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Review

Prognostic Significance of Platelet-to-Lymphocyte Ratio in Patients With Triple-negative Breast Cancer: Systematic Review and Meta-Analysis

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Abstract

Background/Aim: The platelet-to-lymphocyte ratio (PLR), a systemic inflammatory biomarker, has been linked to treatment response in breast cancer (BC). However, its prognostic value in triple-negative breast cancer (TNBC) remains unclear. This meta-analysis evaluated the association between PLR and survival outcomes in patients with TNBC.

Materials and Methods: This study was registered on PROSPERO in January 2024 under protocol number CRD42024506786. Databases searched were PubMed, Embase and Cochrane Library in December 2024. Hazard ratios (HRs) with 95% confidence intervals (CIs) were pooled to evaluate the association between PLR and overall (OS), progression-free (PFS), and disease-free (DFS) survival. Heterogeneity was assessed using I^2 statistics.

Results: Six studies with 819 patients with TNBC were included. PLR cut-off values were reported in five studies, determined either from previous research or receiver operating characteristic curves. A high PLR was not significantly associated with OS (HR=1.35, 95% CI=0.99-1.84; p=0.06; I^2=43%). However, after excluding a high-risk bias study, high PLR was associated with reduced OS (HR=1.55, 95% CI=1.21-2.00; p=0.006; I^2=0%). PLR was not significantly associated with PFS (HR=1.73, 95% CI=0.69-4.33; p=0.24; I^2=79%) but was significantly associated with lower DFS (HR=1.69, 95% CI=1.25-2.28; p=0.0006; I^2=0%).

continued

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Conclusion: While PLR was not significantly associated with OS or PFS, it correlated with DFS in TNBC: These findings suggest that PLR may have prognostic value, but further large-scale studies are needed to establish its clinical utility and optimal cut-off values.

Keywords: Platelet-to-lymphocyte ratio, triple-negative breast cancer, prognosis, survival outcomes, review.

Introduction

Breast cancer (BC) is the most frequently diagnosed malignancy in women worldwide. Triple-negative breast cancer (TNBC), a highly aggressive BC subtype lacking estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2 overexpression, accounts for 10-24% of all BC cases (1, 2). Due to the absence of targeted receptors, TNBC treatment is largely limited to chemotherapy, and prognosis remains poor (3-5). Recent advancements in chemotherapy, targeted therapies, and immunotherapy have shown promise; however, challenges persist regarding their clinical optimization and application (6).

Increasing evidence highlights the critical role of inflammatory and nutritional status in cancer progression, treatment response, and survival (7, 8). This has led to the identification of various prognostic biomarkers, such as the Royal Marsden Hospital score (8) or tumourr-infiltrating lymphocytes (TILs). TILs are well-established predictive and prognostic biomarkers for the efficacy of neoadjuvant chemotherapy (NACT) in patients with BC: However, their assessment relies on invasive pathological analysis, making them less practical for routine clinical use (9). In contrast, peripheral blood markers, such as neutrophils, monocytes, platelets, and lymphocytes, offer a non-invasive alternative and are closely linked to tumourr biology (10, 11).

A recent meta-analysis evaluated the prognostic significance of the platelet-to-lymphocyte ratio (PLR) in patients with BC receiving NACT. High PLR was linked to a lower pathological complete response rate and poorer overall (OS) and disease-free (DFS) survival in patients with BC (12). However, a subgroup analysis specifically for TNBC was not performed.

Given the unique biological characteristics of TNBC and the growing interest in inflammation-based prognostic markers, this meta-analysis aimed to assess the association between PLR and survival outcomes in patients with TNBC treated with NACT, providing further insights into its prognostic value in this high-risk BC subtype.

Materials and Methods

This meta-analysis was performed in accordance with the recommendations of the Cochrane Collaboration, directed by Preferred Reporting Items for Systematic Reviews and Meta-Analysis (13, 14). This study was registered on PROSPERO in January 2024 under protocol number CRD42024506786.

Eligibility criteria and endpoints. The inclusion criteria were as follows: (i) Enrollment of patients with TNBC; and (ii) assessment of the primary outcome of OS or any of the following secondary outcomes of interest: DFS, progression-free survival (PFS). Exclusion criteria were: (i) Exclusion of the population of interest; (ii) no outcomes of interest; (iii) conference abstracts or ongoing trials; and (iv) language other than English, Spanish or Portuguese. There were no exclusions based on the population size.

Search strategy and data extraction. We systematically searched PubMed, Embase, and Cochrane Library on December 2024, with the following search strategy: ("blood biomarkers" OR "NLR" OR "MLR" OR "peripheral blood indices" OR "PLR" OR "Neutrophil-Lymphocyte Ratio" OR “platelet-to-lymphocyte” OR "platelet-to-lymphocyte ratio") AND ("triple-negative breast cancer" OR "TNBC"). No publication date restrictions were applied

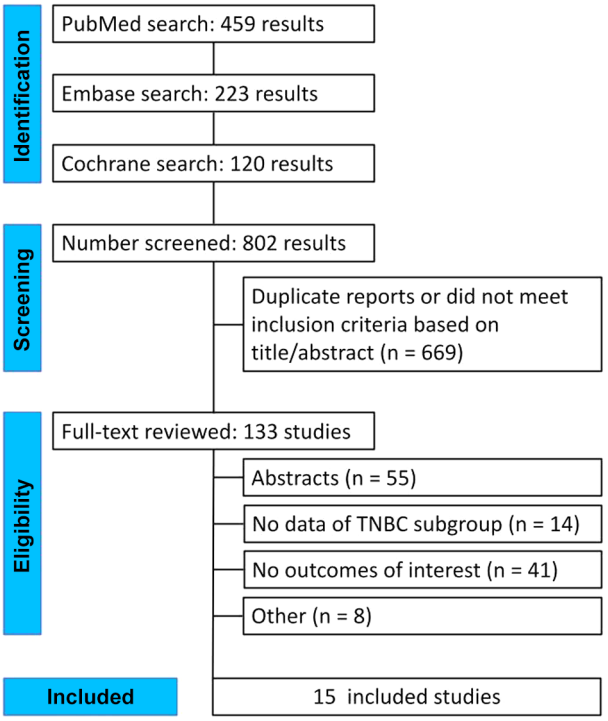

Figure 1. *PRISMA flow diagram of study screening and selection.*

in the systematic search. We also searched the references from included studies, previous systematic reviews, and meta-analyses for additional studies.

Two Authors (V.A. and M.L.R.D.) independently conducted the search, performed the screening, and extracted data following pre-defined search criteria. Disagreements between these Authors were resolved by consensus.

Quality assessment. The methodological quality assessment of prognostic articles was performed by estimating the risk of bias using the Quality in Prognosis Studies (QUIPS) tool (15). The QUIPS tool consists of six domains: Study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis. Based on these risk-of-bias domains, each study was deemed to have a low, moderate or high risk of bias. This assessment was performed independently by two investigators (V.A and M.L.R.D) using a single uniform data extraction sheet. Disagreements were resolved by consensus.

Statistical analysis. Hazard ratios (HR) were used to compare outcomes with the corresponding 95% confidence intervals (CI). We considered values $p<0.05$ as statistically significant. To assess heterogeneity, Cochran's Q test and I^2 statistics were used. Values of $p>0.10$ and $I^2<25\%$ were considered to represent low heterogeneity. The DerSimonian and Laird random-effects model were used for all outcomes. We conducted a leave-one-out sensitivity analysis in the presence of significant heterogeneity ($I^2>25\%$). The leave-one-out sensitivity analyses were performed by systematically removing each study from the pooled estimate. When the included studies did not provide the mean and standard deviation, and data were not significantly skewed, we estimated their values using the method by Wan and Luo (16). Review Manager 5.4 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and R version 4.3.2 (17) for statistical analyses.

Results

Study selection and characteristics. The search strategy yielded 802 results. After removing duplicate records and screening titles and abstracts, 133 studies were fully reviewed. Nine studies were included in the systematic review and six in the meta-analysis, as detailed in Figure 1.

Study characteristics. The main characteristics of the studies are shown in Table I. Six studies containing 819 patients with TNBC were published between 2016 and 2023, with the sample size of each ranging from 62 to 278. Four studies were conducted in China and the other two in Italy and Poland. All studies were retrospective. The follow-up time ranged from 12 to 59 months. Most of the study patients had early-stage TNBC. Cut-off values for PLR were provided in five studies, two of which were derived from previous studies, and another three were obtained from receiver operating characteristic curve (ROC) analyses.

Quality assessment. QUIPS tool identified one study at high risk of bias due to prognostic factor measurement (18)

Table I. *Baseline characteristics of included studies.*

Study (reference)	Year	Country	Patients with TNBC, n	Median follow-up, months	Median age, years	PLR cut-off	TNM stage III, %	M0 status, %	BMI ≥25 kg/m^2, %	Premeno-pausal, %
Li *et al.* (18)	2022	China	278	24	65	NA	9.35	42.08*	NA	33.45
Liu *et al.* (19)	2016	China	161	58.1	45	147	37.1†	100†	NA	NA
Oraczewski *et al.* (20)	2022	Poland	143	53.3	58	185	31	92	64	NA
Vernieri *et al.* (21)	2018	Italy	62	12	56	200	0*	0	NA	NA
Zenan *et al.* (22)	2018	China	94	59	NA	136.6	14.9	100	NA	NA
Zhang *et al.* (23)	2023	China	81	26.3	51	152.3	0	0	30.2	NA

BMI: Body mass index; M0: no distant cancer spread; NA: not available; PLR: platelet-to-lymphocyte ratio; TNBC: triple-negative breast cancer; TNM: tumor/nodes/metastasis staging system, American Joint Committee on Cancer classification. *Values are propensity score-matched. †Value for the entire population.

and five studies at moderate risk of bias due to confounding adjustment (19-23) (Figure 2).

Pooled analysis of all studies. Association between PLR and OS. Six studies comprising 819 patients evaluated the correlation between PLR and overall survival (OS), although the direction of the correlation varied across studies (18-23). Our results indicate that a high PLR was not significantly associated with the OS rate (HR=1.35, 95% CI=0.99-1.84; p=0.06; Figure 3). Moderate heterogeneity was observed (I^2=43%).

The significant heterogeneity found can most likely be attributed to the different duration of follow-up between the studies, which ranged from 12 to 59 months, and the heterogeneous cut-off value of PRL, which ranged from 136.6 to 200. Notably, the study by Li *et al.* (18) had a high risk of bias. Exclusion of this study resulted in a significant decrease of the OS rate in the group with high PRL (HR=1.55, 95% CI=1.21-2.00; p=0.006 and I^2=0%) (Figure 4). Li *et al.* (18) reported a higher median age of participants and determined the cut-off for PLR as the median value without specifying it. Conversely, the other studies utilized ROC analysis (19, 22-23) or referenced literature (20, 21) to establish the optimal PLR cut-off. It is also important to note Li *et al.* (18) was the study with the highest number of patients.

Subgroup analysis of patients only with metastatic TNBC (21, 23) indicated a significant decrease in OS rate in the group with a high PRL level (HR=1.84, 95% CI=1.21-2.81; p=0.004; I^2=0%).

Subgroup analysis of Chinese populations only was also performed (18, 19, 22, 23), and a high PRL was not significantly associated with low OS (HR=1.37, 95% CI=0.85-2.19; p=0.19; I^2=62%). When we eliminated the study of Li *et al.* (18) a high PRL was significantly associated with low OS (HR=1.72, 95% CI=1.25-2.36; p=0.0008; I^2=0%).

Subgroup analysis of the Caucasian population (20, 21) showed a high PRL was not significantly associated with low OS (HR=1.30, 95% CI=0.86-1.97; p=0.21; I^2=0%).

Association between PLR and DFS. Only two studies with 255 patients reported correlation between PLR and DFS (19, 22). Our results indicate that a high PLR was significantly associated with a low DFS rate (HR=1.69, 95% CI=1.25-2.28; p=0.0006; Figure 5), and no significant heterogeneity was observed (I^2=0%).

Association between PLR and PFS. Only two studies with 340 patients reported a correlation between PLR and PFS (18, 21). Our results indicate that high PLR level was not significantly associated with low PFS rate (HR=1.73, 95% CI=0.69-4.33, p=0.24; Figure 6), and significant heterogeneity was observed (I^2=79%). Of note, Vernieri *et al.* (21) was an Italian study that had a population with metastatic disease only while that of Li *et al.* (18) had all the limitations already described.

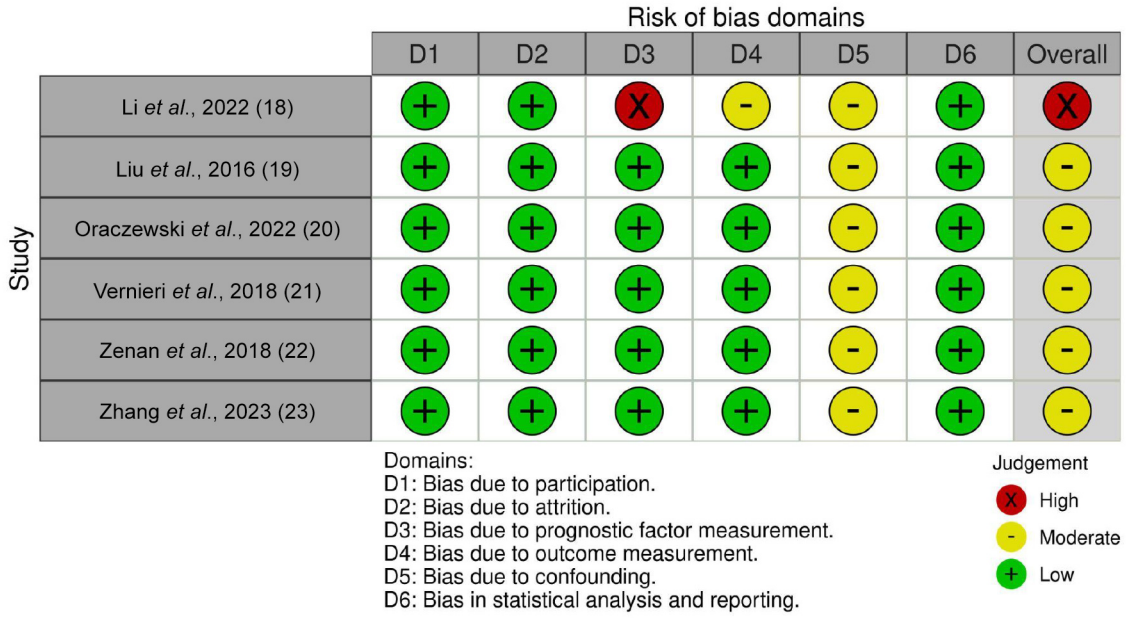

Figure 2. *Quality assessment of included studies.*

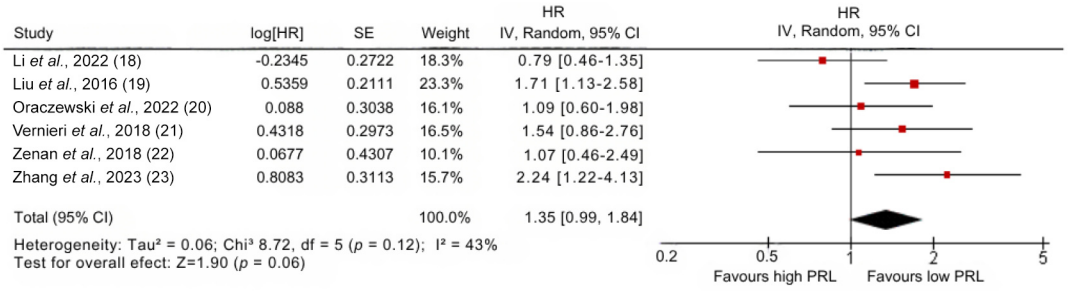

Figure 3. *Forest plot of overall survival in the included studies. CI: Confidence interval; HR: hazard ratio; IV: interval variance; PRL: platelet-to-lymphocyte ratio; SE: standard error.*

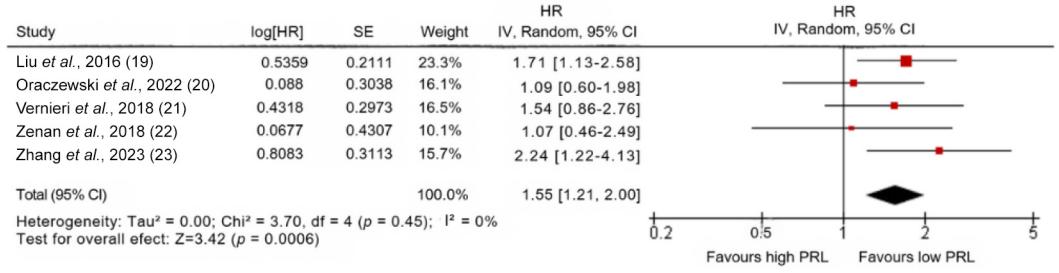

Figure 4. *Forest plot of overall survival without the study of Li et al. 2022 (18). CI: Confidence interval; HR: hazard ratio; IV: interval variance; PRL: platelet-to-lymphocyte ratio; SE: standard error.*

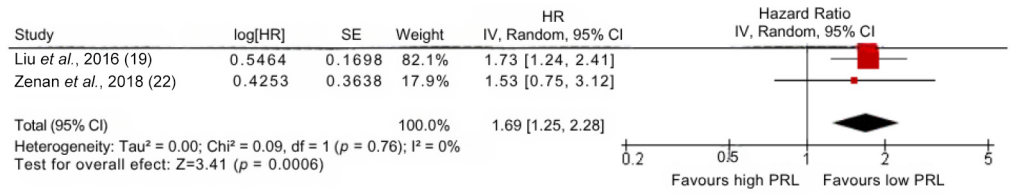

Figure 5. *Forest plot of disease-free survival. CI: Confidence interval; HR: hazard ratio; IV: interval variance; PRL: platelet-to-lymphocyte ratio; SE: standard error.*

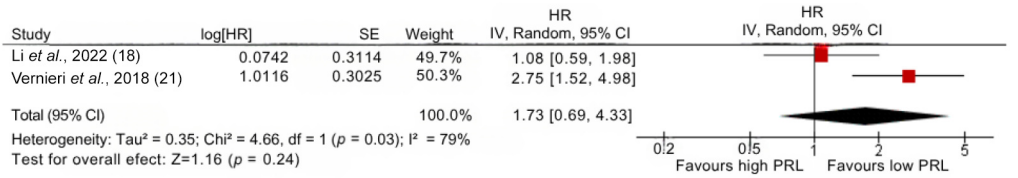

Figure 6. *Forest plot of progression-free survival according to PRL. CI: Confidence interval; HR: hazard ratio; IV: interval variance; PRL: platelet-to-lymphocyte ratio; SE: standard error.*

Discussion

This systematic review and meta-analysis evaluated the prognostic role of PLR in 819 patients with TNBC: Our findings indicate a high PLR to be significantly associated with reduced DFS but not with OS or PFS: However, when excluding a study with a high risk of bias, a high PLR was significantly associated with reduced rates of both OS and PFS but improved DFS: Subgroup analysis indicated a significant association between PLR and survival in Chinese patients, whereas no significant association was observed among Caucasian patients.

These results suggest that PLR may have prognostic potential under specific conditions – such as in certain patient subgroups or populations – particularly in relation to DFS. However, our findings also revealed inconsistencies, with some studies showing improved DFS and others showing reduced DFS associated with PLR: This heterogeneity underscores the complexity of interpreting immune biomarkers like PLR, which do not fully capture the intricacies of the tumor immune microenvironment. Compared to TILs, which require invasive assessment, PLR is a non-invasive and cost-effective marker that may support risk stratification. Nonetheless, its prognostic value in TNBC remains inconclusive and requires further validation.

Several studies have evaluated PLR as a prognostic marker in patients with BC receiving NACT (13, 18-32), although most included all BC subtypes rather than focusing on TNBC: Our findings suggest that PLR does not significantly predict OS or PFS in TNBC but is significantly associated with DFS: Notably, after excluding the study with a high risk of bias (18), PLR was significantly associated with poorer OS and PFS, along with improved DFS.

Conflicting findings in the literature highlight the need for standardized methodologies in assessing the prognostic role of PLR. For example, Lusho *et al.* found no significant association between PLR and TNBC prognosis (31), while Lou *et al.*, using a cut-off value derived from ROC analysis, identified PLR as a significant predictor in TNBC (30). However, neither study provided data on OS, DFS, or pathological complete response in relation to PLR specifically for patients with TNBC – critical information for our analysis. We reached out to multiple authors for clarification but did not receive a response. These discrepancies underscore the influence of methodological variations in PLR threshold determination and patient selection criteria.

Our subgroup analysis revealed that PLR was significantly associated with survival outcomes in Chinese patients but not in Caucasian patients [after excluding the study of Li *et al.* (18)]. This may be attributed to genetic differences, variations in baseline PLR, and differences in chemotherapy regimens. Additionally, racial disparities in adipose tissue distribution and inflammatory response may influence immune-related biomarkers such as PLR (33).

Study limitations. The limited number of patients included may have reduced the statistical power of our analysis. All included studies were observational, making them susceptible to confounding factors. Significant heterogeneity was observed in the PLR cut-off values, with some studies deriving them from previous research and others using ROC curves. Establishing a standardized cut-off value is crucial to improving the reproducibility and clinical applicability of PLR as a prognostic marker.

TNBC is a highly heterogeneous disease comprising distinct molecular and histological subtypes with varying clinical outcomes (25). Moreover, the PLR may be influenced by multiple patient-specific factors, including menopausal status, body mass index, infections, nutritional status, and medication history. Notably, obesity, which is increasingly prevalent, has been linked to TNBC risk and progression through inflammatory and metabolic pathways (34). The interplay between obesity, systemic inflammation, and TNBC pathogenesis remains an area requiring further investigation, as only two studies in our analysis accounted for body mass index as a potential confounder (20, 23). Additionally, menopause is associated with systemic inflammatory changes due to estrogen decline, which may further complicate the interpretation of PLR as a prognostic marker (35, 36).

As research advances, refining the prognostic utility of PLR in TNBC requires addressing existing gaps in knowledge. Standardization of cut-off values and further exploration of racial and molecular differences will be crucial in determining its clinical applicability. Additionally, ongoing studies such as the INSTIGO trial, a prospective study evaluating plasma protein profiles for predicting response to NACT and metastatic relapse in TNBC, may provide novel insights into immun.-inflammatory biomarkers (37). The PERCEPTION trial, currently underway, aims to assess the relationship between blood cell counts, PLR, and TILs both pre- and post-surgery in patients with TNBC, with a focus on their predictive value for metastatic recurrence (38).

Over the next 5 years, integrating PLR with emerging biomarkers such as the Royal Marsden Hospital score, prognostic nutritional index, neutrophil-to-lymphocyte ratio, and pan-immune-inflammation value may enhance its predictive accuracy (8). Additionally, combining PLR with molecular profiling and machine-learning algorithms might improve patient stratification and treatment personalization. Future research should focus on high-quality, multicenter prospective studies to validate the role of PLR and optimize its clinical application in TNBC.

Conclusion

Our systematic review and meta-analysis indicated that a high PLR was not significantly associated with OS or PFS in patients with TNBC: However, a high PLR was significantly associated with a lower DFS rate.

Further high-quality studies with larger sample sizes are needed to establish an optimal PLR cut-off value and to better understand its clinical significance in TNBC.

Conflicts of Interest

All Authors have no conflicts of interest. All Authors report they have no relationships that could be construed as a conflict of interest. All Authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Authors' Contributions

Conceptualization: V.A: Formal analysis and investigation: V.A. and M.L.R.D: Methodology: V.A., M.L.R.D, D.S.G.C., L.A.T., M.B. and A.C.F.M.M.L: Software: V.A: Supervision: M.B. and A.C.F.M.M.L: Validation: V.A., M.L.R.D. and A.C.F.M.M.L:

Visualization: V.A. and M.L.R.D: Writing– original draft: V.A: Writing – review and editing: A.C.F.M.M.L.

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