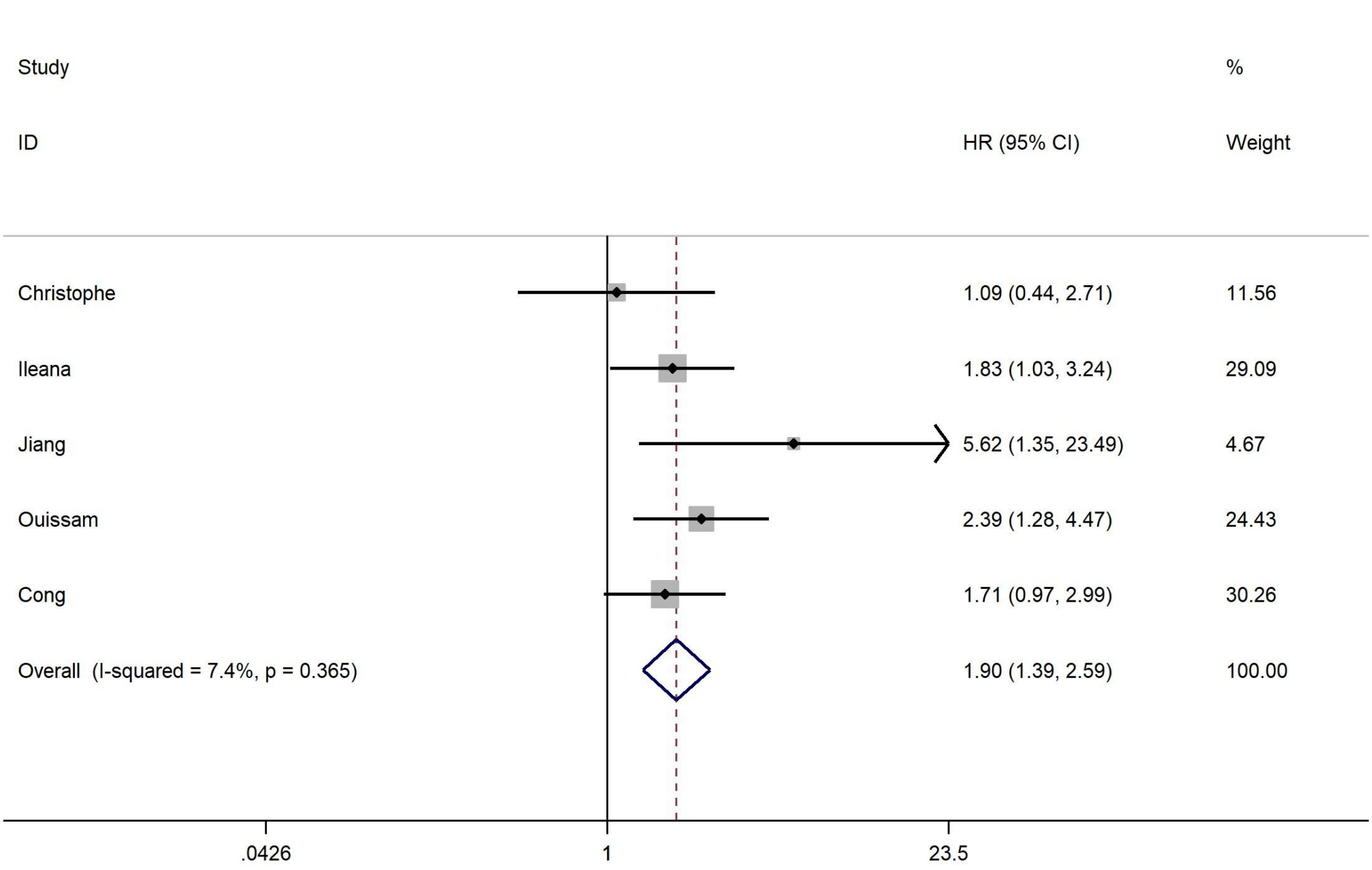

Identification
Screening
Eligibility
Included
Citations Identified and Screened
(n=176)
84 excluded
30 not PLR related research
49 metastatic breast cancer
5 not in English
Records screened on base of abstract
(n=92)
48 excluded
28 not PLR related research
16 no neoadjuvant therapy
4 abstract
Full-text articles assessed for eligibility
(n =44)
13 excluded
3 meta-analysis
4 metastatic breast cancer
6 no data provide
Studies included in qualitative synthesis
(n =31)
9 excluded
9 data unavailable
22 Studies included in quantitative synthesis (meta-analysis)
(n=22)


Study
ID
HR (95% CI)
%
Weight
Christophe
1.09 (0.44, 2.71)
11.56
Ileana
1.83 (1.03, 3.24)
29.09
Jiang
5.62 (1.35, 23.49)
4.67
Ouissam
2.39 (1.28, 4.47)
24.43
Cong
1.71 (0.97, 2.99)
30.26
Overall (I-squared = 7.4%, p = 0.365)
1.90 (1.39, 2.59)
100.00
.0426
1
23.5

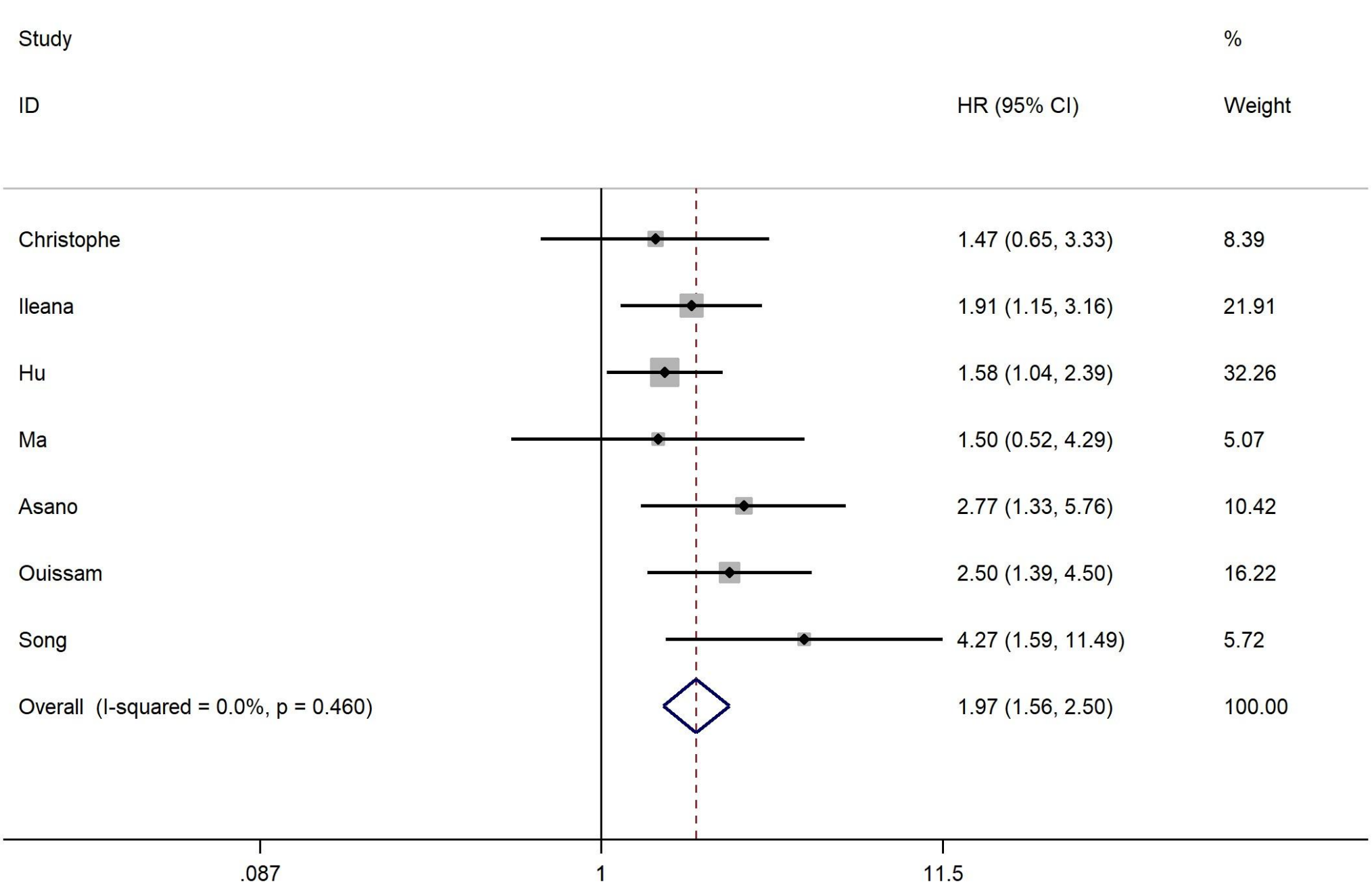

Study
ID
HR (95% CI)
%
Weight
Christophe
1.47 (0.65, 3.33)
8.39
Ileana
1.91 (1.15, 3.16)
21.91
Hu
1.58 (1.04, 2.39)
32.26
Ma
1.50 (0.52, 4.29)
5.07
Asano
2.77 (1.33, 5.76)
10.42
Ouissam
2.50 (1.39, 4.50)
16.22
Song
4.27 (1.59, 11.49)
5.72
Overall (I-squared = 0.0%, p = 0.460)
1.97 (1.56, 2.50)
100.00
.087
1
11.5

Table S1. Characteristics of included studies in meta-analysis.

NO.	Author	Year	Country	Ethnicity	Study design	Study period	Subtype	Patients (n)	Median age (years)	Follow-up (month)	Cut-off value	Method	Outcomes	NOS score
1	Asano	2016	Japan	Asian	retrospective	2007-2013	All	177	NA	3.4 (0.6-6.0)	150	Previous study	pCR/DFS	8
2	Vincenzo	2018	Italy	Caucasian	retrospective	1999-2018	All	373	50 (26-82)	NA	104.47	ROC	pCR	6
3	Losada	2018	Spain	Caucasian	retrospective	2004-2018	All	104	71 (65-89)	48 (6-149）	150	Previous study	pCR/DFS	8
4	Javier	2018	America	Caucasian	retrospective	2013-2016	All	272	51 (27-85)	NA	150	Previous study	pCR	6
5	Peng	2019	China	Asian	retrospective	2013-2017	All	808	50 (20-72)	NA	151.3	ROC	pCR+PR	6
6	Ileana	2020	France	Caucasian	retrospective	2005-2013	All	206	50.3 (25.3-76.6)	80.4 (2.4-135.6)	150	Previous study	pCR/OS/DFS	8
7	Tulay	2020	Turkey	Caucasian	retrospective	2009-2018	All	131	49 (23-74)	NA	119	ROC	pCR	6
8	Hu	2020	China	Asian	retrospective	2012-2016	Luminal B	980	NA	37 (5-77)	NA	NA	pCR/DFS	8
9	Alan	2020	Turkey	Caucasian	retrospective	2015-2017	All	55	48.5 (27-80)	41 (15-49)	225.3	ROC	pCR	7
10	Jiang	2020	China	Asian	retrospective	2014-2018	All	249	51	4-72	88.23	ROC	pCR/OS	8
11	Christophe	2021	France	Caucasian	retrospective	1996-2016	IBC	75	NA	124.8 (68.5-166.8)	150	Previous study	pCR/OS/DFS	8
12	Ahmet	2021	Turkey	Caucasian	retrospective	2008-2019	All	743	48 (22.0-83.5)	67.5 (10.5-194.4)	131.8	ROC	pCR	7
13	Kübra	2021	Turkey	Caucasian	retrospective	2016-2020	All	150	45.6	NA	150	Previous study	pCR	6
14	Ma	2021	China	Asian	retrospective	2017-2018	All	203	NA	31 (1-39)	135	ROC	pCR/DFS	8
15	Ouissam	2021	Morocco	Caucasian	retrospective	2010-2014	IBC	102	49 (29-88)	NA	178	ROC	pCR/OS/DFS	7
16	Cong	2022	China	Asian	retrospective	2012-2016	All	280	49	NA	155	ROC	pCR/OS	7
17	Chung	2022	China	Asian	retrospective	2012-2019	TNBC	88	51	NA	148.14	ROC	pCR	6
18	Jin	2022	China	Asian	retrospective	2014-2019	All	67	51 (27-81)	NA	106.3	ROC	pCR	6
19	Song	2022	China	Asian	retrospective	2016-2018	All	144	50.4	32 (1-40)	158.365	ROC	DFS	8
20	Lou	2022	China	Asian	retrospective	2015-2018	TNBC	92	52.3 (29-67)	NA	141.36	ROC	pCR	6
21	Yang	2022	China	Asian	retrospective	2020-2022	All	95	NA	NA	118.78	ROC	pCR	6
22	Acikgoz	2022	Turkey	Caucasian	retrospective	2014-2019	All	139	45 (25-75)	39.5 (7.5-93)	181.7	ROC	pCR	7

Abbreviations: NA: not available; OS: overall survival; DFS: disease-free survival; pCR: pathologic complete response; ROC: receiver operating characteristic curve; NOS: Newcastle-Ottawa Scale.

Table S2. Meta-analysis of the association between PLR and clinicopathological parameters of BC with NACT.

Variable	No. of studies	No. of patients	Effects model	OR (95% CI)	p	Heterogeneity I^2	Heterogeneity P_H
Age (Yong vs. Old)	9	3273	Fixed	0.86(0.79-0.93)	<0.001	40.60%	0.096
Histologic type (Ductal vs. Others)	4	1520	Fixed	0.97(0.94-1.01)	0.147	7.20%	0.357
Grade (G1+G2 vs. G3+unknown)	4	1692	Fixed	0.96(0.91-1.02)	0.203	0.00%	0.439
T stage (T1–T2 vs. T3–T4)	6	2178	Random	1.05(1.00-1.11)	0.035	70.30%	0.005
Lymph node metastasis (No vs. Yes)	5	2341	Fixed	0.97(0.88-1.06)	0.440	0.00%	0.952
ki-67 (<14 vs. >=14)	7	2783	Fixed	0.99(0.90-1.09)	0.771	0.00%	0.458
Hormone Receptor (－ vs. ＋)	6	2049	Fixed	0.94(0.84-1.06)	0.309	0.00%	0.526
HER-2 (－ vs. ＋)	7	2023	Random	0.91(0.76-1.09)	0.293	69.20%	0.003
Molecular subtype (Luminal vs. TriNeg + HER-2+)	8	2143	Fixed	0.99(0.92-1.07)	0.845	15.20%	0.310
Menopausal status (Pre vs. Post)	5	1604	Fixed	0.83(0.76-0.90)	<0.001	50.80%	0.087

Abbreviations: OR: odds ratio; 95% CI: 95% confidence interval; P_h: p values of Q test for heterogeneity test.

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	5
3	Description of study outcome(s)	5
4	Type of exposure or intervention used	5
5	Type of study designs used	5
6	Study population	5
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	6
8	Search strategy, including time period included in the synthesis and key words	5
9	Effort to include all available studies, including contact with authors	6
10	Databases and registries searched	5
11	Search software used, name and version, including special features used (eg, explosion)	5
12	Use of hand searching (eg, reference lists of obtained articles)	5
13	List of citations located and those excluded, including justification	5
14	Method of addressing articles published in languages other than English	5
15	Method of handling abstracts and unpublished studies	5
16	Description of any contact with authors	5
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	6
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	6
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	6
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	6
22	Assessment of heterogeneity	6-7
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6-7
24	Provision of appropriate tables and graphics	26
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	26
26	Table giving descriptive information for each study included	26
27	Results of sensitivity testing (eg, subgroup analysis)	10
28	Indication of statistical uncertainty of findings	10

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	10
30	Justification for exclusion (eg, exclusion of non-English language citations)	26
31	Assessment of quality of included studies	26
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	10-14
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	15
34	Guidelines for future research	15
35	Disclosure of funding source	16

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

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Prognostic Significance of Platelet-Lymphocyte Ratio (PLR) in Breast Cancer Patients Treated with Neoadjuvant Chemotherapy: A Meta-analysis

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Primary Subject Heading:	Oncology
Secondary Subject Heading:	Evidence based practice, Pathology, Pharmacology and therapeutics, Surgery
Keywords:	ONCOLOGY, Breast tumours < ONCOLOGY, Prognosis

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Prognostic Significance of Platelet-Lymphocyte Ratio (PLR) in Breast Cancer Patients Treated with Neoadjuvant Chemotherapy: A Meta-analysis

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Abstract

Objective: PLR (platelet-lymphocyte ratio), known as a key systemic inflammatory parameter, have been proved to be associated with response to neoadjuvant therapy in breast cancer (BC); however, the results remain controversial. This meta-analysis was carried out to evaluate the prognostic values of PLR in breast cancer patients treated with neoadjuvant chemotherapy.

Design: Meta-analysis.

Data sources: Relevant literature published on the following databases: PubMed, Embase, Web of Science databases and the Cochrane Library.

Eligibility criteria: All studies involving patients with breast cancer treated with NACT and peripheral blood pretreatment PLR recorded were included.

Data extraction and synthesis: Two researchers independently extracted and evaluated hazard ratio (HR) /Odds Ratio (OR) and its 95% confidence (CI) of survival outcomes, pathologic complete response (pCR) rate and clinicopathological parameters.

Results: The last search was updated to Dec 31, 2022. A total of 22 studies with 5533 breast cancer patients treated with neoadjuvant chemotherapy were enrolled in the final meta-analysis. Our results demonstrate that elevated PLR value appears to correlate with low pCR rate (HR: 0.77, 95% CI: 0.67-0.88, $p < 0.001$, I^2=75.80%, $P_h < 0.001$) and poor prognosis, including OS (HR: 1.90, 95% CI: 1.39-2.59, $p < 0.001$; I^2= 7.40%, P_h = 0.365) and DFS (HR: 1.97, 95% CI: 1.56-2.50, $p < 0.001$; I^2= 0.0%, P_h = 0.460). Furthermore, PLR level was associated with age (OR: 0.86, 95% CI: 0.79-0.93, $p < 0.001$, I^2= 40.60%, P_h = 0.096), menopausal status (OR: 0.83, 95% CI: 0.76-0.90, $p < 0.001$, I^2= 50.80%, P_h = 0.087) and T stage (OR: 1.05, 95% CI: 1.00-1.11, p = 0.035; I^2= 70.30%, P_h = 0.005) of breast cancer patients.

Conclusions: This meta-analysis demonstrated that high PLR was significantly related to the low pCR rate, poor OS and PFS of breast cancer patients treated with neoadjuvant chemotherapy. Therefore, PLR can be used as a potential predictor biomarker for the efficacy of neoadjuvant chemotherapy in breast cancer.

Strengths and limitations of this study

1. This is the first meta-analysis to assess the role of platelet-lymphocyte ratio (PLR) in predicting pCR rate and survival in BC patients treated with NACT.

2. Scientific and reliable statistical methods were applied.

3. The association between PLR and clinicopathological parameters of BC with NACT were explored in the stratified analysis.

4. All the studies included in this meta-analysis were retrospective and lacked detailed clinicopathological information, which may lead to bias of our results.

Keywords

Platelet, Lymphocyte, PLR, Breast Cancer, Neoadjuvant Chemotherapy, Meta-Analysis

Word count: 8455

Introduction

Breast cancer (BC) is the most frequently diagnosed malignant neoplasm in women worldwide.[1] BC patients in China account for 12.2% of the total number of newly diagnosed and 9.6% of all breast cancer related deaths in the world.[2] About 20-25% of patients are diagnosed with locally advanced breast cancer, which prone to recurrence and metastasis after surgery without any Preoperative treatment.[3, 4] Survival rates for BC patients have increased dramatically due to the development of treatment strategies, such as individualized treatment plans made by multidisciplinary teams, including surgical, radiation and medical oncology.[5] At present, neoadjuvant chemotherapy (NACT) has become the standard and effective treatment for patients with locally advanced breast cancer.[6] The aim of NACT is mainly to reduce tumor size and the stage of tumors, improve tumor operability, and improve the success rates of breast conservative operation.[7-9] Additionally, the effects of NACT could provide information to assess the efficacy of chemotherapy during the treatment.[10] However, not all patients receiving neoadjuvant therapy can achieve therapeutic benefit, especially pathologic complete response (pCR). Previous studies showed that the pCR rate of NACT is about 30% in human epidermal growth factor receptor 2 (HER2) (+) patients, 30-50% in triple negative breast cancer and less than 10% in estrogen receptor (ER) (+) and HER2 (-) breast cancer patients.[11-13] The situation may be related to different pathological types, ER status, HER-2 status, disease stage, and other factors. Some gene mutations, such as PIK3CA, TP53, SIRT5 and CDKN2A, have been proved to be associated with poor response to NACT in breast cancer patients.[14] However, these above biomarkers are expensive and difficult to obtain. Hence, it's necessary to find a convenient, inexpensive and reliable marker, which can predict response after NACT.

It is well recognized that the systemic inflammatory response plays an essential role in breast cancer progression and development.[15, 16] Numerous studies have shown that inflammatory biomarkers such as neutrophil-tolymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and systemic immune-inflflammation index (SII),

are associated with chemosensitivity and prognosis for different malignancies.[17-21] PLR, as one of the most commonly used markers, was proved to be an convenient and cost-effective blood-derived prognostic marker to evaluate the prognosis of breast cancer. Elevated PLR has been linked with poor prognosis for breast cancer in previous studies.[22-24] Furthermore, some research found that a higher PLR may lead to a worse response to NACT for breast cancer patients.[25, 26] However, some other studies showed that the BC patients with higher PLR may achieve more pCR rate after NACT.[27, 28] Thus, the role of PLR as a predictor for outcomes in BC patients after NACT is still not clear. This meta-analysis is aimed to explore the predictive value of PLR in patients with breast cancer treated with NACT.

Materials and Methods

Patient and Public Involvement

None

Literature search

A systematic literature search was conducted based on the following databases: PubMed, Embase, Web of Science databases and the Cochrane Library. The keywords for the search strategy are as follows: ("PLR" or "platelet lymphocyte ratio" or "platelet-to-lymphocyte ratio" or "platelet-lymphocyte ratio") and ("breast cancer", "breast tumor", "breast carcinoma", "breast neoplasms", "mammary cancer") and ("neoadjuvant chemotherapy", "preoperative chemotherapy", "preoperative systemic treatment", "pre-surgical treatment", "primary chemotherapy"). The last search was updated to Dec 31, 2022, and all the articles were limited to English-language. We also used a hand search for the reference list of the retrieved articles in order to identify additional studies. The selection process of the meta-analysis is shown in Figure S1. This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. No patient consent and ethical approval were required in this study.

Inclusion and exclusion criteria

The included studies in this analysis had to meet the following criteria: (1) patients with breast cancer received neoadjuvant treatment and surgery; (2) studies with the peripheral blood pretreatment PLR values; (3) studies with pathologic response status or survival outcomes after neoadjuvant treatment, including pCR, disease-free survival (DFS), overall survival (OS), OR and HR with 95% confidence intervals (CI). The exclusion criteria were as follows: (1) Abstracts, reviews, case studies, letters, non-human subject studies and non-English language studies; (2) breast cancer participants did not receive neoadjuvant treatment; (3) Research with insufficient data.

Data extraction and quality assessment

Two researchers independently reviewed the available literature and extracted data as follows: (1) study details: first author, country, publication year, study design, study period, sample size, median age, outcomes, follow-up time; (2) clinicopathologic parameters: subtype of BC, cut-off value, cut-off method, numbers in high and low PLR groups stratified by age, histologic type, tumor grade, T stage, lymph node metastasis, ki-67 value, hormone receptor status, HER-2 status, molecular subtype, menopausal status; (3) treatment outcomes: numbers in pCR and non-pCR groups, HR with 95% CIs of DFS and OS.

We used the Newcastle Ottawa Scale (NOS) rating scale to assess the quality of the included studies. The studies was scored from 0 to 9 points, based on the object selection, comparability, outcome, and exposure. High-quality literature should have a score of ≥6. If the two researchers had disagreement, a third researcher was invited to achieve a consistent result.

Statistical analysis

All analyses were performed using Stata software version 12.0 (Stata Corporation, College Station, TX, USA), using two-sided P values. Odds ratio (OR) with corresponding 95% CI was used to evaluate the association between PLR and pCR rate, clinicopathological characteristics. Hazard ratios (HR) with corresponding 95% CI was used as an effect measure to assess the relationship between PLR and

DFS, OS. Then the log OR, log HR, and corresponding standard error (SE) were used to compute pooled effect measures. Moreover, stratified analyses were also performed based on ethnicity, cut-off value, cut-off method and sub-type of breast cancer. Both the Cochran's Q statistic and the I^2 statistic were calculated to estimate heterogeneity among the included studies.[29, 30] If the P value of the Q test was <0.05 or I^2 >50%, indicating significant heterogeneity across studies, the pooled OR and HR were calculated by the random effects model (the DerSimonian and Laird method).[31] Otherwise, fixed effects model (the Mantel–Haenszel method) was used.[31] Publication bias was evaluated using Funnel plots and Egger's linear regression test. Sensitivity analyses were performed by omitting each single study to show the influence of the individual data set to the pooled results. $P < 0.05$ was considered statistically significant.

Results

Study characteristics

As shown in the flow diagram (Figure S1), 176 research articles were identified in the preliminary search. After reviewing the titles, abstracts and full texts, 154 studies were excluded according to the search criteria and 22 studies were finally included in the meta-analysis.[22, 25, 26, 28, 32-41] The main characteristics of the included studies are summarized in Table S1. The 22 enrolled studies containing 5533 BC patients were published between 2016 and 2022 with the sample size ranging from 55 to 980. 11 studies were carried out in Asian countries (China and Japan) and the other 11 studies were conducted in Caucasian countries (Turkey, America, Spain, Italy, France and Morocco). All studies were retrospective, with study period ranging from 1996 – 2022. The follow-up time ranged from 3.4 to 124.8 months in these studies, with NOS scores of 6 – 8 points. Most of the study subjects contained all breast cancer types, and included two studies of inflammatory breast cancer, two studies of triple negative breast cancer and one study of Luminal B breast cancer. All patients received standardized neoadjuvant chemotherapy and surgery, with the median age ranged from 45 to 71 years old. Cut-off values for PLR were provided in

21 studies, 6 of which were derived from previous studies and another 15 were obtained from ROC curves.

Association between PLR and pCR of BC

19 studies with 4301 patients reported the correlation between the PLR and pCR.[22, 26, 28, 32-40, 42-48] Our results indicate that high PLR level was significantly associated with low pCR rate (HR: 0.77, 95% CI: 0.67-0.88, p < 0.001), and significant heterogeneity was observed (I^2=75.80%, P_h < 0.001, Table 1, Figure 1). When stratified analyses were performed based on ethnicity, the results showed that Caucasian studies were still statistically significant (HR: 0.77, 95% CI: 0.68-0.88, p < 0.001; I^2=61.60%, P_h = 0.004). On the other hand, there was no statistically significance observed for PLR and pCR among the Asian studies (HR: 0.83, 95% CI: 0.58-1.17, p = 0.288; I^2= 85.00%, P_h < 0.001). Subgroup analysis were also performed to determine the effects of cut-off values and methods on the outcomes. Studies with cut-off value >=150 showed a significant association between the PLR and pCR (HR: 0.78, 95% CI: 0.67-0.91, p = 0.001; I^2= 68.20%, P_h = 0.001), while cut-off values <150 did not achieve statistical significance (HR: 0.80, 95% CI: 0.59-1.10, p = 0.172; I^2= 82.90%, P_h < 0.001). On the other hand, we observed statistically significant relationship between PLR and pCR, no matter the cut-off values obtained from ROC curves (HR: 0.72, 95% CI: 0.57-0.92, p = 0.008; I^2= 81.10%, P_h < 0.001) or previous studies (HR: 0.86, 95% CI: 0.78-0.94, p = 0.001; I^2= 39.30%, P_h = 0.144). Further subgroup analysis was also conducted by tumor subtypes. In the all types group (HR: 0.76, 95% CI: 0.64-0.89, p = 0.001; I^2= 74.00%, P_h < 0.001) and inflammatory breast cancer group (HR: 0.83, 95% CI: 0.70-0.97, p = 0.021; I^2= 0.00%, P_h = 0.368), statistical significance were noted between PLR and pCR. In comparison, studies in the triple negative breast cancer group did not show a significant association (HR: 0.91, 95% CI: 0.26-3.21, p = 0.885; I^2= 94.70%, P_h < 0.001).

Association between PLR and survival of BC

5 studies with 912 patients evaluated the relationship between OS and PLR.[25,

35, 40, 43, 49] The pooled results demonstrated that high PLR was significantly associated with poor OS in patients with breast cancer (HR: 1.90, 95% CI: 1.39-2.59, $p < 0.001$; I^2= 7.40%, P_h = 0.365) (Table 2, Figure S2). Subgroup analyses by ethnicity showed that PLR had significantly prognostic value for OS both in Asian and Caucasian populations (HR: 2.00, 95% CI: 1.19-3.38, p = 0.009, I^2= 56.70%, P_h = 0.128; HR: 1.85, 95% CI: 1.26-2.71, p = 0.002, I^2= 0.0%, P_h = 0.378). Moreover, when stratified by subtypes of breast cancer, the results indicated that the prognostic effect of PLR on OS was similarly significant among the all types group (HR: 1.92, 95% CI: 1.31-2.83, p = 0.001; I^2= 15.30%, P_h = 0.307) and inflammatory breast cancer group (HR: 1.86, 95% CI: 1.11-3.11, p = 0.018; I^2= 48.60%, P_h = 0.163). Furthermore, when considering different cut-off value methods, high PLR significantly predicted shorter OS when cut-off values were conducted by ROC (HR: 2.15, 95% CI: 1.44-3.22, $p < 0.001$; I^2= 19.80%, P_h = 0.288), but did not show significantly prognostic efficiency in the group of cut-off value obtained from previous studies (HR: 1.58, 95% CI: 0.97-2.56, p = 0.065; I^2= 0.0%, P_h = 0.345).

7 studies with 1887 patients analyzed the relationship between the PLR and DFS.[25, 26, 35, 37, 38, 43, 50] The pooled results indicated that DFS was significantly shorter in high PLR group than in low PLR group (HR: 1.97, 95% CI: 1.56-2.50, $p < 0.001$; I^2= 0.0%, P_h = 0.460) (Table 2, Figure S3). We also performed further subgroup analysis based on ethnicity, subtypes of BC and cut-off value methods. Compared with the overall results, no significant changes were identified after stratification, and no significant heterogeneity was observed.

Association between PLR and clinicopathological parameters of BC

To analyze the impact of PLR on the clinicopathological characteristics in breast cancer patients, we pooled the results from included studies according to age, histologic type, tumor grade, T stage, lymph node metastasis, ki-67 value, hormone receptor status, HER-2 status, molecular subtype, menopausal status. As shown in Table S2, young patients and pre-menopausal status patients had significantly higher PLR value than old or post-menopausal status patients (OR: 0.86, 95% CI: 0.79-0.93,

p < 0.001, I^2= 40.60%, P_h = 0.096; OR: 0.83, 95% CI: 0.76-0.90, p < 0.001, I^2= 50.80%, P_h = 0.087). In comparison to low PLR groups, the high PLR groups had a higher T stage (OR: 1.05, 95% CI: 1.00-1.11, p = 0.035; I^2= 70.30%, P_h = 0.005). Whereas the other results indicated no significant association of PLR with histologic type, tumor grade, lymph node metastasis, ki-67 value, hormone receptor status, HER-2 status and molecular subtype.

Sensitivity analysis

Sensitivity analysis results showed that the pooled ORs are not altered materially when deleted a single study each time. The sensitivity analysis plot presented that all the included studies are near the central line with no clear deviation, suggesting that our results were statistically robust (Figure 2A).

Publication bias

Begg's funnel plot and Egger's test were used to evaluate the publication bias of the literature. The funnel plots did not reveal obvious evidence of asymmetry (Figure 2B). Then, the Egger's test still did not show any significant statistical evidence of publication bias (P = 0.862).

Discussion

This meta-analysis assessed the association between pretreatment PLR with pCR and survival on 5533 breast cancer patients treated with neoadjuvant chemotherapy. Our results demonstrate that elevated PLR value appears to correlate with low pCR rate and poor prognosis, including OS and DFS. Consistent with previous studies, our findings suggest that PLR could be a significant prognostic marker for breast cancer patients who received NACT.[26, 35, 37, 40, 43]

Neoadjuvant chemotherapy is increasingly used to treat locally advanced breast cancer, so as to reduce the size of tumors and increase the possibility of breast-conserving surgery.[51] However, there are no ready-made and reliable biomarkers to predict the response to NACT. In recent years, many studies have focused on the relationship between inflammation related biomarkers and tumors. These studies showed that tumor related inflammation, which may contribute to the

tumor growth, invasion and metastasis, was associated with the occurrence, development, and prognosis of cancers.[52, 53] Common components in peripheral blood, such as neutrophils, monocytes, platelets, and lymphocytes, are closely related to the biological behavior of tumor cells.[54] Numerous studies have shown that lymphocytes can inhibit tumor progression and metastasis, which play an important role in tumor immune monitoring.[55, 56] Lymphopenia is commonly seen in immune system defects caused by tumor cells. The possible mechanism is that lymphocytes can control growth of tumor cells through cytotoxicity and induction tumor cell apoptosis.[57] Another research showed that lymphocytes could inhibit tumor cell growth by secreting interferon-gamma and tumor necrosis factor-α.[58] Studies have found that the more infiltrating lymphocyte by tumor, the better prognosis of breast cancer patients.[59, 60] In addition, previous studies have reported that tumor-infiltrating lymphocyte can be used as a predictor of the response to neoadjuvant and adjuvant chemotherapy in breast cancer patients.[61, 62] On the other hand, platelets, as key actors in the process of inflammation, play important roles in tumor progression. Firstly, platelets can protect tumor cells in peripheral blood from high flow shear stress and immune attacks by aggregating and adhering to tumor cells.[63] Secondly, platelets could contribute tumor progression by secreting various cell growth factors, which could stimulate tumor angiogenesis and growth.[64-66] Thirdly, platelets could induce epithelial mesenchymal transition and impede cell-mediated immune clearance effects, leading to the tumor cell metastasis.[67] Therefore, high platelet count may be associated with poor prognosis of breast cancer patients.

Platelet-to-lymphocyte ratio (PLR), as a commonly used indicator of inflammatory status, could predict the prognosis of variant tumors. Elevated value of PLR, with a high platelet count and/or low lymphocyte count, often lead to a low antitumor activity and poor prognosis. Previous studies showed that PLR is significantly related to the survival of colorectal cancer, gastric cancer and liver cancer.[68-70] Gunduz et al. showed that elevated PLR value was associated with

poor DFS in breast cancer.[71] However, Ulas et al. reported that there is no association between PLR and DFS or OS in breast cancer.[72] What's more, when subgroup analysis by different molecular types of breast cancer was performed, Koh et al. found that elevated PLR could result in an increased risk of mortality in ER+ and HER2+ group but not in ER− and HER2+ group.[73] Studies focused on the relationship between PLR and metastatic breast cancer could achieve positive results easily.[74] However, the predictive efficacy of PLR in early stage breast cancer was limited. The possible explanation is that inflammatory reaction may not be so obvious in early breast cancer. Recently, many studies have be devoted to explore whether PLR could be a predictor for locally advanced breast cancer treated with neoadjuvant chemotherapy. Tekyol et al. found that PLR value was associated with chemotherapy sensitivity and could serve as a predictive marker of the therapeutic effect of NACT in breast cancer.[34] Similarly, Ouissam and Ma showed that PLR was associated with OS and DFS in breast cancer treated with NACT.[43, 75] However, some other studies reported that the PLR value has no significant predictive effect on pCR rate, DFS or OS in breast cancer treated with NACT.[25, 49] So far, the above studies indicated that the prognostic role and clinical value of PLR in locally advanced breast cancer with NACT is still controversial.

We conducted this meta-analysis to explore the predictive value of PLR in breast cancer patients treated with NACT. Our results indicate that high PLR level was significantly associated with low pCR rate (HR: 0.77, 95% CI: 0.67-0.88, $p < 0.001$). This finding is consistent with previous studies confirming that PLR may act as a significant marker for predicting the effective of NACT in BC patients.[33, 34, 37] In subgroup analysis, we found that PLR was only significantly associated with Caucasian patients but not Asian patients. The possible explanations were the differences in baseline PLR values due to different genetic backgrounds, different chemotherapy regimens and doses. What's more, the heterogeneity of the Asian group is also more obvious than that of the Caucasian group, which may lead to no significance in the Asian group. Previous studies reported that high PLR value may

indicate a lower pCR rate and poor prognosis of TNBC patients.[46] Subgroup analysis by tumor subtypes in this meta-analysis including two studies showed no significant association between PLR and pCR in the triple negative breast cancer group. One of the reasons for the negative statistical significance is the small number of included studies. On the other hand, TNBC is a heterogeneous disease that includes several subtypes of tumors. There are differences in prognosis among the different subtypes of TNBC.[44] Further more research is needed to evaluate the predictive value of PLR in TNBC treated with NACT. How to identify the optimal critical value for the clinical application of PLR may be a major concern for doctors. Unfortunately, this value has not been determined for predicting the efficacy and prognosis of neoadjuvant therapy in breast cancer patients. Because of the different phase of evaluation of the blood sample or basic blood values of different populations, the cutoff values of PLR were varied. Some studies reported that high PLR was associated with poor prognosis using a cut-off value of 292 and 200,[76, 77] while other studies did not find significant association between PLR and prognosis of breast cancer patients with a cut-off value of 161, 107, and 160, respectively.[22, 37, 78] Different studies use variant cut-off values from different methods. Traditionally, we believe that the ROC curve is the most suitable for getting the optimal cutoff value.[33, 43, 46-48] However, other studies have also achieved significant results using the cut-off values from previous studies.[26, 28, 34] We performed subgroup analysis to determine the effects of cut-off values and methods on the outcomes. The results showed statistically significant relationship between PLR and pCR, no matter the cut-off values obtained from ROC curves or previous studies. This result indicated that the source and method of optimal cut-off values are not the key influence factors for PLR acting as a predictive factor for breast cancer. On the other hand, our results also showed that studies with cut-off value >=150 showed a significant association between the PLR and pCR, while cut-off values <150 did not achieve statistical significance. Therefore, a higher cut-off value for PLR may increase its predictive value for breast cancer patients. However, a higher cut-off value may lead to the

omission of a large number of patient and reduce its predictive sensitivity in clinical practice.[79] Therefore, further researches are needed to determine the optimal cut-off value of PLR for future individualized treatment.

We also evaluated the association between PLR and prognosis of breast cancer patients treated with NACT. Zhang et al. conducted a meta-analysis which including 5542 breast cancer patients with different stages and indicated that high PLR level is significantly associated with poor OS and DFS of breast cancer patients.[80] However, the results were inconsistent when evaluated the prognosis value for NACT. Christophe et al. and Jiang et al. reported that the PLR value has no significant effect on DFS or OS in breast cancer treated with NACT.[25, 49] Contradictory results made by Ileana and Ouissam showed that PLR was associated with OS and DFS in breast cancer treated with NACT.[35, 43] In our study, the pooled results demonstrated that high PLR was significantly associated with poor OS and PFS in patients with breast cancer. Subgroup analyses by ethnicity, method and subtype showed the same results with no significant heterogeneity. The consistency of this result may be due to the fact that the included patients are all local advanced stage patients who have received NACT. Therefore, further studies are needed to evaluate the prognostic value of PLR in different clinical stages and molecular subtypes of breast cancer. What's more, this meta-analysis also explored the association between PLR and clinicopathological characteristics. Our results indicated that high PLR level was more common in young women and patients with premenopausal status. One possible explanation is that young people may have more lymphocyte and platelet reserves and a more sensitive inflammatory state. On the other hand, we also found that elevated PLR is associated with tumor stage, which indicated that PLR may be involved in the occurrence and progression of breast cancer. Some exploration experiments are needed to prove the mechanisms between PLR and breast cancer.

There are still several limitations to be considered in this meta-analysis. First, All of the studies included were retrospective, and some studies have incomplete data, which may have some impact on the final results. Second, the cut-off values of PLR

were inconsistent among the studies, some of them determined the optimum PLR value according to the previous studies instead of using ROC curve. Even if using ROC curve, the different phase of evaluation of the blood sample or basic blood values of different populations may also result in different cutoff values, which may lead to the introduction of selection bias in the meta-analysis. Third, breast cancer is a heterogeneous tumor with many subtypes. The biological behavior, malignant degree and immune response of different subtypes were varied. Variant molecular subtypes of breast cancer respond differently to neoadjuvant therapy, and the heterogeneity of the results may be affected for the lacking of relevant information about molecular typing in most studies. Finally, PLR may be influenced by some factors, including bacterial and viral infections, nutritional state and history of medication. These intrinsic factors were not statistically available and uncontrollable, which were unavoidable sources of heterogeneity in this meta-analysis. Further more studies were needed to accurately focus on the different subtype of breast cancer and provide more detailed clinicopathological information for stratified analysis, which may reduce heterogeneity to some extent.

Conclusions

This study indicated that PLR level was associated with age, menopausal status and T stage of breast cancer patients. In addition, high PLR was significantly related to the low pCR rate, poor OS and PFS of breast cancer patients treated with neoadjuvant chemotherapy. Therefore, PLR can be used as a potential predictor biomarker for the efficacy of neoadjuvant chemotherapy. However, further high quality and well-designed studies with larger samples are needed to identify the optimal cut-off value of PLR and explore the mechanism of PLR with breast cancer.

Abbreviations

HR: hazard ratio; OR: odds ratio; 95% CI: 95% confidence interval; Ph: p values of Q test for heterogeneity test; OS: overall survival; DFS: disease-free survival. PLR: platelet-lymphocyte ratio; BC: breast cancer; NACT: neoadjuvant chemotherapy; ROC: receiver operating characteristic curve; NOS: Newcastle-Ottawa Scale;

Declarations

Ethics approval and consent to participate

All the data supporting our findings in this paper were freely downloaded from the PubMed, EMBASE, Web of Science databases and the Cochrane Library. No ethical approval or written informed consent for participation was required.

Consent for publication

Not applicable.

Availability of data and materials

All data for this study are publicly available and are ready for the public to download at no cost from the official websites of the PubMed, EMBASE, Web of Science databases and the Cochrane Library. There is no need to have the formal permission to use data for this study. The sources and data robustness have been described in the section of "Methods".

Competing interests

The authors declare that they have no competing interests.

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Author Contributions

XQ, JC and XZ were involved in drafting the manuscript. SW and JN made contributions to the concepts, acquisition and analysis of the data. LS was involved in acquisition of data and preparing the Figs. LY and CJ designed and revised the manuscript. All authors have read and approved the final manuscript.

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Table 1. Meta-analysis of the association between PLR and pCR of BC with NACT.

Factors	No. of studies	No. of patients	Effects model	OR (95% CI)	p	Heterogeneity	
						I^2	P_H
Overall	19	4301	Random	0.77(0.67-0.88)	<0.001	75.80%	<0.001
Ethnicity							
Caucasian	11	2350	Random	0.77(0.68-0.88)	<0.001	61.60%	0.004
Asian	8	1951	Random	0.83(0.58-1.17)	0.288	85.00%	<0.001
Method							
Previous study	6	984	Fixed	0.86(0.78-0.94)	0.001	39.30%	0.144
ROC	12	2337	Random	0.72(0.57-0.92)	0.008	81.10%	<0.001
Subtype							
All	14	2964	Random	0.76(0.64-0.89)	0.001	74.00%	<0.001
IBC	2	177	Fixed	0.83(0.70-0.97)	0.021	0.00%	0.368
TNBC	2	180	Random	0.91(0.26-3.21)	0.885	94.70%	<0.001
Luminal B	1	980	Fixed	0.76(0.61-0.94)	0.013	—	—
Cut-off							
<150	9	2041	Random	0.80(0.59-1.10)	0.172	82.90%	<0.001
>=150	9	1280	Random	0.78(0.67-0.91)	0.001	68.20%	0.001

Abbreviations: ROC: receiver operating characteristic curve; IBC: inflammatory breast cancer; TNBC: triple negative breast cancer; OR: odds ratio; 95% CI: 95% confidence interval; P_h: p values of Q test for heterogeneity test.

Table 2. Meta-analysis of the association between PLR and OS, DFS of BC with NACT.

	Factors	No. of studies	No. of patients	Effects model	HR (95% CI)	p	Heterogeneity	
							I^2	P_H
OS	**Overall**	5	912	Fixed	1.898(1.394-2.586)	<0.001	7.40%	0.365
	Ethnicity							
	Caucasian	3	383	Fixed	1.845(1.258-2.706)	0.002	0.00%	0.378
	Asian	2	529	Fixed	2.002(1.187-3.377)	0.009	56.70%	0.128
	Method							
	Previous study	2	281	Fixed	1.579(0.973-2.564)	0.065	0.00%	0.345
	ROC	3	631	Fixed	2.153(1.442-3.216)	<0.001	19.80%	0.288
	Subtype							
	All	3	735	Fixed	1.922(1.306-2.828)	0.001	15.30%	0.307
	IBC	2	177	Fixed	1.857(1.110-3.109)	<0.018	48.60%	0.163
DFS	**Overall**	7	1887	Fixed	1.972(1.557-2.499)	<0.001	0.00%	0.460
	Ethnicity							
	Caucasian	3	383	Fixed	2.001(1.415-2.831)	<0.001	0.00%	0.568
	Asian	4	1504	Fixed	1.948(1.409-2.692)	<0.001	33.90%	0.209
	Method							
	Previous study	3	458	Fixed	1.990(1.374-2.884)	<0.001	0.00%	0.513
	ROC	3	449	Fixed	2.544(1.614-4.010)	<0.001	1.50%	0.362
	Subtype							
	All	4	730	Fixed	2.260(1.576-3.240)	<0.001	0.00%	0.407
	IBC	2	177	Fixed	2.086(1.295-3.361)	0.003	6.50%	0.301
	Luminal B	1	980	Fixed	1.576(1.039-2.390)	0.032	—	—

Abbreviations: ROC: receiver operating characteristic curve; IBC: inflammatory breast cancer; HR: hazard ratio; 95% CI: 95% confidence interval; P_h: p values of Q test for heterogeneity test.

Figure legends

Figure 1: The forest plot between elevated PLR and pCR in BC with NACT. The results showed that high PLR is significantly related to the low pCR rate.

Figure 2: Sensitivity analysis and Begg's funnel plot of publication bias test of PLR for pCR in BC with NACT. (A): Sensitivity analysis plot showed that all the included studies are near the central line with no clear deviation, suggesting that the results are statistically robust. (B): The funnel plots did not reveal obvious evidence of asymmetry.

Supplemental files

Table S1. Characteristics of included studies in meta-analysis.

Table S2. Meta-analysis of the association between PLR and clinicopathological parameters of BC with NACT.

Figure S1: The flow diagram of publications selection.

Figure S2: The forest plot between elevated PLR and OS in BC with NACT.

Figure S3: The forest plot between elevated PLR and DFS in BC with NACT.

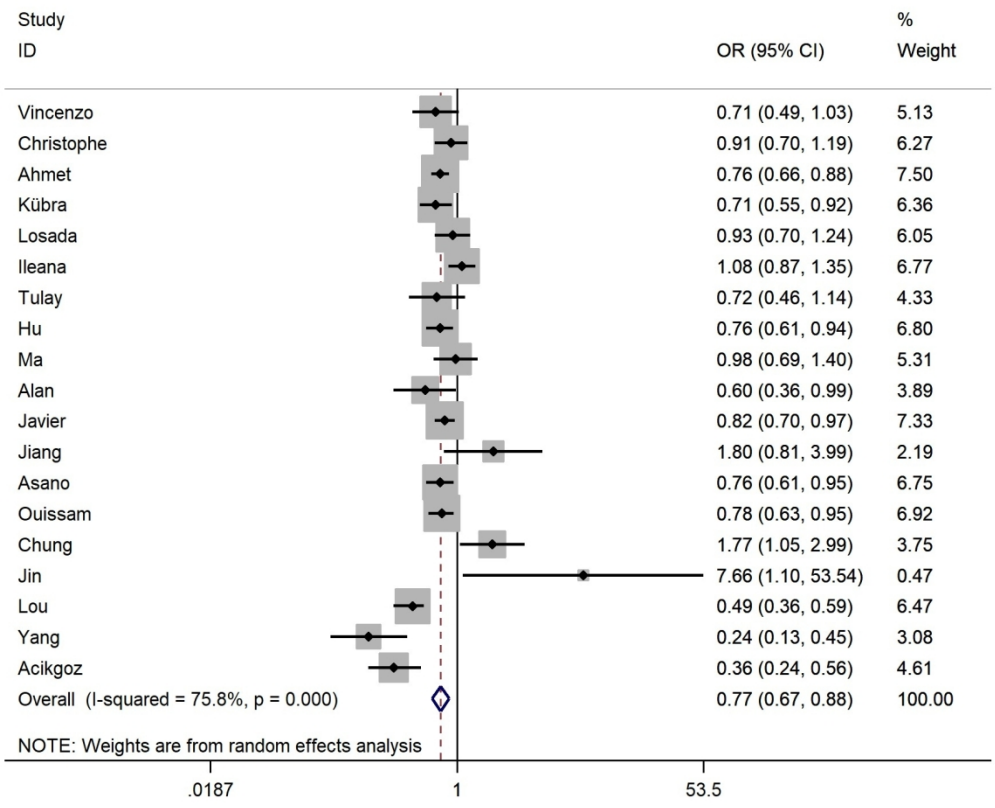

Figure 1

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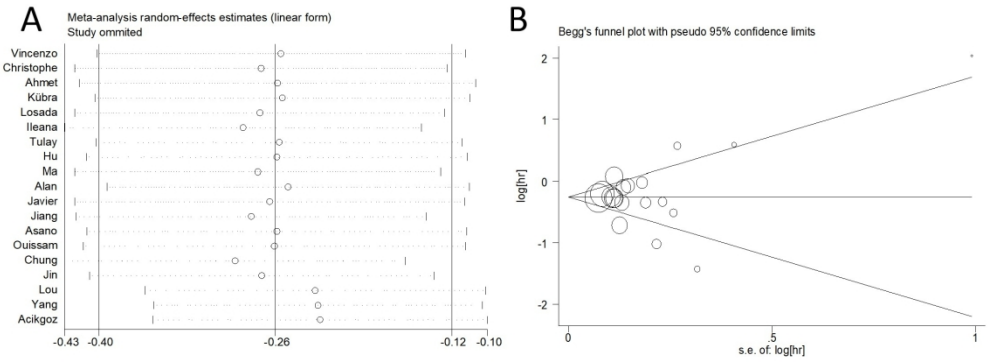

Figure 2

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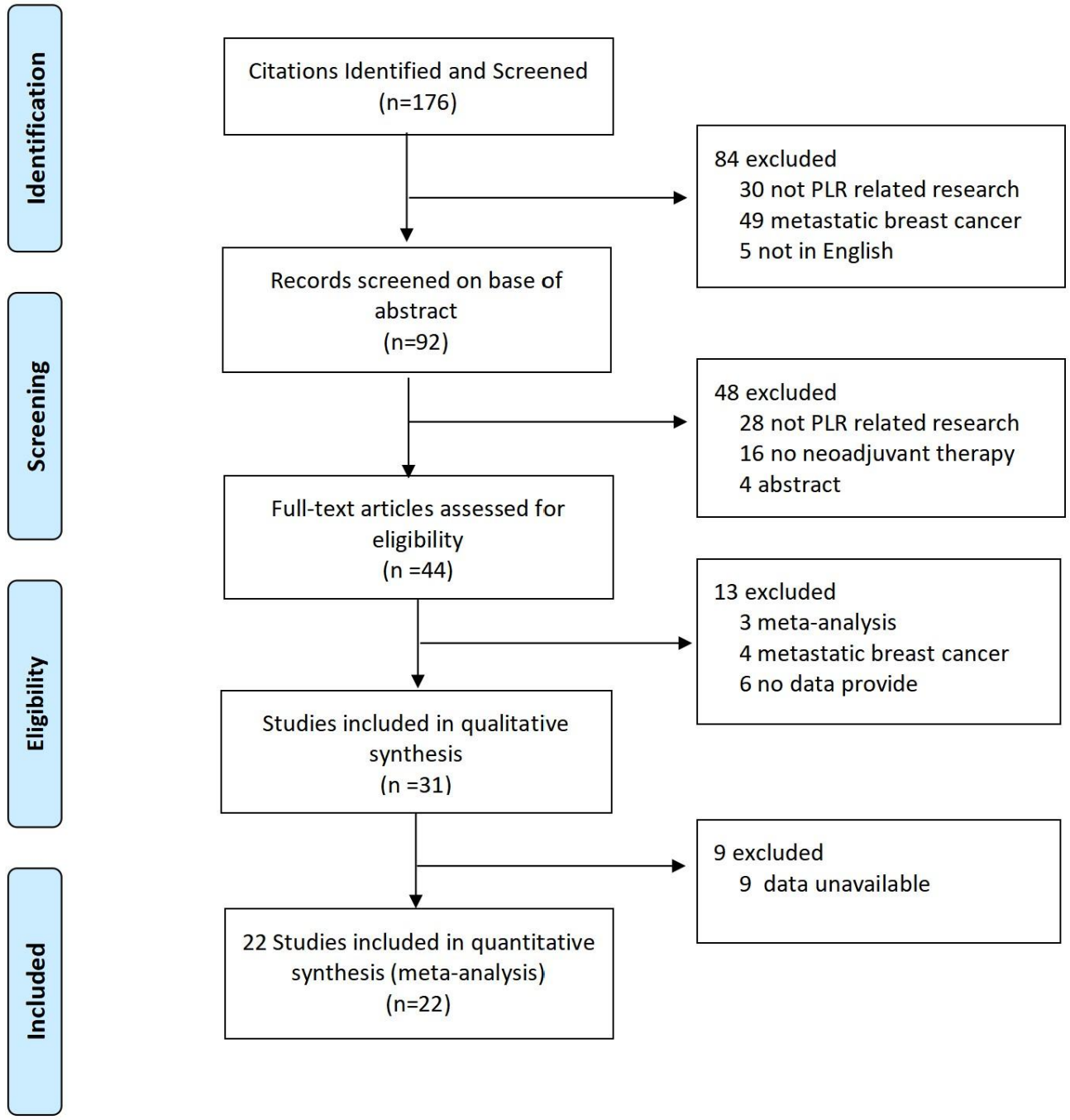
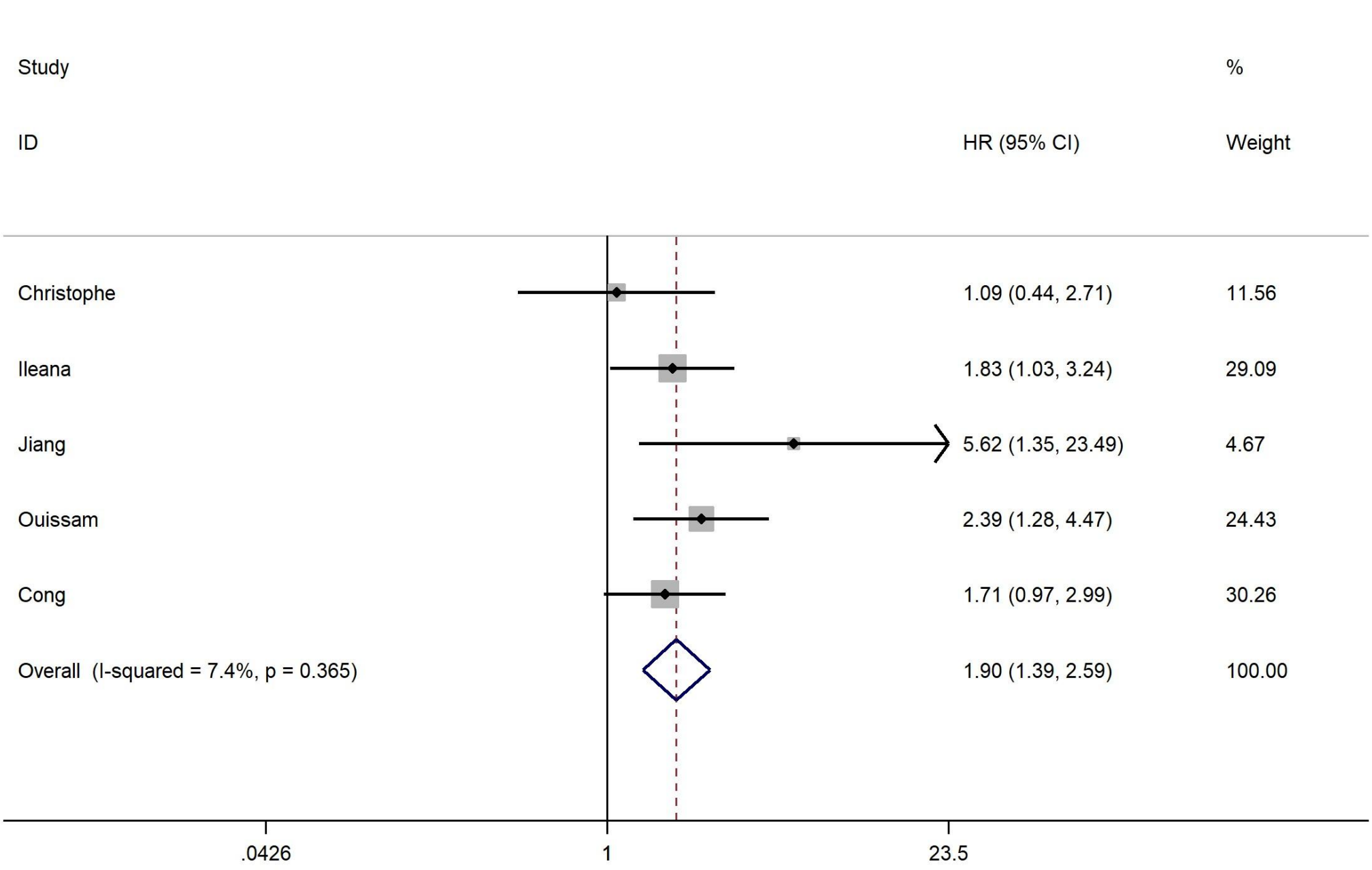

Identification
Screening
Eligibility
Included
Citations Identified and Screened
(n=176)
84 excluded
30 not PLR related research
49 metastatic breast cancer
5 not in English
Records screened on base of abstract
(n=92)
48 excluded
28 not PLR related research
16 no neoadjuvant therapy
4 abstract
Full-text articles assessed for eligibility
(n =44)
13 excluded
3 meta-analysis
4 metastatic breast cancer
6 no data provide
Studies included in qualitative synthesis
(n =31)
9 excluded
9 data unavailable
22 Studies included in quantitative synthesis (meta-analysis)
(n=22)


Study
ID
HR (95% CI)
%
Weight
Christophe
1.09 (0.44, 2.71)
11.56
Ileana
1.83 (1.03, 3.24)
29.09
Jiang
5.62 (1.35, 23.49)
4.67
Ouissam
2.39 (1.28, 4.47)
24.43
Cong
1.71 (0.97, 2.99)
30.26
Overall (I-squared = 7.4%, p = 0.365)
1.90 (1.39, 2.59)
100.00
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1
23.5

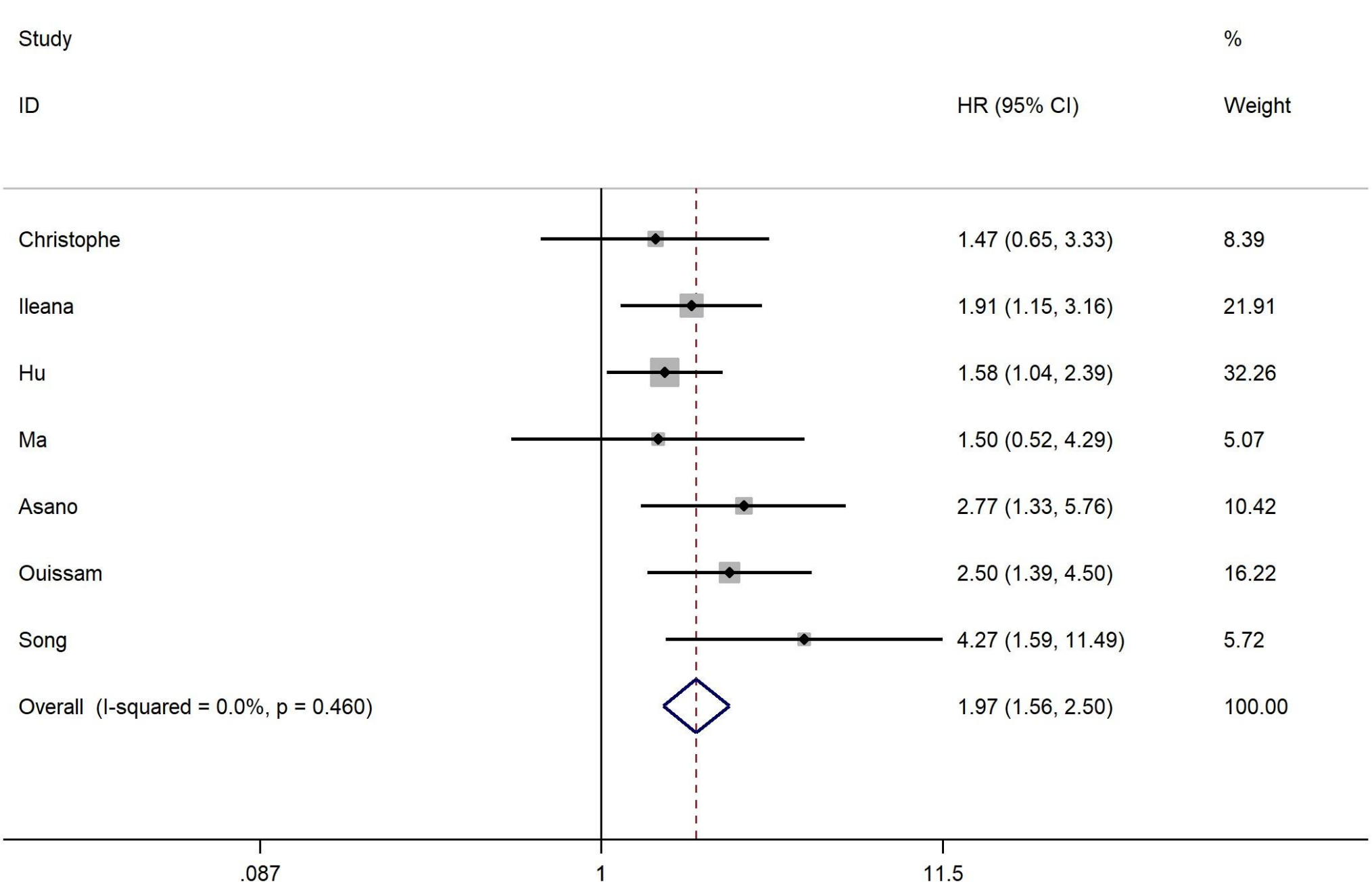
Study
ID
HR (95% CI)
%
Weight
Christophe
1.47 (0.65, 3.33)
8.39
Ileana
1.91 (1.15, 3.16)
21.91
Hu
1.58 (1.04, 2.39)
32.26
Ma
1.50 (0.52, 4.29)
5.07
Asano
2.77 (1.33, 5.76)
10.42
Ouissam
2.50 (1.39, 4.50)
16.22
Song
4.27 (1.59, 11.49)
5.72
Overall (I-squared = 0.0%, p = 0.460)
1.97 (1.56, 2.50)
100.00
.087
1
11.5

Table S1. Characteristics of included studies in meta-analysis.

NO.	Author	Year	Country	Ethnicity	Study design	Study period	Subtype	Patients (n)	Median age (years)	Follow-up (month)	Cut-off value	Method	Outcomes	NOS score
1	Asano	2016	Japan	Asian	retrospective	2007-2013	All	177	NA	3.4 (0.6-6.0)	150	Previous study	pCR/DFS	8
2	Vincenzo	2018	Italy	Caucasian	retrospective	1999-2018	All	373	50 (26-82)	NA	104.47	ROC	pCR	6
3	Losada	2018	Spain	Caucasian	retrospective	2004-2018	All	104	71 (65-89)	48 (6-149）	150	Previous study	pCR/DFS	8
4	Javier	2018	America	Caucasian	retrospective	2013-2016	All	272	51 (27-85)	NA	150	Previous study	pCR	6
5	Peng	2019	China	Asian	retrospective	2013-2017	All	808	50 (20-72)	NA	151.3	ROC	pCR+PR	6
6	Ileana	2020	France	Caucasian	retrospective	2005-2013	All	206	50.3 (25.3-76.6)	80.4 (2.4-135.6)	150	Previous study	pCR/OS/DFS	8
7	Tulay	2020	Turkey	Caucasian	retrospective	2009-2018	All	131	49 (23-74)	NA	119	ROC	pCR	6
8	Hu	2020	China	Asian	retrospective	2012-2016	Luminal B	980	NA	37 (5-77)	NA	NA	pCR/DFS	8
9	Alan	2020	Turkey	Caucasian	retrospective	2015-2017	All	55	48.5 (27-80)	41 (15-49)	225.3	ROC	pCR	7
10	Jiang	2020	China	Asian	retrospective	2014-2018	All	249	51	4-72	88.23	ROC	pCR/OS	8
11	Christophe	2021	France	Caucasian	retrospective	1996-2016	IBC	75	NA	124.8 (68.5-166.8)	150	Previous study	pCR/OS/DFS	8
12	Ahmet	2021	Turkey	Caucasian	retrospective	2008-2019	All	743	48 (22.0-83.5)	67.5 (10.5-194.4)	131.8	ROC	pCR	7
13	Kübra	2021	Turkey	Caucasian	retrospective	2016-2020	All	150	45.6	NA	150	Previous study	pCR	6
14	Ma	2021	China	Asian	retrospective	2017-2018	All	203	NA	31 (1-39)	135	ROC	pCR/DFS	8
15	Ouissam	2021	Morocco	Caucasian	retrospective	2010-2014	IBC	102	49 (29-88)	NA	178	ROC	pCR/OS/DFS	7
16	Cong	2022	China	Asian	retrospective	2012-2016	All	280	49	NA	155	ROC	pCR/OS	7
17	Chung	2022	China	Asian	retrospective	2012-2019	TNBC	88	51	NA	148.14	ROC	pCR	6
18	Jin	2022	China	Asian	retrospective	2014-2019	All	67	51 (27-81)	NA	106.3	ROC	pCR	6
19	Song	2022	China	Asian	retrospective	2016-2018	All	144	50.4	32 (1-40)	158.365	ROC	DFS	8
20	Lou	2022	China	Asian	retrospective	2015-2018	TNBC	92	52.3 (29-67)	NA	141.36	ROC	pCR	6
21	Yang	2022	China	Asian	retrospective	2020-2022	All	95	NA	NA	118.78	ROC	pCR	6
22	Acikgoz	2022	Turkey	Caucasian	retrospective	2014-2019	All	139	45 (25-75)	39.5 (7.5-93)	181.7	ROC	pCR	7

Abbreviations: NA: not available; OS: overall survival; DFS: disease-free survival; pCR: pathologic complete response; ROC: receiver operating characteristic curve; NOS: Newcastle-Ottawa Scale.

Table S2. Meta-analysis of the association between PLR and clinicopathological parameters of BC with NACT.

Variable	No. of studies	No. of patients	Effects model	OR (95% CI)	p	Heterogeneity I^2	Heterogeneity P_H
Age (Yong vs. Old)	9	3273	Fixed	0.86(0.79-0.93)	<0.001	40.60%	0.096
Histologic type (Ductal vs. Others)	4	1520	Fixed	0.97(0.94-1.01)	0.147	7.20%	0.357
Grade (G1+G2 vs. G3+unknown)	4	1692	Fixed	0.96(0.91-1.02)	0.203	0.00%	0.439
T stage (T1–T2 vs. T3–T4)	6	2178	Random	1.05(1.00-1.11)	0.035	70.30%	0.005
Lymph node metastasis (No vs. Yes)	5	2341	Fixed	0.97(0.88-1.06)	0.440	0.00%	0.952
ki-67 (<14 vs. >=14)	7	2783	Fixed	0.99(0.90-1.09)	0.771	0.00%	0.458
Hormone Receptor (－ vs. ＋)	6	2049	Fixed	0.94(0.84-1.06)	0.309	0.00%	0.526
HER-2 (－ vs. ＋)	7	2023	Random	0.91(0.76-1.09)	0.293	69.20%	0.003
Molecular subtype (Luminal vs. TriNeg + HER-2+)	8	2143	Fixed	0.99(0.92-1.07)	0.845	15.20%	0.310
Menopausal status (Pre vs. Post)	5	1604	Fixed	0.83(0.76-0.90)	<0.001	50.80%	0.087

Abbreviations: OR: odds ratio; 95% CI: 95% confidence interval; P_h: p values of Q test for heterogeneity test.

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	5
3	Description of study outcome(s)	5
4	Type of exposure or intervention used	5
5	Type of study designs used	5
6	Study population	5
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	6
8	Search strategy, including time period included in the synthesis and key words	5
9	Effort to include all available studies, including contact with authors	6
10	Databases and registries searched	5
11	Search software used, name and version, including special features used (eg, explosion)	5
12	Use of hand searching (eg, reference lists of obtained articles)	5
13	List of citations located and those excluded, including justification	5
14	Method of addressing articles published in languages other than English	5
15	Method of handling abstracts and unpublished studies	5
16	Description of any contact with authors	5
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	6
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	6
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	6
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	6
22	Assessment of heterogeneity	6-7
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6-7
24	Provision of appropriate tables and graphics	26
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	26
26	Table giving descriptive information for each study included	26
27	Results of sensitivity testing (eg, subgroup analysis)	10
28	Indication of statistical uncertainty of findings	10

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	10
30	Justification for exclusion (eg, exclusion of non-English language citations)	26
31	Assessment of quality of included studies	26
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	10-14
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	15
34	Guidelines for future research	15
35	Disclosure of funding source	16

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

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