Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio as Prognostic Biomarkers in Ovarian Cancer Among the Asian Population: A Systematic Review and Meta-Analysis

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Abstract

Introduction: Despite its rare incidence, ovarian cancer is one of the worst malignancies with a poor prognosis. This study aimed to evaluate the role of NLR, PLR, and LMR as prognostic biomarkers in ovarian cancer among the Asian population in a meta-analysis design.

Methods: The literature search was performed systematically via online databases such as PubMed, ScienceDirect, and Cochrane Library using BOOLEAN operators. The primary outcomes in this study were survival outcomes (overall survival and disease/event/progression-free survival). All analysis was performed with Review Manager v5.4.

Results: This study included 20 studies with a total of 5.316 ovarian cancer patients. There was a significant association of NLR in OS ([univariate] HR = 2.82 (95%CI 1.63 - 4.88; p-value <0.01; I^2 = 97%); [multivariate] HR = 1.44 (95%CI 1.16 - 1.80; p-value <0.01; I^2 = 70%), and in DFS/EFS/PFS ([univariate] HR = 2.43 (95%CI 1.59 - 3.73; p-value <0.01; I^2 = 91.2%); [multivariate] HR = 1.41 (95%CI 1.17-1.69; p-value=0.0002; overall I^2 = 69.3%). Significant results of PLR in OS ([univariate] HR = 2.00 (95%CI 1.37-2.92; p-value <0.01; I^2 = 92%); [multivariate] HR = 1.82 (95%CI 1.31-2.54; p-value <0.01; overall I^2 = 68%), and in DFS/EFS/PFS ([univariate] HR = 1.85 (95%CI 1.32-2.59; p-value <0.01; overall I^2 = 92%); [multivariate] HR = 1.47 (95%CI 1.02-2.12; p-value = 0.04; overall I^2 = 77%).

Conclusion: Inflammatory markers, NLR, and PLR can be considered as prognostic markers in ovarian cancer among the Asian population.

Keywords: Asian, NLR, ovarian cancer, PLR, prognosis.

Introduction

Ovarian cancer is a general phrase that may be applied to any malignancy that affects the ovaries.[1,2] Ovarian cancer is the sixth major cause of cancer fatalities in women, ranking seventh among all cancers that happen in women, with roughly 4% of all incidences of cancer. Two hundred twenty-five thousand new cases of ovarian cancer are detected each year; 140,000 of these cases result in death. The prevalence of ovarian cancer is higher in industrialized than in undeveloped nations. However, the highest proportion of age-specific mortality in ovarian cancer is found in developing countries.[3]

Asia is one of the continents with the highest population, with roughly 60% of the world population, and diverse in culture and socioeconomic development.[4] The development of healthcare facilities is also rapidly increasing in Asia; one aspect is cancer diagnosis and treatment by implementing screening programs for early diagnosis. Therefore, the number of recorded cases of cancer in Asia has significantly increased in the past few years.[5] Additionally, other factors that contributed to lifestyle changes, such as sedentary lifestyle, alcoholic behavior, smoking, and unhealthy diet, aside from the unchangeable factors such as gender, age, and family history.[6] Therefore, studies regarding the diagnostic and prognostic markers of cancer are widely conducted. Some of those prognostic markers that are widely being studied are platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR).

The platelet-to-lymphocyte ratio (PLR) is a laboratory hematological marker that is repeatable, affordable, and generally available. Recently, it has been proposed that PLR is a marker of thrombotic and inflammatory disorders, primarily in patients with malignancies.[7,8] As a result, inflammatory biomarkers like PLR may be used to predict a patient's prognosis for cancer.[9] Elevated PLR demonstrated the activation of the transcription factors nuclear factor-kB (NF-kB), signal transducer and activator of transcription 3 (STAT3), and hypoxia-inducible factor 1a (HIF1a) in the inflammatory response. TNF-a, IL-1, and IL-6 are significant tumor growth-promoting cytokines produced in concert by these transcription factors.[10]

The neutrophil-to-lymphocyte ratio (NLR) is one of the most widely used hematological markers being evaluated in various diseases.[11] In patients with cancer, individuals with other illnesses, and members of the general community, NLR has repeatedly been discovered to be predictive of survival.[12] Across all cancer types, people with cancer who have an NLR over the established threshold have consistently been demonstrated to have poorer outcomes than those who have a lower NLR.[13,14] However, in ovarian cancer with various types of classifications that indirectly affect clinical outcomes and non-specific application of NLR and PLR only in cases of malignancy, the application of PLR and NLR in predicting clinical outcomes of ovarian cancer patients requires comprehensive evaluation. Therefore, this study aimed to evaluate the role of NLR and PLR as prognostic biomarkers in ovarian cancer among the Asian population in a meta-analysis design.

Methods

This study assessed the association between PLR, NLR, and LMR and ovarian cancer as prognostic markers in the Asian population based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocol. This study is a meta-analysis and only used the data of the previous studies; therefore, ethical approval was unnecessary.

Identification of relevant literature

A systematic search was conducted in online databases, including PubMed, Cochrane Library, ScienceDirect, and Google Scholar, to identify relevant studies based on specific keywords. Boolean operators used in the search included ("PLR" OR "Platelet-to-Lymphocyte Ratio" OR "NLR" OR "Neutrophil-to-Lymphocyte Ratio") AND ("Ovarian Cancer") AND ("Prognosis"). All authors participated in the screening process, followed by an independent evaluation of each study according to predetermined eligibility criteria. The final selection of included trials was determined through discussion among all authors, requiring unanimous agreement before inclusion. Any disagreements among reviewers were resolved by consensus.

Eligibility criteria

Five independent investigators carefully screened the candidate publications. Studies were considered eligible if they fulfilled the following criteria: 1) Original research articles including patients diagnosed with ovarian cancer; 2) Studies including the relevant inflammatory markers (NLR and/or PLR) and the cut-off values; and 3) Studies reporting the prognostic outcomes regarding NLR and/or PLR evaluation, with enough data of hazard ratio (HR) and 95% confidence interval (95%CI) for disease-free survival (DFS) or event-free survival (EFS) or progression-free survival (PFS) or overall survival (OS). The study selection process is illustrated in Figure 1.

Data extraction

The following correlative information was collected in a predefined table from the eligible articles. The general information, namely first author, publication year, and country. Patient characteristics including treatment status, type of cancer, the number of patients diagnosed with poor prognosis type of cancer (including serous, clear-cell, and mucinous), the number of patients diagnosed with advanced stage (stage III and IV), disease grade, the presence of infection, and the use of NSAID and/or corticosteroid and endpoint parameters (DFS/EFS/PFS and OS).

Assessment of risk of bias

The Risk of Bias 2 (RoB2) Cochrane tool evaluates the included studies' methodological and reporting biases. Two impartial reviewers will assess the risk of bias and assign it a rating of either low bias, moderate concerns, or high bias based on the biases in each category.

Statistical analysis

The primary outcomes in this study were survival outcomes, which included DFS/EFS/PFS and OS presented in HR. The heterogeneity of the studies was assessed and determined using the Cochran Q-test and I-squared test. $I^2 > 50\%$ and $p < 0.10$ were considered indicators of apparent heterogeneity, and a random effects model was used. The sources of heterogeneity in the included studies were determined using subgroup analysis and sensitivity analysis. Additionally, funnel plots with Egger's tests were adopted to assess potential publication bias precisely. Revman software ver 5.4.1 was employed for all statistical analyses, and p-values<0.05 were considered statistically significant.

Results

Literature Searching

In the search process of the study, 337 articles from online databases (PubMed, ScienceDirect, Cochrane Library, and Google Scholar) were obtained. A total of 303 articles were received after the removal of duplicates using computer software (Citation Manager). While filtering titles and abstracts, 57 articles were obtained that were accessible for later evaluation. Thirty-seven studies were excluded because they could not be retrieved. None were released because they did not have complete or relevant data on survival rates, resulting in qualitative (systematic) and quantitative (meta-analysis) analyses using the 20 studies included. Flowchart using the PRISMA guidelines is described as follows (**Figure 1**).

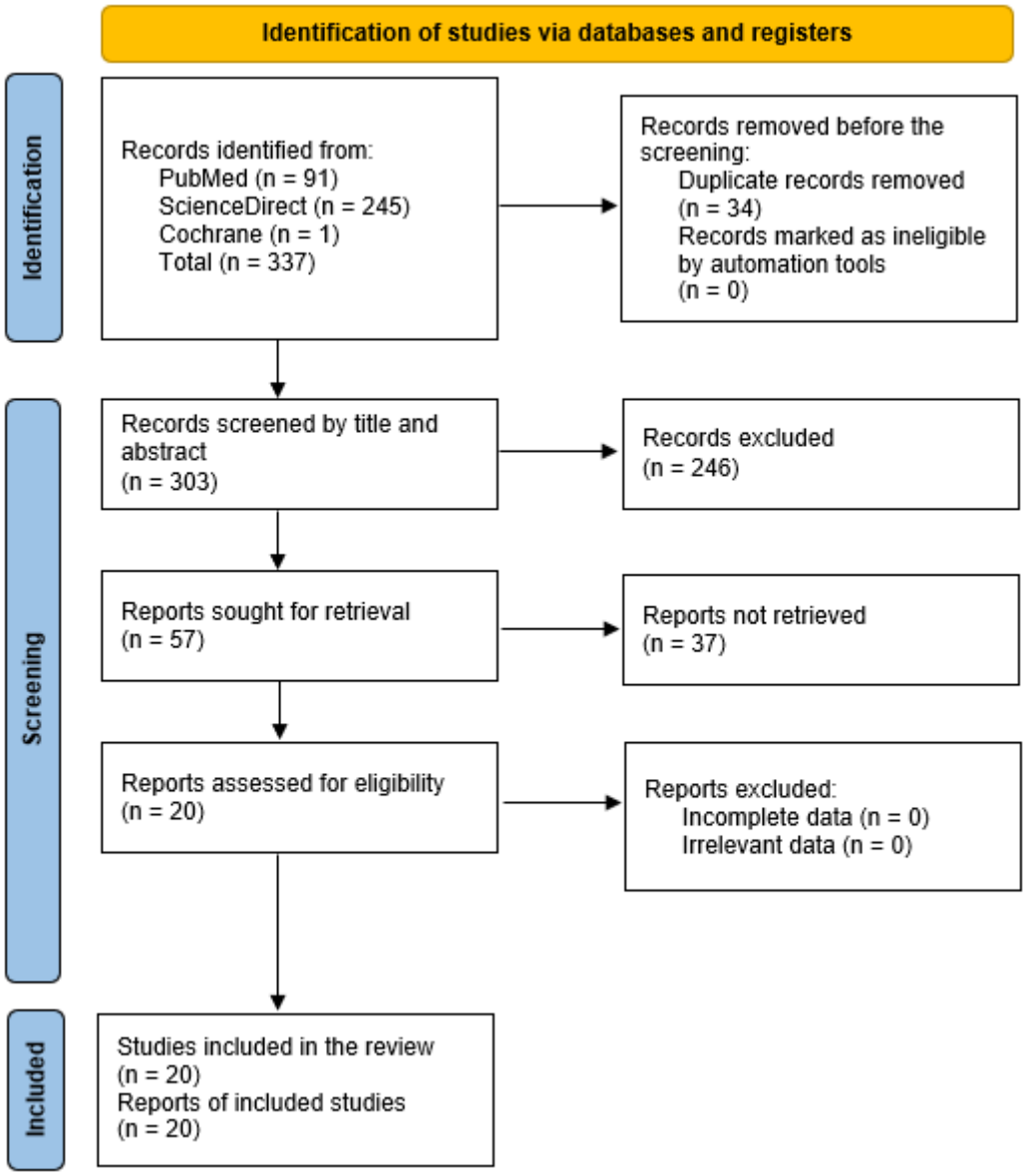

Figure 1. PRISMA Flowchart.

Characteristic of the Study

A total of 20 studies were obtained in the study, with the majority of studies coming from China, with 8 studies, followed by South Korea with 5 studies, Thailand and Japan with 2 studies, and 1 from Israel with a total sample of 5.316 ovarian cancer patients. The complete data on the characteristics of the study is presented in Table 1.

Egger's test showed no potential publication bias.

Table 1. Characteristic of the Study

Characteristics of The Study					Characteristics of The Patients						
Author, year	**Country**	**Mean/Median Age**	**Treatment Status**	**Type of Ovarian Cancer**	**Number of Patients with Poor Prognosis Type (Serous, mucinous and clear-cell)**	**Sample Size**	**Disease Stage**	**Number of Patients with Advanced Stage**	**Disease Grade**	**Presence of Infection**	**NSAID and Corticosteroid Administration**
Chen et al., 2020	China	52	Post-treatment (surgery)	Epithelial ovarian cancer Clear-cell (100%)	84	84	IC-II 47 (56%) III-IV 37 (44%)	37	N/R	No (Infection excluded)	N/R
Chon et al., 2020	South Korea	N/R	Post-treatment (surgery + platinum-based chemotherapy, paclitaxel)	Epithelial ovarian cancer Serous (73.5%), mucinous (3,9%), clear-cell (6.9%)	86	102	III 83 (81.37%) IV 19 (18.62%)	102	G1 5 (4.90%) G2 37 (36.27%) G3 60 (58.82%)	No (Infection excluded)	N/R
Eo et al., 2016	South Korea	54	Post-treatment (surgery)	Epithelial ovarian cancer Serous (56.4%), mucinous (15.0%), clear-cell (15.0%)	202	234	I-II 97 (41.5%) III-IV 137 (58.5%)	137	G1 46 (19.7%) G2 65 (27.8%) G3 113 (48.3%) N/R 10 (4.3%)	No (Infection excluded)	N/R
Feng et al., 2016	China	56	Post-treatment (surgery)	Epithelial ovarian cancer High-grade serous (100%)	875	875	I-II 75 (8.6%) III-IV 800 (91.4%)	800	N/R	N/R	N/R
Kwon et al., 2017	South Korea	70	Post-treatment (surgery +	Epithelial ovarian cancer	33	42	III 35 (83.3%)	42	G1 7 (16.7%)	N/R	N/R

			platinum-based chemotherapy)	Serous (78.6%)			IV 7 (16.7%)		G2/3 35 (83.3%)	
Kwon et al., 2018	South Korea	50	Post-treatment (surgery + platinum-based chemotherapy)	Epithelial ovarian cancer Clear-cell (100%)	109	109	I-II 64 (58.7%) III-IV 45 (41.3%)	45	N/R	N/R	N/R
Miao et al., 2016	China	55	Post-treatment (surgery + platinum-based chemotherapy, paclitaxel)	Epithelial ovarian cancer Serous (66.8%)	216	344	I-II 168 (48.83%) III-IV 176 (51.16%)	176	G1/2 136 (39.53%) G3 208 (60.46%)	N/R	N/R
Paik et al., 2016	South Korea	51	Post-treatment (surgery + adjuvant chemotherapy)	Epithelial ovarian cancer Serous (63.4%), mucinous (8.6%), clear-cell (8.2%)	540	674	I 150 (22.3%), II 73 (10.8%), III 389 (57.7%), IV 62 (9.2%)	451	G1 55 (8.2%), G2 146 (21.7%), G3 473 (70.2%)	N/R	N/R
Salman et al., 2018	Israel	61.8 and 67.0	Post-treatment (surgery + adjuvant chemotherapy)	Epithelial ovarian cancer Serous (59.5%), mucinous + clear-cell (10.8%)	78	111	IIIC 88 (79.3), IV 23 (20.7%)	111	N/R	N/R	N/R
Supoken et al., 2014	Thailand	52	Post-treatment (adjuvant paclitaxel and carboplatin)	Epithelial ovarian cancer Clear-cell (100%)	36	36	I 17 (47.2%), II 3 (8.3%),III 11 (30.6%), IV 5 (13.9%)	16	N/R	N/R	N/R

Wang et al., 2016	China	52.27	Post-treatment (surgery)	Epithelial ovarian cancer 85% (Unspecified)	122	143	I-II 54 (38%), III-IV 89 62%)	89	N/R	No (Infection excluded)	N/R
Tang et al., 2020	China	50	Post-treatment (adjuvant chemotherapy)	Epithelial ovarian cancer Serous (69.3%), mucinous (4.9%), clear-cell (5.3%)	179	214	I 62 (27.6%), II 39 (17.3%), III 109 (48.4%), IV 15 (6.7%)	124	G1 42 (18.7), G2 48 (21.3), G3 135 (60.0)	N/R	N/R
Yoshida et al., 2019	Japan	53	Post-treatment (surgery)	Epithelial ovarian cancer Clear-cell (100%)	83	83	I 76 (91.6%), II 7 (8.4%)	0	N/R	N/R	N/R
Zhang et al., 2015	China	50.6	Post-treatment (surgery + platinum-based chemotherapy)	Epithelial ovarian cancer Serous (53.2%), mucinous (6.3%), clear-cell (3.7%)	120	190	I 22 (11.6%), II 31 (16.3%), III 128 (67.4%), IV 9 (4.7%)	137	G1 64 (33.7%), G2 44 (23.2%), G3 69 36.3%)	No (Infection excluded)	N/R
Zhou et al., 2018	China	54.3	Post-treatment (surgery + platinum-based chemotherapy)	Epithelial ovarian cancer Serous (64.3%), mucinous (0.8%), clear-cell (1.1%)	245	370	III 370 (100.0%)	370	G1 24 (6.5%), G2 133 (35.9%), G3 213 (57.6%)	N/R	N/R
Li et al., 2020	China	N/R	Pre-treatment	Epithelial ovarian cancer Serous (73.5%)	86	117	I-II 45 (38.5%), III-IV 72 (61.5%)	72	G1 67 (57.3%), G2-G3 50 (42.7%)	No (Infection excluded)	N/R
Kim et al., 2018	South Korea	57	Pre-treatment	Epithelial ovarian cancer	180	197	III 52 (26.4%),	197	N/R	N/R	N/R

Komura et al., 2017	Japan	N/R	Post-treatment (surgery)	High-grade serous (91.4%) Epithelial ovarian cancer Serous (38.1%), mucinous (9.3%), clear-cell (24.1%)	246	344	IV 145 (73.6%) I-II 189 (54.9%), III-IV 155 (45.1%)	155	N/R	N/R	N/R
Sowannakul et al., 2023	Thailand	54.52	Post-treatment (platinum-based chemotherapy)	Epithelial ovarian cancer Serous (55.4%), mucinous (5.4%), clear-cell (21.4%)	46	56	I 11 (19.6%), II 2 (3.6%), III 29 (51.8%), IV 14 (25.0%)	43	N/R	No (Infection excluded)	N/R
Song et al., 2023	China	55	Post-treatment (surgery)	Epithelial ovarian cancer Serous (83.7%)	829	991	I 55 (5.5%), II 84 (8.5%), III 682 (68.8%), IV 170 (17.2%)	798	G1 376 (37.9%), G2 233 (23.5%), G3 275 (27.7%)	N/R	N/R

Neutrophile-to-Lymphocyte Ratio

Univariate analysis of NLR showed a significant relationship between NLR and OS in the overall effect analysis with a random effect model showing HR = 2.82 (95%CI 1.63 - 4.88; p-value <0.01; overall I^2 = 97%). In the subgroup analysis, the study group with patients with post-treatment status who only underwent surgery had significant results with a random effect model showing HR = 3.13 (95%CI 2.17 - 4.50; I^2 = 70%), the study group with patients who received a combination of surgery and chemotherapy had significant results with a random effect model showing HR = 2.62 (95%CI 1.03 - 6.6; I^2 = 98%), the study group with patients who only received chemotherapy only contained one study by Sowannakul et al. with HR = 2.72 (95%CI 1.31 - 5.63). There was no significant difference in subgroup analysis with the random effects model (χ^2 = 0.20, p-value = 0.90) (**Figure 2**).

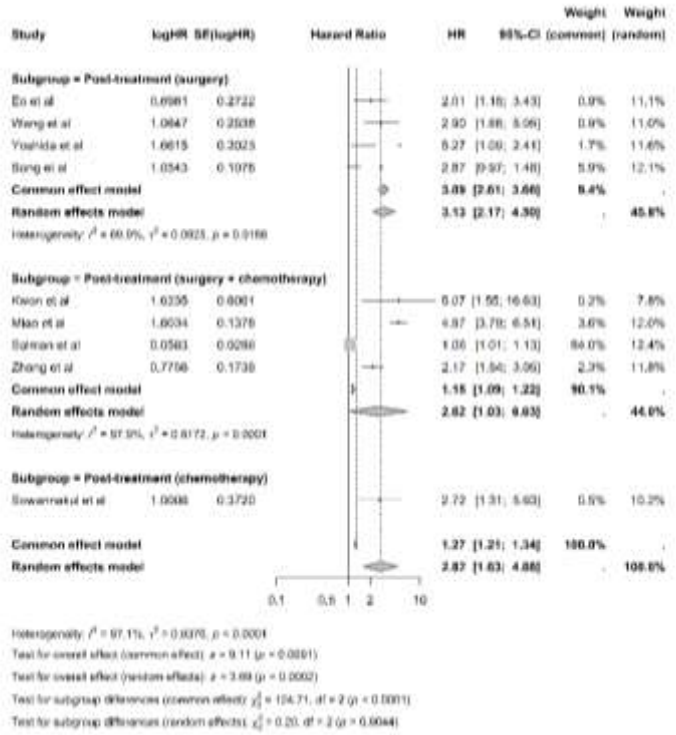

Figure 2. Overall survival based on univariate analysis.

Multivariate analysis of NLR showed a significant relationship between NLR and OS in the overall effect analysis with a random effect model showing HR = 1.44 (95%CI 1.16 - 1.80; p-value <0.01; overall I^2 = 70%). In the subgroup analysis, no significant results were found in the study group with patients with post-treatment status who only underwent surgery with a random effect model showing HR = 2.51 (95%CI 0.89 - 7.10; I^2 = 78%), the study group with patients who received a combination of surgery and chemotherapy had significant results with a random effect model showing HR = 1.30 (95%CI 1.01 - 1.67; I^2 = 70%), the study group with patients who had not received treatment (pre-treatment) only had one study by Kim et al. with HR=1.89 (95%CI 1.11-3.24), the study group with patients who only received chemotherapy only contained one study by Sowannakul et al. with HR=1.25 (95%CI 0.40 – 3.92). There was no significant difference in subgroup analysis with a random effects model (χ^2 = 7.18, p-value = 0.07) (**Figure 3**).

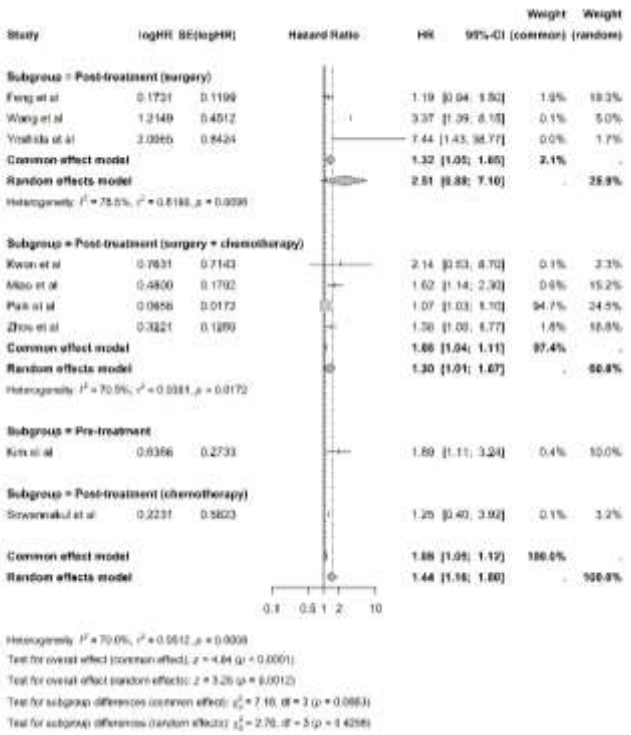

Figure 3. Overall survival based on multivariate analysis.

Univariate analysis of NLR showed a significant relationship between NLR and DFS/EFS/PFS in the overall effect analysis with a random effect model showing HR = 2.43 (95%CI 1.59 - 3.73; p-value <0.01; overall I^2 = 91.2%). In the subgroup analysis, significant results were found in the study group with patients with post-treatment status who only underwent surgery with a random effect model showing HR = 1.99 (95%CI 1.28 - 3.10; I^2 = 84%), the study group with patients who received a combination of surgery and chemotherapy had significant results with a random effect model showing HR = 3.28 (95%CI 1.60 - 6.71; I^2 = 90%), the study group with patients who only received chemotherapy only contained one study by Sowannakul et al. with HR = 2.57 (95%CI 1.37 - 4.81). There was no significant difference in subgroup analysis with the random effects model (χ^2 = 1.46, p-value = 0.48) (**Figure 4**).

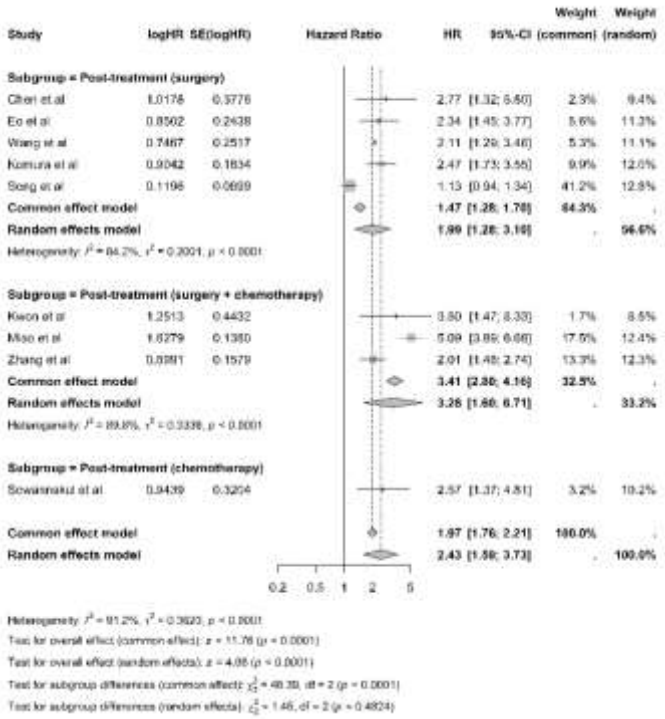

Figure 4. DFS/EFS/PFS based on univariate analysis.

Multivariate analysis of NLR showed a significant relationship between NLR and DFS/EFS/PFS in the overall effect analysis with a random effect model showing HR = 1.41 (95%CI 1.17-1.69; p-value=0.0002; overall I^2 = 69.3%). In the subgroup analysis, significant results were found in the study group with patients with post-treatment status who only underwent surgery with a common effect model showing HR = 1.32 (95%CI 1.13-1.55; I^2 = 30.8%), the group with patients who received a combination of surgery and chemotherapy had insignificant results with a random effect model showing HR = 1.36 (95%CI 0.95-1.93; I^2 = 69.5%), the group with patients who only received chemotherapy only contained one study by Sowannakul et al. with HR = 1.52 (95%CI 0.54-4.31), the pre-treatment group showed a significant result with HR = 1.53 (95%CI 1.02-2.28). There was no significant difference in subgroup analysis with the random effects model (χ^2 = 0.21, p-value = 0.98) (**Figure 5**).

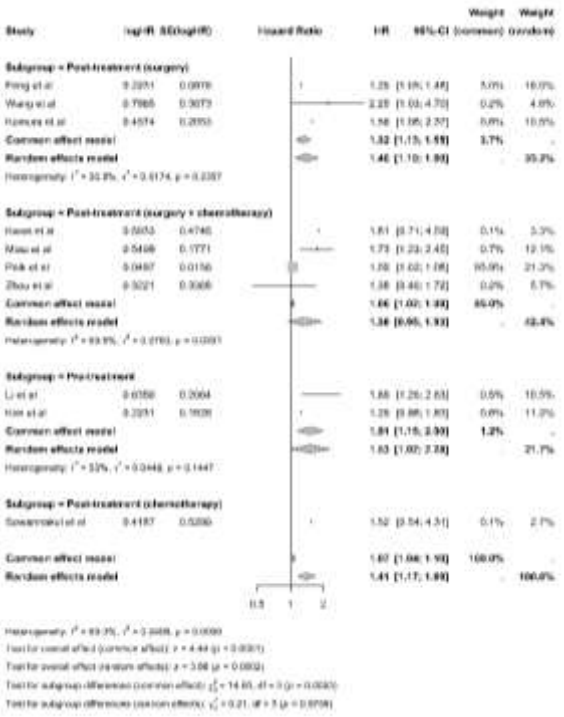

Figure 5. DFS/EFS/PFS based on multivariate analysis.

Platelet-to-Lymphocyte Ratio

Univariate analysis of PLR showed a significant relationship between PLR and OS in the overall effect analysis with a random effect model showing HR = 2.00 (95%CI 1.37-2.92; p-value <0.01; overall I^2 = 92%). In the subgroup analysis, significant results were found in the study group with patients with post-treatment status who only underwent surgery with a random effect model showing HR = 1.72 (95%CI 1.06-2.79; I^2 = 75%), the study group with patients who received a combination of surgery and chemotherapy had significant results with a random effect model showing HR = 2.13 (95%CI 1.09-4.18; I^2 = 96%), the study group with patients who only received chemotherapy only contained one study by Sowannakul et al. with HR = 2.20 (95%CI 1.02-4.77). There was no significant difference in subgroup analysis with the random effects model (χ^2 = 0.41, p-value = 0.81) (**Figure 6**).

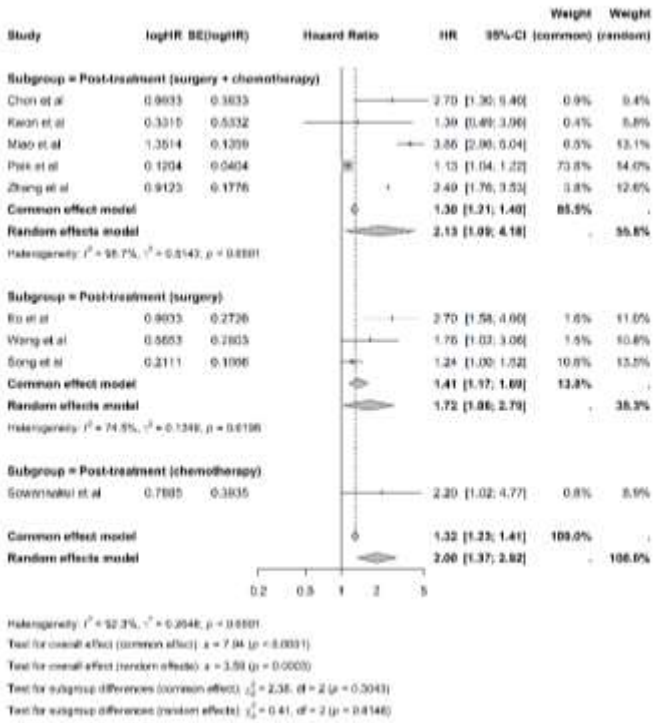

Figure 6. Overall survival based on univariate analysis

Multivariate analysis of PLR showed a significant relationship between PLR and OS in the overall effect analysis with a random effect model showing HR = 1.82 (95%CI 1.31-2.54; p-value <0.01; overall I^2 = 68%). In the subgroup analysis, the study group with patients with post-treatment status who only underwent surgery with a common effect model did not show significant results with HR = 1.20 (95%CI 0.97-1.47; I^2 = 34%), the study group with patients who received a combination of surgery and chemotherapy had significant results with a common effect model showing HR = 2.13 (95%CI 1.69-2.68; I^2 = 0%), the study group with patients who only received chemotherapy only contained one study by Sowannakul et al. with HR = 2.54 (95%CI 0.93-6.39). There was no significant difference in subgroup analysis with the random effects model (χ^2 = 3.81, p-value = 0.15) (**Figure 7**).

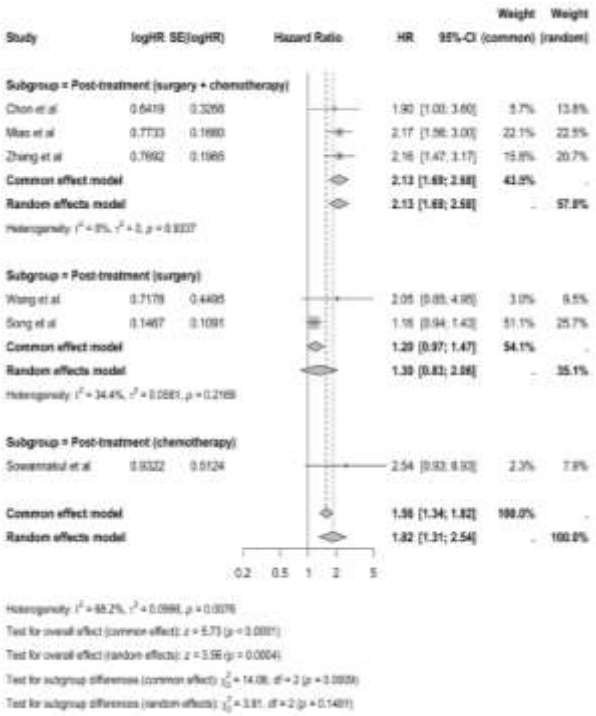

Figure 7. Overall survival based on multivariate analysis

Univariate analysis of PLR showed a significant relationship between PLR and DFS/EFS/PFS in the overall effect analysis with a random effect model showing HR = 1.85 (95%CI 1.32-2.59; p-value <0.01; overall I^2 = 92%). In the subgroup analysis, the study group with patients who only underwent surgery with a common effect model showed significant results with HR = 1.32 (95%CI 1.13-1.54; I^2 = 44%), the study group with patients who received a combination of surgery and chemotherapy had significant results with a random effect model showing HR = 2.09 (95%CI 1.01-4.33; I^2 = 97%), the study group with patients who only received chemotherapy with a random effect model did not show significant results with HR = 2.22 (95%CI 0.73-6.73; I^2 = 69%). There was no significant difference in subgroup analysis with the random effects model (χ^2 = 1.40, p-value = 0.50) (**Figure 8**).

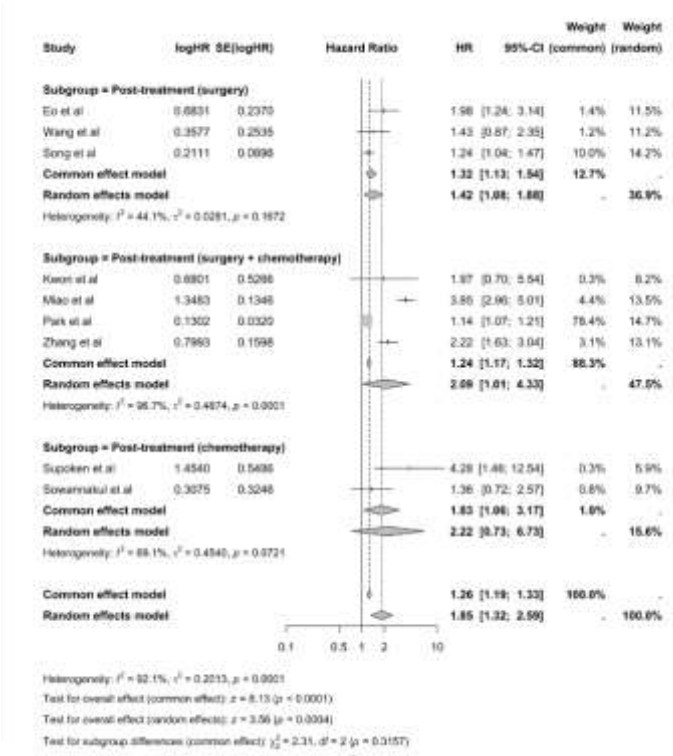

Figure 8. DFS/EFS/PFS based on univariate analysis.

Multivariate analysis on PLR showed a significant relationship between PLR and DFS/EFS/PFS in the overall effect analysis with a random effect model showing HR = 1.47 (95%CI 1.02-2.12; p-value = 0.04; overall I^2 = 77%). In the subgroup analysis, the study group with patients who only underwent surgery with a random effect model did not show significant results with HR = 1.11 (95%CI 0.61-2.03; I^2 = 62%), the study group with patients who received a combination of surgery and chemotherapy had significant results with a common effect model showing HR = 1.80 (95%CI 1.45-2.23; I^2 = 0%), the study group with patients who only received chemotherapy with a random effect model did not show significant results with HR = 1.81 (95%CI 0.38-8.62; I^2 = 68%). There was no significant difference in subgroup analysis with the random effects model (χ^2 = 2.18, p-value = 0.34) (**Figure 9**).

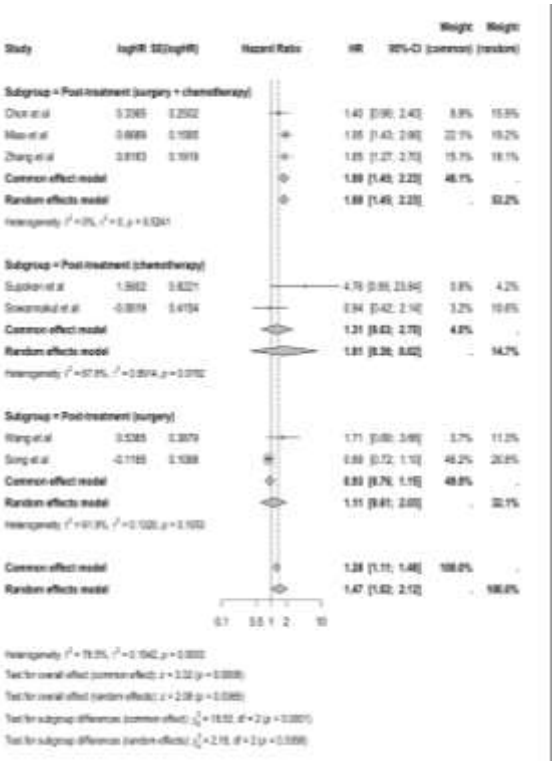

Figure 9. DFS/EFS/PFS based on multivariate analysis.

Discussion

In the pooled univariate and multivariate analysis, there was a significant association between OS and PFS with NLR. This result aligns with the meta-analysis conducted by Zhang et al., 2024 who found that there was a strong inverse correlation between NLR values with OR and PFS (HR=1.21; 95%CI 1.09 - 1.34; p<0.001 and HR=1.20; 95%CI 1.03 - 1.38; p<0.001).[15] Ovarian cancer patients with high NLR were significantly associated with decreased OS and PFS, indicating a worse prognosis. The mechanism underlying the association between high NLR and poor prognosis remains unclear in cancer patients.[16] A biological explanation behind this relationship may lie in the complex interaction between inflammation and tumorigenesis. The balance between neutrophils and lymphocytes reflects the host's systemic inflammatory and immune status. An increase in NLR may reflect both an increase in neutrophil-mediated inflammatory response and a decrease in lymphocyte-mediated anti-tumor immune response that may promote a favorable environment for tumor growth and development. The occurrence of a reduction of the number of lymphocytes is also supported by the study of Milne et al. who found that ovarian cancer patients had significantly reduced lymphocyte levels at the time of diagnosis compared to 2 years before diagnosis, and the rate of decline was higher as the cancer stage increased.[17] Thus, the presence of accelerated tumor growth and development will lead to poor survival outcomes.[18] In this study, the difference in results obtained between univariate and multivariate analysis can be caused by differences in the number of studies used. Some studies in the univariate analysis were not used in the multivariate analysis because they didn't contain the required data. The results of univariate or multivariate analysis each have high heterogeneity. Potential contributing factors include geographic variation, differences in study sample size, diverse patient characteristics, and differences in the type of therapy used. The use of different NLR cut-off values per study also further increased heterogeneity.

Univariate and multivariate subgroup analysis showed a significant association between OS and PFS with NLR based on pre-treatment and post-treatment. Post-treatment received by patients in this study consisted of surgery, chemotherapy, or both. Wang et al., 2016 mentioned that NLR value pre-treatment can be used as a predictor for malignant ovarian cancer and associated with advanced tumor stage.[15] In contrast to this, the study of Topcu et al., 2014 actually states that NLR is an ineffective marker in assessing the malignant potential of an ovarian mass.[19] In ovarian clear cell carcinoma (OCCC), pre-operative NLR level is associated with postoperative prognostic indicators, such as FIGO stage, residual tumor, and platinum-based chemotherapy resistance.[20] A high NLR indicates a failure to respond to therapy in OCCC. In addition, high NLR represents a poor prognosis;

therefore, post-treatment NLR levels can also be used to identify high-risk patients for survival after therapy.[15] A previous study using 49 ovarian cancer patients found that patients with higher NLR were significantly associated with shorter survival or poorer prognosis after chemotherapy.[21] A meta-analysis of 10 studies with 2,919 ovarian cancer patients reported that patients with higher NLR pretreatment rates had shorter OS and PFS (OS: HR=2.36; 95%CI 1.91–2.91; PFS: HR=1.82; 95%CI 1.51-2.18) compared to patients with lower NLR pretreatment.[22] In addition, chronic inflammation in ovarian cancer patients is one of the triggers for metastasis. High NLR reflects the formation of an immunosuppressive tumor environment that encourages metastasis. Therefore, NLR levels can also be used as a predictive marker in metastatic patients.[23]

The OS and PFS results versus PLR in both multivariate and univariate analyses seem to have significant outcomes across the overall test results in different studies, according to the study's findings. These findings also align with the research conducted by Raungkaewmanee et al. (2012), which found that PLR significantly predicts surgical outcomes and residual disease for ovarian cancer in both univariate and multivariate models. The study's findings, however, did not indicate the importance of OS because the focus was primarily on surgical outcomes rather than other variables like PLR, and the sample size was too small to identify the significance of OS results in connection to PLR.[24] The high sample size of 5.316 individuals may have contributed to the study's noteworthy findings on OS values for ovarian cancer patients. An additional study by Tian et al. (2018) demonstrated noteworthy outcomes regarding the decline in OS and PFS values with elevated PLR, hence validating PLR as a viable inflammatory biomarker agent in patients with ovarian cancer. With PLR ≥200, the analysis of the study's findings indicates a significant increase in PLR towards OS and PFS in the Asian community of ovarian cancer patients. This suggests that PLR is a reliable predictor of the prognosis of ovarian cancer.[25]

Numerous investigations have raised the possibility that the inflammatory response to tumor progression involves cross-talk.[26,27] By binding PDGF, VEGF, TGF-β, and FGF, platelets—a crucial component of cytokines—act as a reservoir for growth factors that regulate angiogenesis in cell proliferation, malignancies, metastasis, and migration.[28] Then, by causing cytotoxic cell death and preventing tumor cell migration and proliferation, lymphocytes contribute to the defensive system against cancer cells. After entering tumor cells, lymphocytes—immune cells that are in charge of the antitumor immune response—will cause cytotoxicity.[29] A low lymphocyte count may result in less-than-ideal immune responses.[30,31] Furthermore, in a number of malignancies, this process of lymphocyte decrease has been employed as a single predictive indicator.[32,33] Thus, this process shows how PLR might be used to forecast the prognosis of ovarian cancer patients.

Furthermore, the multivariate and univariate outcomes of OS and PFS against PLR showed significant results ($p < 0.001$) depending on the post-treatment subgroup of patients who had surgery, had neoadjuvant and/or adjuvant chemotherapy, or both. Megakaryocytes are stimulated to create more platelets as a result of the rise in platelet count, which is correlated with the release of inflammatory mediators.[24] The Winata et al. (2023) study also demonstrates a connection between PLR and ovarian cancer recurrence.[34] Additionally, research by Kawahara et al. (2023) demonstrated that the treatment of neoadjuvant chemotherapy (NACT) increased the lymphocyte count, which was predictive of OS and PFS.[35] These findings, however, contradict earlier research that found a drop in platelet count following NACT delivery to be a sign of a bad patient prognosis.[36,37]

When ovarian cancer cells appear, the body's immune system automatically produces an adaptive immune response. This is caused by the increased mutation burden and immune identification of the mechanisms underlying cancer mutations.[38,39] The immune system helps restrict the proliferation of cancer cells by entering tumor cells with lymphocytes, improving quality of life.[40,41] Additionally, Kawahara et al.'s study from 2023 verified that the rise in tumor-infiltrating lymphocytes (TILs) in peripheral blood flow prior to surgery had a suppressive effect on tumor cells and increased the sensitivity of malignant tumor cells. To optimize therapeutic results, more aggressive treatment is therefore required, such as adjuvant chemotherapy with a longer duration.[35]

The rise in PLR and NLR shows an increase in inflammation within tumor cells. Inflammatory mediators, including cytokines and chemokines, are correlated with an increase in platelets and leukocytes.[42] This happens because the immune system and tumor cells interact. Although the immune system contributes to the inhibition of cancer, it also raises inflammation associated with angiogenesis and immune cell evasion.[43] Numerous inflammatory factors, including platelets, lymphocytes, and neutrophils, develop in response to the action of these tumor cells.[44] This subsequently accelerates the growth of the tumor in the direction of inflammation.[45] Inflammation is crucial to the carcinogenesis process in several mechanisms, including proliferation, angiogenesis, invasion, metastasis, and the inhibition of cancer cell death.[46] Chronic inflammation is another way that cancer cells might spread. Numerous research findings have demonstrated a connection between cancer cells and cytokines and chemokines. Cytokines are involved in controlling the growth and survival of cancer cells in

ovarian cancer.[43] Consequently, the occurrence of heightened inflammatory reactions, as shown by elevated PLR and NLR, might serve as a reliable indicator of the prognosis and how well patients will respond to the prescribed treatment.[47]

In many cancer types, an increase in PLR and platelet count indicates a poor prognosis. Patients with ovarian cancer have a worse prognosis if their PLR is more significant than 300.[48] According to earlier research, poor clinical outcomes, including recurrence, aggressive tumor formation, and accelerated tumor progression in a variety of cancer types, are linked to elevated levels of NLR, PLR, neutrophils, and platelets. A decline in OS and PFS is likewise linked to a rise in PLR. Another meta-analysis study on 1250 patients with ovarian cancer supports this claim by showing that, with an HR of 1.63, an increase in PLR is closely linked to a decline in OS and PFS.[49] Because these inflammatory indicators are readily available, reasonably priced, and non-invasive when used in conjunction with laboratory data, their application in ovarian cancer is also advantageous.[42] Because of this, PLR is a better predictor of the incidence of inflammation in ovarian cancer than the neutrophil ratio and other indicators.[50]

The use of systemic inflammatory markers, such as NLR and PLR, as biomarkers for ovarian cancer aligns with findings from Ma et al. (2022) and Zhao et al. (2018).[49,51] While these studies reported higher pooled discriminatory values, disparities in ethnicity beyond the Asian population may have influenced the outcomes. Ovarian cancer has shown significant survival differences between different racial groups, with Asians exhibiting better survival outcomes. Another study showed that although Asians are presented at a younger age, which partly explains the better outcomes due to age differences compared to whites, the survival advantage of the Asian race remains an independent prognostic factor.[52] Furthermore, it has been reported that East Asian populations have some of the lowest ovarian cancer mortality rates globally. In contrast, Southeast Asian mortality cases are quite high but lower than Europeans. The increased mortality observed in low-income countries raises concerns,[53] Given the disparity in socio-economic conditions in Asian countries.

Though NLR and PLR show a good predictive value, yet compared to other methods, KELIM, this method still has a lower discriminatory value. Corbaux et al. (2022) showed that patients with unfavorable KELIM SCORE had a 49 times higher risk of death (favorable vs unfavorable SCORE OS HR = 0.51). The PFS analysis also showed a higher discriminatory value with favorable vs unfavorable SCORE PFS HR = 0.59. The prognostic value of KELIM was found to be stable through analyses performed at different time horizons, up to 5 years of follow-up.[54] The stability of KELIM's prognostic value, regardless of chemotherapy dosing schedules,[55] or the combination with additional drugs, such as bevacizumab or veliparib,[56-58] suggests that KELIM reflects the intrinsic characteristics of cancer cells. However, the study failed to confirm the value of KELIM as a surrogate marker for OS and PFS,[59] providing an opportunity for alternative biomarkers to gain prominence. It should also be noted that the study did not focus on the Asian population, which could support this high predictive value. On the other hand, systemic inflammatory markers, NLR and PLR, retain significant potential as clinical markers of solid tumors in predicting patient prognosis, considering that NLR and PLR can be easily determined from blood tests.[60] These markers are simple, affordable, and easily accessible and are routinely measured biomarkers of inflammation. This underscores the application of predictive methods with systemic inflammatory markers in everyday oncology practice.[61]

In several similar studies evaluating PLR and NLR in ovarian cancer, the presence of comorbid infection can be a significant factor and bias the results. Infection can increase the number of neutrophils and platelets and affect the ratio.[62] Thus, it is argued that higher NLR and PLR values may not fully reflect the condition of ovarian cancer itself. Therefore, it is imperative to take into the patient's infection status when analyzing these data. However, based on the articles included in the meta-analysis, most studies did not explicitly mention the infection status of the patients. This is a significant limitation as it is unclear whether the patient had an infection at the time of data collection, which may bias the results. Some studies did state that patients with infection at the time of data collection were excluded, but this was not consistent across the included articles, so the results obtained may have high variability.

In addition, the use of drugs such as NSAIDs (non-steroidal anti-inflammatory drugs), regular analgesics, and steroids in cancer patients can affect the results of NLR and PLR measurements. NSAIDs can affect the number of neutrophils, lymphocytes, and platelets in the body, which in turn affects the NLR and PLR values. For example, NSAIDs can reduce the number of lymphocytes/neutrophils. At the same time, steroids can increase the number of neutrophil and platelet cells, which can lead to changes in the NLR and PLR ratios that do not fully reflect the cancer condition itself.[63,64] However, none of the identified inclusion studies explicitly mentioned the use of these drugs in the patient records. This is an important limitation, as the absence of this information may

lead to bias in the results. Some studies mentioned that patients with infections at the time of data collection were excluded, but information regarding the use of other medications was not always reported.

The strength of this study lies in the subgroup analysis conducted based on patient treatment status, which quantitatively states that there is no significant difference between treatment groups. Although, in theory, it can be explained that treatment status can affect the results of the study, the results of the analysis in this study showed the opposite results, which are likely caused by other factors. In this study, there are several limitations, including the potential for significant bias caused by the influence of variability in the study population. Several things that could possibly cause variability, such as the combination of populations with various stages, pathological grading, and types of ovarian cancer that cannot be grouped and stratified clearly because the inclusion studies in this study did not perform separate grouping and analysis based on these confounding variables which could affect the study outcomes. However, in this study, the percentage of the population tendency included in the analysis was calculated based on the number of samples in each inclusion study. In this study involving 5,316 patients with ovarian cancer, 82.67 of the total samples were patients with ovarian cancer types with worse prognoses, such as serous, mucinous, and clear-cell types. In addition, as many as 73.40% of the study subjects were ovarian cancer patients with advanced stage with a median age trend in the 50s. Although no quantitative analysis was conducted in this study related to these data, the data showed that there was a trend of the characteristics of the study subjects dominated by advanced-stage ovarian cancer patients with epithelial ovarian cancer sub-types of serous, mucinous, and clear-cell, which indirectly can be an advantage of this study in providing an overview of the trends in the study population.

Conclusion

Inflammatory markers, such as PLR and NLR, can be considered prognostic markers in ovarian cancer to predict the patient's survival. The insignificant result in each subgroup comparison analysis indicated that there were no significant changes in inflammatory markers among patients who underwent surgery, chemotherapy, or both. However, these findings could be biased by the heterogeneity of the samples. Therefore, more specific studies by strictly controlling the eligibility criteria are needed to validate and confirm these findings.

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