REVIEW

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Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio as an Early Prognostic Marker in Patients with Ovarian Cancer: A Systematic Review and Meta-Analysis

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Abstract

Objective: Presently, ovarian cancer remains the leading cause of death in gynecological malignancies. The survival rate of these patients is low, which might be caused by early metastases and delayed diagnosis. Therefore, it is crucial to investigate novel practical markers that provide early prognostic value which helps construct individualized treatment. **Methods:** A thorough investigation of the neutrophil-lymphocyte ratio (NLR) and lymphocyte ratio (PLR) in ovarian cancer patients was conducted using article selection from PubMed, Cochrane, Science Direct, and Google Scholar databases. The outcomes and hazard ratio (HR) were obtained using Review Manager 5.4, and the 95% Confidence Interval (CI) result was calculated. The chief endpoints of interest in this study include overall survival (OS) and progression-free survival (PFS). **Results:** Sixteen studies with 3,862 patients were included with a mean age of 50.6 years and a mean follow-up of 45.84 months. Multivariate studies demonstrated that a higher NLR is associated with worse PFS and OS, HR 1.35;95% CI [1.05–1.74] and HR 1.46; 95% CI [1.16–1.83] respectively. Similar results are observed with PLR and poorer PFS and OS, HR 1.62; 95% CI [1.09–2.43] and HR 1.66; 95% CI [1.12–2.46]. **Conclusion:** Pre-treatment PLR and NLR were found to be prognostic factors in determining PFS and OS in ovarian cancer. High values in pre-treatment PLR and NLR may indicate worse clinical outcomes.

Keywords: Cervical cancer- neutrophil- lymphocyte- platelet- prognostic

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Introduction

Cancer is a highly debilitating disease and accounts for a sizable number of mortalities worldwide. In women, ovarian cancer is one of the most common types reported with approximately 200,000 new cases of ovarian cancer diagnosed annually. This number is expected to increase to 371,000 new cases yearly by 2035, which is a major cause for concern [1-2]. Ovarian cancer has a high mortality rate of 6.3 per 100,000 women every year, making it one of the deadliest and most challenging cancers to treat [3-4]. It is often called the "silent killer" because patients commonly show no symptoms until it reaches an advanced stage [5-6]. However, when patients do exhibit symptoms, primary care providers often fail to notice them [7].

Ovarian cancer alone has a 5-year survival rate of <50%, it's worth noting that the majority of ovarian cancers, roughly 80%, are detected in the later stages of the disease when it has spread beyond the ovaries [8-10]. Thus, earlier diagnosis is exceptionally crucial in ovarian cancer patients, with the help of standard parameters to help clinicians identify the disease and start individualized treatment earlier.

Several studies have demonstrated systemic inflammatory activation induced by these cancer cells that anticipates tumor development by causing cancer multiplication and metastasis or facilitating angiogenesis. This inflammatory response is closely related to cancer initiation, development, and metastasis [11-12]. Therefore, we systematically searched scientific data on inflammatory markers such as the neutrophil-lymphocyte ratio (NLR) and lymphocyte-platelet ratio (PLR), to explore their association with overall survival (OS) and progression-free survival (PFS) of ovarian cancer patients. NLR and PLR might prove to be a valuable prognostic marker, given that these markers are widely available in clinical practice.

Materials and Methods

This study performed a systematic review and meta-analysis while adhering to the Preferred Reporting Items

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for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The research utilized data from previously published studies, therefore ethical approval was not necessary. The study's protocol has been registered with the CRD number 42024500275 on the International Prospective Register of Systematic Reviews (PROSPERO) (www.crd.york.ac.uk/prospero).

Search Strategy

According to Medical Literature Analysis and Retrieval System Online (MEDLINE), a systematic research on PubMed, Cochrane Library, Science Direct, and Google Scholar databases from 2002-2023 was conducted using the terms: "Ovarian Neoplasm OR Ovarian Cancer OR Ovary Cancer OR Ovary Neoplasm", "Platelets lymphocyte ratio OR platelet to lymphocyte ratio OR PLR", "Neutrophil lymphocyte ratio OR Neutrophil to lymphocyte ratio OR NLR", "Prognosis OR Outcome", in English and full-text publication. We performed an additional manual search by reviewing the references of all included and appropriate studies later. The conclusive research inquiry pertains to the potential association between the Neutrophil-to-Lymphocyte Ratio (NLR) and/or the Platelet-to-Lymphocyte Ratio (PLR) in the context of ovarian cancer or ovarian neoplasm as a predictive marker.

Inclusion Criteria

To ensure the selected study is comprehensive and relevant, it must meet several specific criterias. These include: (1) being a retrospective or prospective study with full-text available; (2) examining the significance of pre-treatment NLR and/or PLR parameter as a prognostic marker for ovarian cancer; (3) providing hazard ratios (HR) or provided sufficient information in calculating HR for either progression-free survival (PFS) or overall survival (OS), as well as their corresponding 95% confidence intervals (CIs) or p-values; (4) the study reported the cut-off value of NLR and PLR; and (5) being published in the English language.

Data Extraction and Quality Assessment

Standardized forms were used during data extraction and quality assessment by three researchers. Each study extracted information includes the authors, design and methodology, total and mean patient age, NLR and PLR values, progression-free survival values, and Overall Survival values for each NLR or PLR group compared to the control group. In instances of unclear or missing data in the primary results, the original publication authors were contacted via email for clarification.

Modified Newcastle-Ottawa Scale is used to analyze the risk of bias for Cohort Studies [13]. The scale comprises eight items that are categorized into three domains. The outcome domain carries three points, while the comparability domain is worth two points. There are four total points for domain selection. The study quality was deemed "good" if the total score was between 7-9, "moderate" for scores between 4-6, and anything below that was considered "poor." Additionally, the three reviewers took the risk bias assessment independently with any disputes settled through dialogues with the fourth reviewer. The prevailing quality of the non-comparative studies was sufficient, with an average score of 7.7 points.

Data Synthesis and Analysis Quality Assessment

We utilized Review Manager 5.4 to analyze the data gathered in this study. Our findings will be presented as hazard ratios (HRs) with 95% confidence intervals (CIs). To assess heterogeneity between study populations, we employed the I^2 statistic. This metric categorizes results as follows: no heterogeneity (0-24%), moderate heterogeneity (25%-49%), considerable heterogeneity (50-74%), and extreme heterogeneity (75%-100%). To summarize data across groups, we used the Mantel-Haenszel (M-H) method for hazard ratio (HR). We applied a fixed effect model if I^2 was less than 25%. Random effect model will be used if I^2 transcended 25% [14]. Moreover, to assess publication bias, we employed funnel plots. Our analysis was conducted using Review Manager 5.4.

Results

Literature Search

Our initial search found 1,255 studies from highly regarded sources like Cochrane, Science Direct, PubMed, and Google Scholar. After carefully sifting through these studies and eliminating duplicates, we assessed the titles and abstracts of 1,067 studies against specific criteria. Of these, we excluded many based on our inclusion criteria, leaving us with 184 observational studies for further review. Unfortunately, 168 of these studies did not meet our parameters and were excluded. Only 16 final eligible studies, mostly were retrospective observational studies, and was conducted in Asians [10,11, 15-28]. A total of 3,862 patients, with 2,793 Asian patients, were included in the systematic review and meta-analysis. The mean age was 50.6 years old, with a mean follow-up of 45.8 months. Moreover, cut-off lab parameters were 209.78 for PLR and 3.24 for NLR. The flow diagram of the study selection process is provided in Figure 1.

Progression Free Survival

Pooled univariate studies of ovarian cancer patients showed that higher pre-treatment NLR values are associated with worse PFS (HR 1.76; 95% CI [0.99–3.13], I^2=93%). The forest plot shows that from the six studies analyzed, only two had no notable difference between the two groups, and the difference was only marginal. Interestingly, when we further analyzed the multivariate studies, higher NLR had remarkably worse PFS (HR 1.35; 95% CI [1.05-1.74], I^2=74%). Figure 2 shows the forest plot of PFS for the NLR parameter.

Six univariate studies were reported for the correlative value between PLR and PFS in patients with ovarian cancer. The forest plot demonstrated that higher PLR is significantly linked to poorer PFS (HR 2.20; 95% CI [1.56–3.09], I^2=73%). Furthermore, the forest plot of the multivariate studies showed a similar result: patients with high PLR have significantly worse PFS (HR 1.62, 95% CI [1.09–2.43], I^2=87%). Figure 3 provides the forest plot of PFS for the PLR parameter.

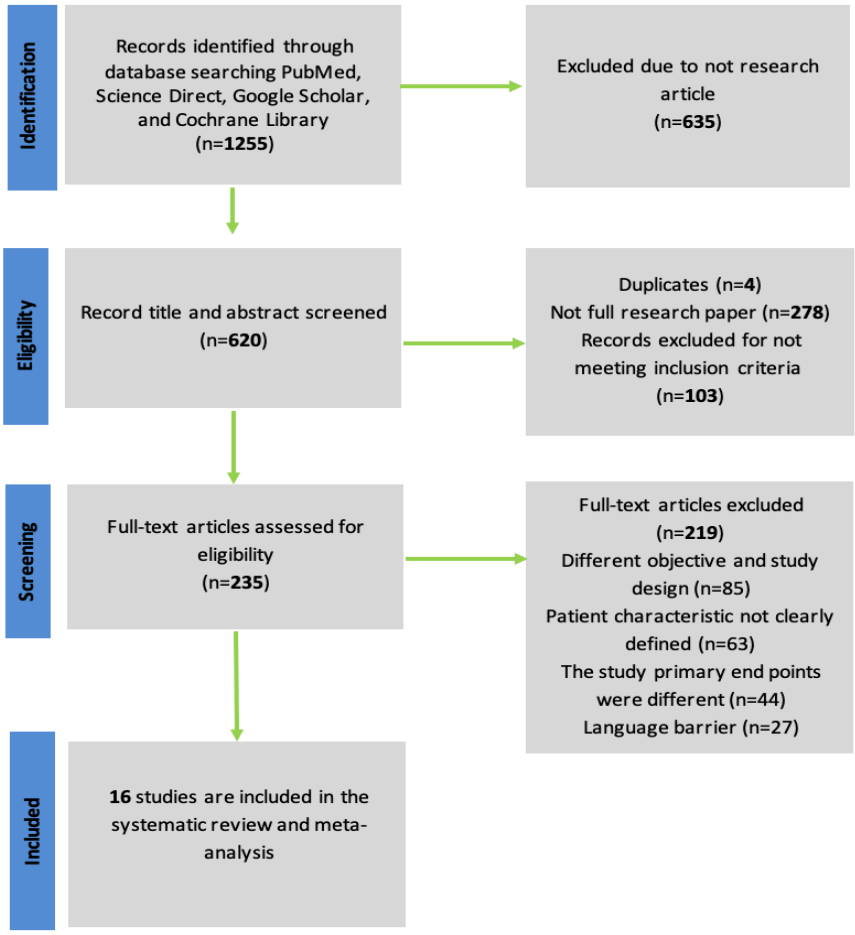

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram

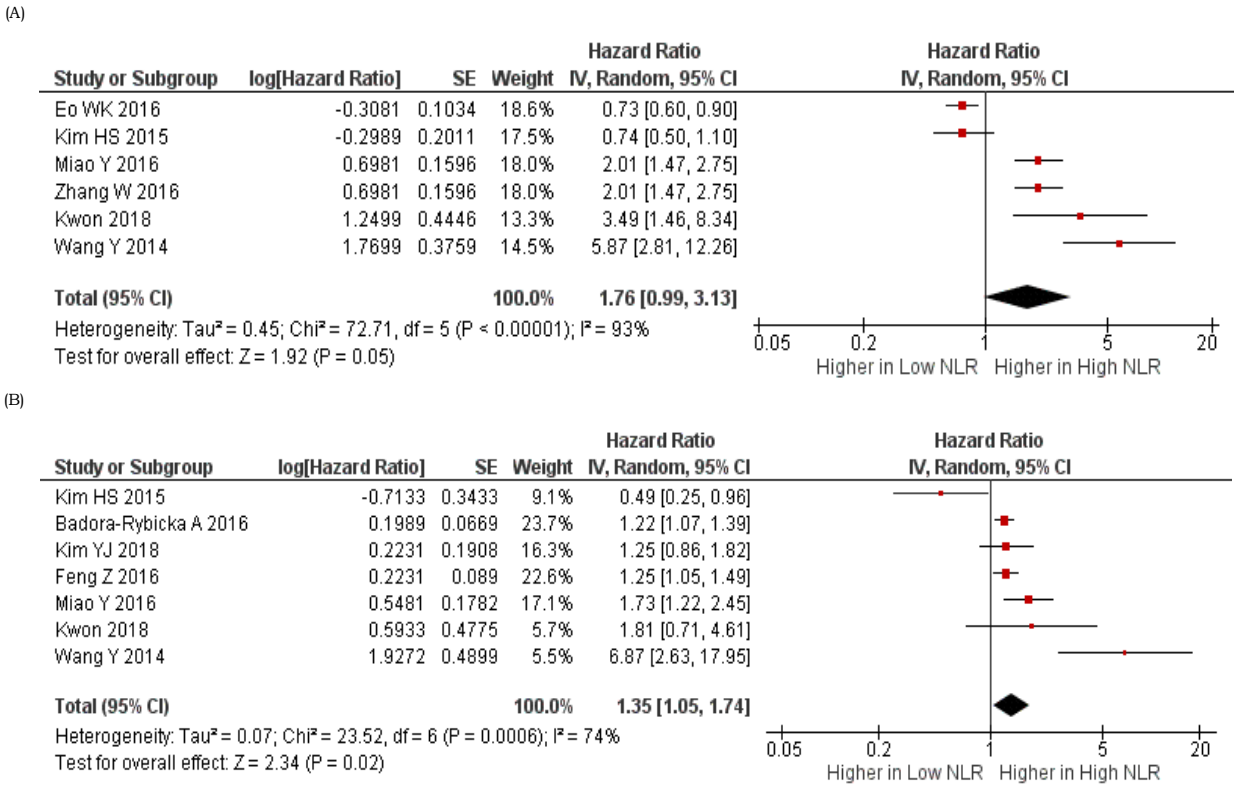

Figure 2. Forest Plot of Univariate Studies (A) and Multivariate Studies (B) of NLR on PFS in Patients with Ovarian Cancer. Note: SE, (Standard Error); IV, (Inverse Variance); CI, (Confidence Interval); NLR, (Neutrophil to lymphocyte Ratio); PFS, (Progression Free Survival)

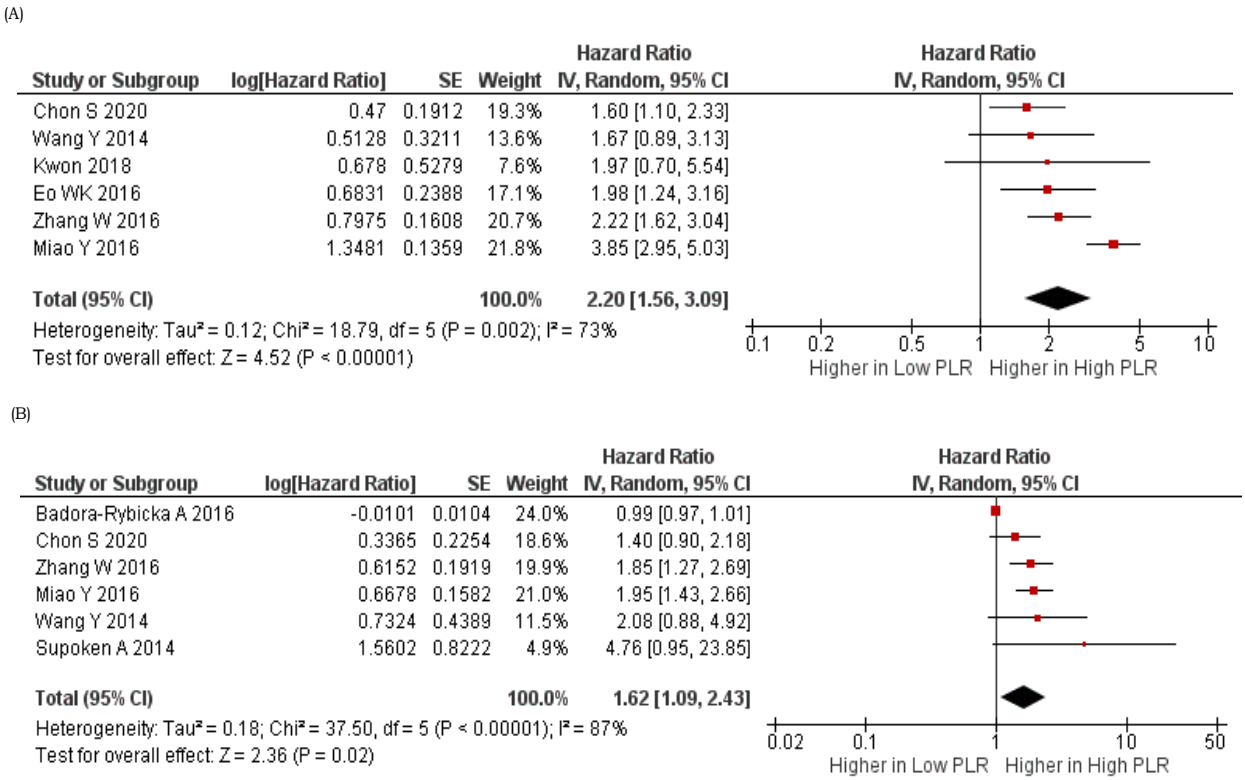

Figure 3. Forest Plot of Univariate Studies (A) and Multivariate Studies (B) of PLR on PFS in Patients with Ovarian Cancer. Note: SE, (Standard Error); IV, (Inverse Variance); CI, (Confidence Interval); NLR, (Neutrophil to lymphocyte Ratio); PFS, (Progression Free Survival)

Overall Survival

This analysis includes eight univariate studies of NLR on OS in ovarian cancer patients. The forest plot reveals a correlative value between higher NLR and worsening OS (HR 2.49; 95% CI [1.42-4.35], I^2=90%). Only one study reported an insignificant difference between the two groups. Nine multivariate studies were included for pooled multivariate analysis and showed analogous results (HR 1.46; 95% CI [1.16-1.83], I^2=63%).

Analysis for PLR includes seven univariate studies and seven multivariate studies. Higher PLR correlates with worse OS both in the analysis of univariate and multivariate studies (HR 2.47; 95% CI [1.86–3.26], I^2=61% and HR 1.66; 95% CI [1.12–2.46], I^2=88%) respectively.

Discussion

Many prognostic parameters have been studied to improve the treatment and outcomes of ovarian cancer patients. Currently, patients rely on conventional tests such as TNM staging, CA125, and CA199. However, these tests have limitations and are often unavailable and expensive in many health facilities, particularly in low to middle-income countries. Additionally, these parameters may not fully represent the true burden of ovarian cancer in patients.

Survival rates for ovarian cancer can vary, even when patients have similar disease stages, tumor subtypes, and receive identical treatments. As a result, there is a critical need for novel prognostic biomarkers that can help accurately predict patient prognosis and identify new therapeutic targets [29-30].

Recent studies suggest a correlation between tumor occurrence and development with the inflammatory response in the body. Various parameters related to inflammation, such as neutrophils, platelets, and lymphocytes, have been observed to play a critical role in tumor growth, invasion, and metastasis [10,11, 15-28]. The complete blood count is one of the most commonly used laboratory test and is widely available at all levels of health facilities. It provides information about the neutrophil count, platelet count, NLR, and PLR. Studies have reported a strong association between inflammation and the immune cells that mediate communication between tumor cells and the tumor microenvironment [31-32]. Inflammatory mediators such as interleukin-1 (IL-1), interleukin-6 (IL-6), vascular endothelial growth factor, and tumor necrosis factor can accumulate in neutrophils. This accumulation may promote the survival and multiplication of cancer cells. Neutrophils can also suppress the cytolytic activity of lymphocytes, natural killer cells, and T-cell proliferation [33-34].

Inversely, lymphocytes act as the main defense against tumor cells, inhibiting tumor cell growth and spread. The increased systemic inflammatory response release inhibitory mediators such as interleukin-10 (IL-10) found in the peritoneal fluid and sera of patients with ovarian cancer. This may contribute to the lymphopenia often observed in patients with ovarian cancer [35-37].

Proportion between neutrophils and lymphocytes, such as NLR, might be a promising novel prognostic factor. In addition, NLR parameter from a complete blood count is readily available in health facilities.

On the other hand, mechanism on on how tumors influence the Platelet to Lymphocyte Ratio (PLR) in ovarian cancer patients is not fully understood. The increase in PLR may be caused by a rise in platelet-dependent systemic inflammatory response and a decrease in lymphocyte-mediated antitumor immune response, which creates a favorable environment for tumor growth. Platelets play a vital role in hemostasis, thrombosis, inflammation, and vascular biology. A study with mouse models reported that tumors can cause thrombocytosis and thrombosis by stimulating IL-6 and hepatic thrombopoietin expression. According to recent studies, cancer patients have a high incidence of platelet-derived venous thromboembolism. Tumor cells activate platelets, which in turn promote accelerated tumor growth, angiogenesis, and metastasis. Once the tumor volume exceeds 1-2 mm3, angiogenesis occurs within the tumor from existing blood vessels. This process provides the necessary oxygen and nutrients to support tumor growth [39].

In this meta-analysis, it was found that patients with high NLR and PLR indeed have a worse prognosis. Among fourteen NLR-specific studies, two reported no significant relationship between an increase in NLR and a worsening prognosis [16, 24]. One study found no significant association between an increase in NLR and a deteriorating prognosis in univariate or multivariate analysis regarding PFS (progression-free survival) and OS (overall survival) [16]. After conducting a pooled analysis using a random effects model, the forest plot demonstrated that, overall, patients with increased NLR did have worse PFS and OS when compared to patients who had lower NLR. Notably, the study utilized a retrospective study design, limiting its ability to account for confounding variables such as smoking or oral contraceptive use that may impact systemic inflammatory response. Although the included studies might be affected by bias due to unmeasured confounding factors, NLR's prognostic value can still be attributed due to its relationship with inflammation.

It is well known that for various types of cancer, a high NLR indicates an advanced stage, or larger tumors with aggressive behavior. Although data on NLR for ovarian cancer is limited, Cho et al. discovered that prediagnostic NLR levels are more significant than platelet count in predicting both overall and progression-free survival in negative CA 125 cases. They also found that NLR levels were significantly higher in ovarian cancer cases than in other benign gynecologic diseases or healthy controls [23].

PLR is found to be a better predictor of tumor response after primary treatment compared to other factors. This is due to the interaction between tumor cells and platelets, which can promote tumor growth, invasion, and angiogenesis. Additionally, platelets can protect tumor cells from attacks by natural killer cells, leading to increased metastasis. As a result, individuals with ovarian cancer often experience thrombocytosis, which is linked to an inadequate response in solid tumors and lymphocytopenia. This occurs because tumor cells release thrombopoietin cytokines such as interleukin-6. [20].

The NLR and PLR are easily accessible and relatively inexpensive parameters that reflect the host's immune response. These parameters have been shown to be independent prognostic factors in many cancers [38-39]. In patients with ovarian cancer, NLR and PLR serve as markers of malignancy, but there is still conflicting data regarding their significance. This meta-analysis aims to evaluate whether NLR and PLR are significant prognostic factors in patients with ovarian cancer. Due to the lack of established NLR and PLR cut-off points, the results of this pooled analysis suggest that NLR and PLR may be potential predictive markers of ovarian cancer prognosis.

Limitations

There is significant variation among research studies in both NLR and PLR parameters on PFS and OS in pooled analysis. This could be due to the different characteristics of the studies, such as multiple cut-offs, different races, varying definitions of optimal studies, and other factors. In addition, the studies included are retrospective and have relatively small sample sizes. In attempts to address this, we utilize a random sample model in pooled analysis to better represent the results according to the general population.

In conclusion, in our systematic review and meta-analysis, we found that both high Neutrophil to Lymphocyte Ratio (NLR) and Platelet to Lymphocyte Ratio (PLR) are associated with worse progression-free survival (PFS) and five-year overall survival (OS) of patients with ovarian cancer. Our analysis suggests that NLR/PLR could be utilized as an early prognostic marker for ovarian cancer patients. However, a more extensive study which included a greater number of publications, as well as studies with a prospective design are needed to obtain more conclusive results.

Author Contribution Statement

Contributions are shared equally, all authors participate in the conceptualization, data collection, data analysis and interpretation, as well as the writing of the manuscript.

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General

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Ethical Declaration

This study is a systematic review and meta-analysis, therefore ethical clearance is not required.

Data Availability

Data supporting the findings in this study is accessible on the attached supplementary materials. Raw datas are available upon request to the corresponding authors.

Study Registration

The study registered on the International Prospective Register of Systematic Reviews (PROSPERO) with the CRD number 42024500275 (www.crd.york.ac.uk/prospero).

Conflict of Interest

The authors state no conflict of interest.

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