Clinical Research

Prognostic value of neutrophil-to-lymphocyte ratio and fibrinogen levels in ovarian cancer

Roudhona Rosaudyn[1], Faradillah Mutiani[2], Indra Yuliati[1], Birama Robby Indraprasta[1]

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Authors' affiliations:
[1]Department Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Hospital, Surabaya, Indonesia, [2]Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Hospital, Surabaya, Indonesia

Corresponding author:
Roudhona Rosaudyn
Department Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Hospital, Jalan Mayjen Prof. Dr. Moestopo 47, Surabaya 60131, Indonesia
Tel/Fax: +62-31-5501640/ +62-31-5012632
E-mail: rosaudyn@gmail.com

ABSTRACT

BACKGROUND High neutrophil-to-lymphocyte ratio (NLR) and fibrinogen levels have been associated with mortality in several malignancies. However, the studies on the association between NLR or fibrinogen levels and ovarian cancer prognosis are inconsistent. This study aimed to investigate the prognostic roles of NLR and fibrinogen in ovarian cancer.

METHODS A systematic search of electronic databases was performed to analyze studies on the association of pre-treatment NLR and fibrinogen levels with overall survival (OS) and progression-free survival (PFS) among patients with ovarian cancer. The hazard ratio (HR) and corresponding 95% confidence intervals [CIs] were analyzed. All statistical analyses were done using RevMan version 5.4 (Cochrane, United Kingdom).

RESULTS A total of 7,312 patients from 27 studies were included. The median cut-off for high NLR was 3.6 for OS among 17 studies and 3.23 for PFS among 11 studies reporting an NLR HR. The median cut-off for fibrinogen levels was 4.0 in 9 studies reporting fibrinogen levels HR. High NLR was associated with lower OS (HR 1.35, 95% CI 1.18 to 1.55, $p<0.0001$, $I^2 = 76\%$) and PFS (HR 1.35, 95% CI 1.14 to 1.60, $p = 0.0005$, $I^2 = 71\%$). High fibrinogen levels were associated with lower OS (HR 1.44, 95% CI 1.14 to 1.82, $p = 0.002$, $I^2 = 81\%$) and PFS (HR 1.34, 95% CI 1.17 to 1.55, $p<0.0001$, $I^2 = 15\%$). This association occurred in all ovarian cancer types.

CONCLUSIONS High pre-treatment NLR and plasma fibrinogen levels were related to poor OS and PFS in ovarian cancer.

KEYWORDS meta-analysis, ovarian cancer, prognosis, progression-free survival, survival analysis

In 2020, ovarian cancer was the third most common gynecological cancer worldwide. Ovarian carcinoma accounts for over 90% of all ovarian cancers and is the deadliest gynecological cancer because it is often diagnosed at an advanced stage.[1] It is the foremost cause of death in patients with gynecological cancer and the fifth most common cause of death in women.[2]

The prognosis of ovarian cancer depends on the disease stage at diagnosis. The 5-year relative survival rate of patients with ovarian cancer is approximately 49%, mainly because at least half the patients are diagnosed with distant-stage disease.[3] In patients with advanced-stage ovarian cancer (stage IV), the 5-year survival rate falls to 17%, indicating a poor prognosis.[1,4] In women under 65 years of age, the rate is almost twice as high (61%) as in those aged 65 years and older (33%).[3] However, a better prognosis of ovarian cancer can be predicted by numerous favorable factors,

including younger age, good performance status, histological type other than clear cell or mucinous, well-differentiated tumor, early-stage tumor, smaller volume before debulking surgery, smaller residual tumor after primary cytoreductive surgery, BRCA1 or BRCA2 mutation carrier status, and lack of ascites.[5]

Cancer pathogenesis can be affected by inflammatory pathways. Hence, identifying the systemic inflammation status is a high priority.[6] Inflammation is a significant prognostic risk factor. Appropriate biological indicators, such as CA125, soluble cytokeratin, serum human kallikreins, serum cytokines, serum vascular endothelial growth factor, plasma D-dimer, and fibrinogen, may reflect the inflammatory state.[7] The neutrophil-to-lymphocyte ratio (NLR) is a marker of systemic inflammation assessed through a complete blood count examination, providing absolute neutrophil and lymphocyte counts.

A high pretreatment NLR is primarily associated with poor survival outcomes, based on several meta-analyses of patients with cancer.[6,8,9] In recent studies, plasma fibrinogen levels have been associated with tumor progression and poor prognosis in patients with several cancers. For example, increased plasma fibrinogen levels in hepatocellular carcinoma are independently associated with advanced disease stages and poor prognosis.[10] Other studies have also revealed that pretreatment with fibrinogen is a strong predictor of poor survival in gastric and digestive cancers with different traits.[11,12] Recent studies have revealed an association between the NLR or fibrinogen levels and ovarian cancer prognosis. However, these findings are varied. Therefore, this study aimed to investigate the prognostic roles of NLR and fibrinogen levels in ovarian cancer.

METHODS

Search strategy

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A systematic literature search was performed using the PubMed and ScienceDirect databases for relevant studies published until July 7, 2023. The subsequent search phrases used were ("NLR ratio" OR "neutrophil-lymphocyte ratio" OR "Neutrophil to Lymphocyte ratio" OR "fibrinogen") AND ("ovarian cancer" OR "ovarian malignancy" OR "ovarian carcinoma" OR "cancer ovary" OR "carcinoma ovary").

Inclusion and exclusion criteria

Two investigators (RR and MF) independently identified all the articles. The included studies met all the following criteria: (1) studies in women with ovarian cancer that reported the prognostic effect of NLR and/or plasma fibrinogen; (2) NLR and/or plasma fibrinogen values collected before all treatments; (3) studies investigating the correlation of pretreatment NLR and/or fibrinogen levels with overall survival (OS) and/or progression-free survival (PFS); (4) studies with adequate data to evaluate the hazard ratio (HR) with a 95% confidence interval (CI); and (5) clinical trials, cohort, or case-control studies. The exclusion criteria were as follows: (1) overlapping or duplicate publications; (2) abstracts, reviews, letters, case reports, case series, editorials, and comments; (3) non-English studies; (4) non-human research; (5) unpublished trials; (6) studies presenting data in graphic form only (e.g., Kaplan–Meier curves) without reporting numerical HR values; and (7) full-text unavailability. Disagreements between the two researchers were resolved through discussion and consensus.

Data extraction

The following characteristics were extracted from each included study: name of the first author, year of publication, number of patients included in the analysis, mean or median age, disease stage, study design (prospective or retrospective), boundaries used to determine scores, high plasma NLR or fibrinogen levels, treatment gain, and HR with 95% CI for OS and/or PFS.

Quality assessment of primary study

The quality of the included studies was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS). An NOS score of more than five was considered high quality. Disagreements were resolved through discussion and consensus.

Statistical analysis

The extracted data were collected using the RevMan 5.4 software (Cochrane, United Kingdom). This analysis was conducted on all included studies for each relevant outcome. The main outcomes of interest were OS and PFS. HR estimates were pooled, weighted by generic inverse variance, and calculated using a random-effects model. Heterogeneity was evaluated

using Cochran's Q test and I^2 statistics. A random-effects model was used if significant heterogeneity was present (I^2>50% or Cochran's Q<0.1). Sensitivity analysis was performed to investigate the effect of omitting studies that could contribute to data heterogeneity, including studies that provided a multivariate HR or in which NLR or plasma fibrinogen levels were used as continuous variables. Predefined subgroup analyses were performed according to the disease stage and specific treatment. Disease stages were classified as per the International Federation of Gynecology and Obstetrics (FIGO) stages (I, II, III, and IV), and advanced stages referred to FIGO stages III and IV. Specific treatments were classified into surgery, chemotherapy, and mixed therapy (surgery and/or chemotherapy). Publication bias was assessed by visual inspection of funnel plots. All statistical tests were two-sided, and statistical significance was defined as p<0.05.

RESULTS

Extraction process and study characteristics

A total of 302 studies were identified using the search strategy. The initial search and study selection processes are presented in Figure 1. As a result, 27 studies published between 2009 and 2021, which included 7,312 patients, were included in this meta-analysis.

The majority of the patients included in the studies were above 50 years of age. Most ovarian cancers were of epithelial type. However, 15% of the 143 samples in the study by Wang et al[13] were non-epithelial ovarian cancers. Most ovarian cancers were classified as advanced stage III or IV based on the FIGO criteria. The studies used different cut-offs to classify high NLR (range 0.89 to 6.00) and high fibrinogen (range 3.63 to 4.85). The median cut-off for a high NLR was 3.6 for OS in 17 studies and 3.23 for PFS in 11 studies that reported an NLR HR. The median cut-off for high fibrinogen was 4.0 in nine studies reporting HR fibrinogen levels. The main characteristics of the included studies are summarized in Table 1.[13–39]

Characteristics of high NLR and high plasma fibrinogen

The pretreatment NLR and fibrinogen values were obtained from blood tests prior to the initial primary treatment in most studies, except for two studies[14,24] that included patients with recurrent disease and one study[21] that included patients with previous surgical treatment. Patients in eight studies[15,18,23,28,29,37–39] underwent surgical intervention or neoadjuvant chemotherapy (NACT), and patients in 13 studies[13,16,17,19,20,25–27,31–33,35,36] underwent primary surgery (primary staging or debulking surgery) with or without adjuvant chemotherapy as the initial intervention for treatment. Four studies[14,21,22,28] included patients who were treated with chemotherapy (Table 1).

Of the 5,018 patients in the studies evaluating NLR, 29.5% (1,482 patients) had high NLR levels, 74.0% (1,097 patients) were diagnosed with advanced-stage ovarian cancer, and the majority had serous carcinoma. Most patients with a high NLR were >50 years of age and had CA125 levels varying from <35 U/ml to 2,306 U/ml (Supplementary Table 1). High plasma fibrinogen levels were seen in 26.9% (618 of 2,294 patients in plasma

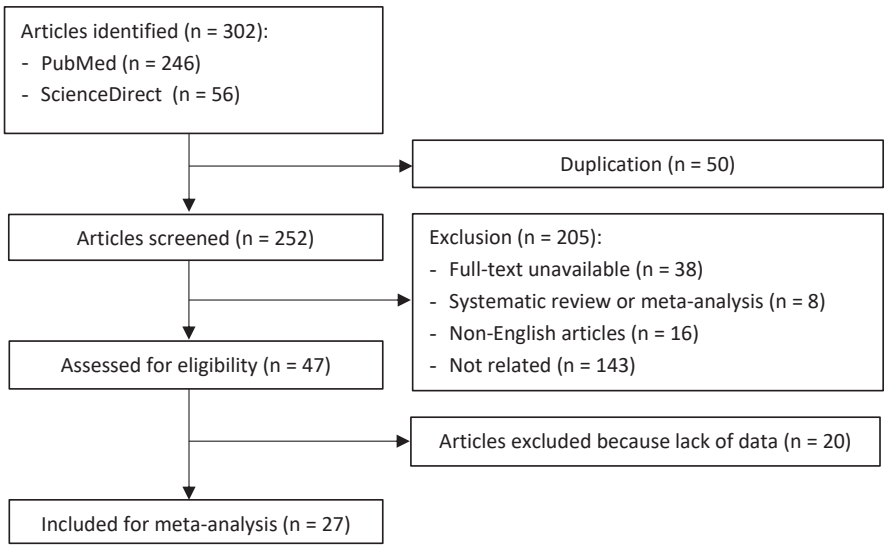

Figure 1. Flow chart of the study selection process

Table 1. Baseline characteristics of the included studies

First author, year	Study	Country	Outcomes	Cut-off	N	Duration of follow-up (months), median/ mean (range/SD)	Age (years), median/mean (range/SD)	FIGO stage, n (%)	Treatment strategy	NOS
NLR										
Henriksen,[14] 2020	Prospective cohort	Denmark	OS	≥4.1	69	19.3 (11.7–33.3)	69 (47–92)	NA	Chemotherapy	7
Marchetti,[15] 2021	Prospective cohort	Italy	PFS and OS	>4	397	24 (4–47)	60.2 (27–89)	1. III: 282 (71.8) 2. IV: 111 (28.2)	1. PDS: 76 (38.2%) 2. NACT: 123 (61.8%)	7
Asher,[16] 2011	Retrospective	United Kingdom	OS	>4	235	NA	62 (24–90)	1. I: 55 (23.4) 2. I: 28 (11.9) 3. III: 107 (45.5) 4. IV: 34 (14.5) 5. Missing: 11 (4.7)	Primary surgery	6
Komura,[17] 2018	Retrospective	Japan	PFS	≥4	344	NA	NA	1. I/II: 189 (54.9) 2. III/IV: 155 (45.1)	Primary surgery with/ without adjuvant chemotherapy	7
Wang,[13] 2016	Retrospective	China	PFS and OS	>3.43	143	NA	52.27 (14.09)	1. I/II: 54 (38) 2. III/IV: 89 (62)	Primary surgery	7
Baert,[18] 2018	Retrospective cohort	Belgium	PFS and OS	6	39	NA	NA	NA	PDS and NACT	6
Miao,[19] 2016	Retrospective	China	PFS and OS	>3.02	344	72 (61–97)	55 (45–84)	1. I/II: 168 (48.8) 2. III/IV: 176 (51.2)	Surgical staging or PDS and adjuvant chemotherapy	7
Zhou,[20] 2018	Retrospective	China	PFS and OS	>3.08	370	>10 years	54.3 (8.7)	IIIC	Surgery and adjuvant chemotherapy	7
Badora-Rybicka,[21] 2016	Retrospective	Poland	PFS and OS	0.89	315	NA	54 (22–77)	1. I: 61 (19.4) 2. II: 30 (9.5) 3. III: 186 (59) 4. IV: 38 (12.1)	Platinum-taxane regimen (after previous surgery)	6
Salman,[22] 2020	Retrospective cohort	Israel	OS	6	111	NA	NA	1. IIIC: 88 (79.3) 2. IV: 23 (20.7)	NACT 3–4 cycles then with/ without IDS	6
Jeerakornpassawat,[23] 2020	Retrospective	Thailand	OS	>3.38	306	NA	54.14 (9.72)	1. I: 92 (30.1) 2. II: 22 (7.19) 3. III: 129 (42.2) 4. IV: 18 (5.9)	1. NACT: 75 (24.5%) 2. Upfront surgery: 231 (75.5%) 3. Adjuvant chemotherapy	6
Cho,[24] 2009	Retrospective cohort	South Korea	OS	2.61	192	20.9	51.8 (12.9)	1. I/II: 59 2. III/IV: 125 3. Recurrence: 8	Elective surgery	8

Table continued on next page

Table 1. (continued)

First author, year	Study	Country	Outcomes	Cut-off	N	Duration of follow-up (months), median/ mean (range/SD)	Age (years), median/mean (range/SD)	FIGO stage, n (%)	Treatment strategy	NOS
Feng,[25] 2016	Retrospective	China	PFS and OS	>3.24	875	29 (1–115)	56 (30–90)	1. I/II: 75 (8.6) 2. III/IV: 800 (91.4)	PDS or primary staging with/without received platinum-based adjuvant chemotherapy	6
Wang,[26] 2015	Retrospective	China	PFS and OS	3.77	126	41.3 (3.3–70.4)	NA	1. I/II: 33 2. III/IV: 93	PDS or primary staging with/without received platinum-based adjuvant chemotherapy	7
Li,[27] 2017	Retrospective cohort	USA	OS	5.25	654	49.5 (0.1–175.3)	63 (28–93)	1. I: 87 (13.3) 2. II: 34 (5.2) 3. III: 416 (63.6) 4. IV: 117 (17.9)	PDS or primary staging with/without received platinum-based adjuvant chemotherapy	7
Kim,[28] 2018	Retrospective cohort	South Korea	PFS and OS	3.81 (OS) and 2.23 (PFS)	197	NA	57 (27–80)	1. IIIB: 7 (3.6) 2. IIIC: 45 (22.8) 3. IVA: 89 (45.2) 4. IVB: 56 (28.4)	NACT then underwent IDS	8
John-Olabode,[29] 2021	Retrospective cohort	Nigeria	PFS and OS	1.93	93	NA	47.1	1. I/II: 28 (30.2) 2. III/IV: 65 (69.8)	PDS and NACT	7
Williams,[30] 2014	Retrospective	USA	OS	NA	519	5.7 years (1 month–21 years)	NA	1. I: 150 (30) 2. II: 44 (9) 3. III: 266 (53) 4. IV: 42 (8)	NA	6
Fibrinogen										
Qiu,[31] 2012	Retrospective	China	OS	4.0	136	NA	44.42 (12.97)	1. I: 22 2. II: 26 3. III: 81 4. IV: 7	Primary surgical staging then platinum-based chemotherapy	7
Li,[32] 2019	Retrospective cohort	China	OS	3.63	186	NA	59.2 (51.1–65.9)	1. I/II: 52 (28.0) 2. III/IV: 134 (72.0)	Primary CRS	7
Polterauer,[33] 2009	Retrospective	Austria	OS	4.0	422	29.2 (25.1)	59.9 (13.9)	1. I: 88 2. II: 29 3. III: 252 4. IV: 53	Surgery and adjuvant chemotherapy	6
Hu,[34] 2020	Retrospective cohort	China	PFS and OS	4.0	104	NA	53 (37–81)	1. I/II: 23 2. III/IV: 81	NA	7

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Table 1. (continued)

First author, year	Study	Country	Outcomes	Cut-off	N	Duration of follow-up (months), median/ mean (range/SD)	Age (years), median/mean (range/SD)	FIGO stage, n (%)	Treatment strategy	NOS
Feng,[35] 2016	Retrospective	China	PFS	4.0	724	29 (1–115)	56 (30–90)	1. I/II: 62 2. III/IV: 662	Primary staging or PDS with/without platinum-based adjuvant chemotherapy	6
Zhang,[36] 2015	Retrospective	China	OS and PFS	4.0	190	43 (2–164)	50.6 (11.1), (24–76)	1. I: 22 2. II: 31 3. III: 128 4. IV: 9	CRS and platinum-based adjuvant chemotherapy	7
Man,[37] 2015	Retrospective	China	PFS and OS	4.0	190	48 (2–150)	55 (25–8)	1. I/II: 89 2. III/IV: 101	1. PDS and adjuvant chemotherapy 2. NACT	7
Liu,[38] 2015	Retrospective	China	PFS	4.0	125	49 (5–85)	51 (25–73)	1. I/II: 39 2. III/IV: 86	1. CRS then adjuvant chemotherapy 2. NACT	7
Luo,[39] 2017	Retrospective cohort	NA	OS	4.852	217	44.5 (7–167.2)	54.4 (25–84)	1. IIIA: 3 (1.4) 2. IIIB: 15 (6.9) 3. IIIC: 149 (68.7) 4. IV: 50 (23)	NACT and non-NACT	7

CRS=cytoreductive surgery; FIGO=The International Federation of Gynecology and Obstetrics; IDS=interval debulking surgery; NA=not available; NACT=neoadjuvant chemotherapy; NLR=neutrophil-to-lymphocyte ratio; NOS=Newcastle-Ottawa Quality Assessment Scale; OS=overall survival; PFS=progression-free survival; PDS=primary debulking surgery; SD=standard deviation

fibrinogen studies), and 81.4% (503 patients) were diagnosed with advanced-stage ovarian cancer. Almost all the patients had serous epithelial ovarian cancer (Supplementary Table 1).

NLR and OS

Multivariate analysis demonstrated an association between an NLR greater than the cut-off value and a lower OS. In the subgroup analysis, a higher NLR was associated with lower OS in patients with ovarian cancer at all stages and at the advanced stage (Figure 2a). In addition, subgroup analyses based on the type of therapy administered revealed that patients with a higher NLR who underwent surgery and chemotherapy had a shorter OS (Supplementary Figure 1).

NLR and PFS

According to the multivariate analysis, an NLR higher than the cut-off was associated with a lower

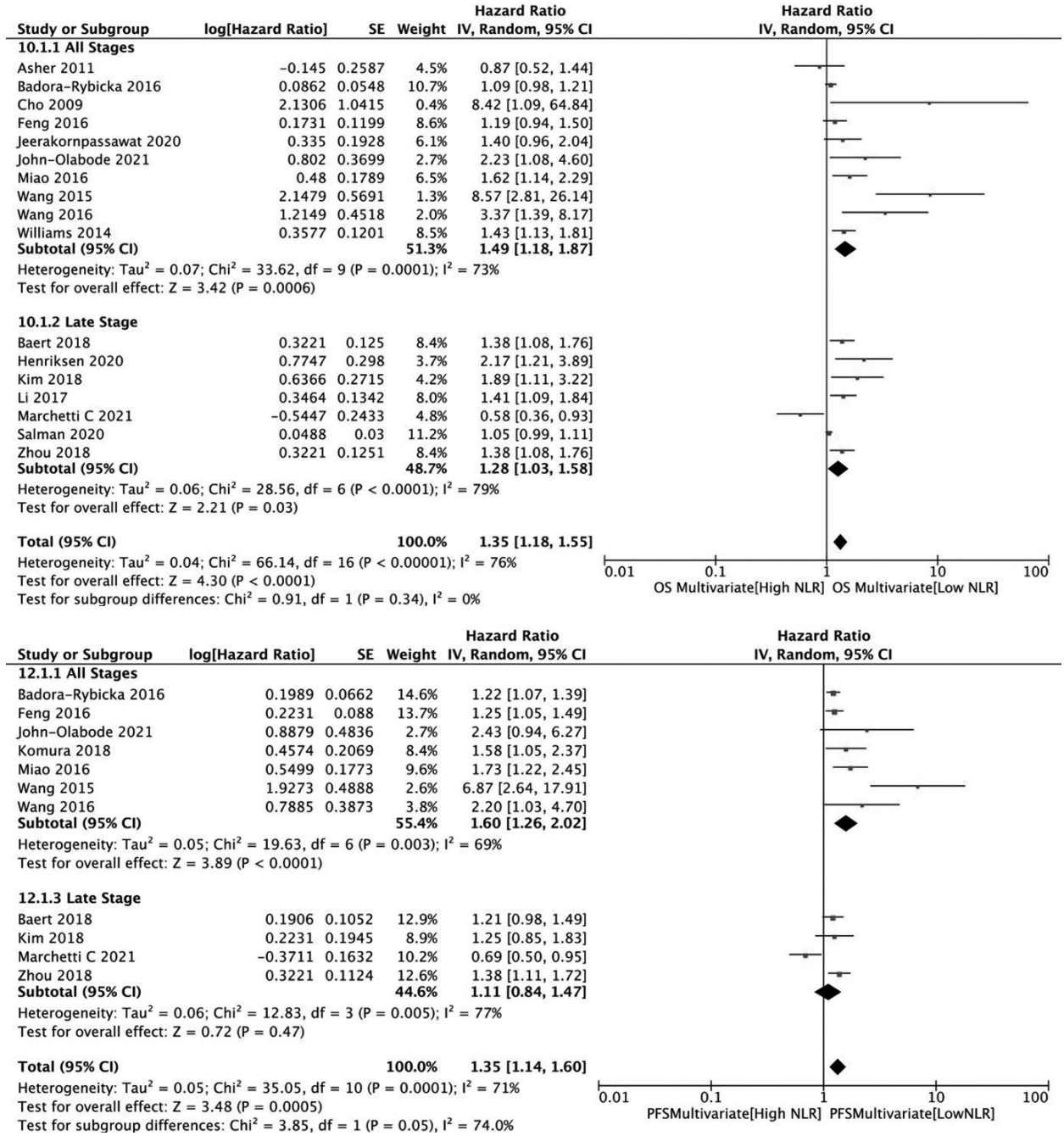

Figure 2. Forest plots showing HR of OS (a) and PFS (b) according to pretreatment NLR. CI=confidence interval; HR=hazard ratio; NLR=neutrophil-to-lymphocyte ratio; OS=overall survival; PFS=progression-free survival; SE=standard error

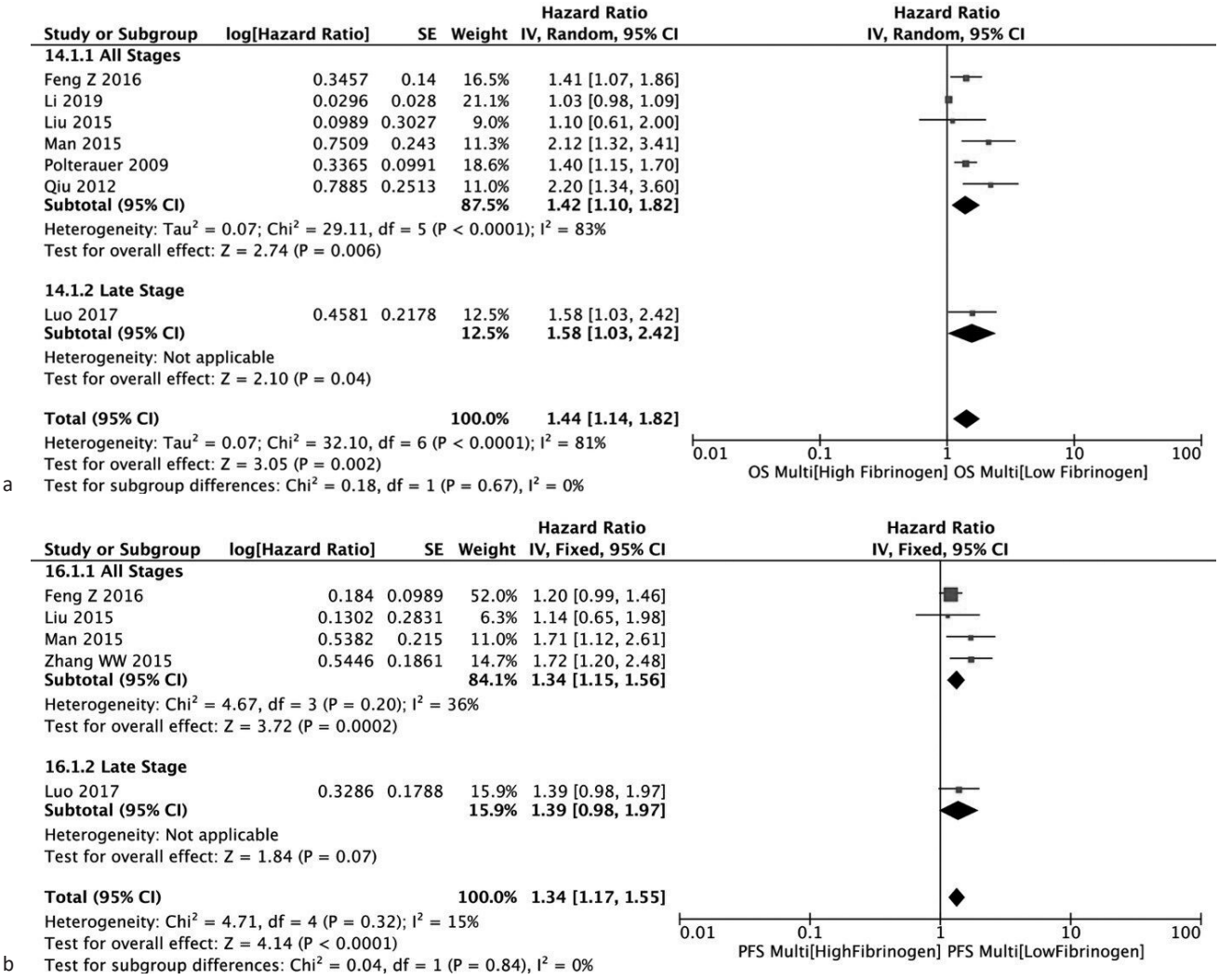

Figure 3. Forest plots showing HR of OS (a) and PFS (b) according to pretreatment fibrinogen level. CI=confidence interval; HR=hazard ratio; OS=overall survival; PFS=progression-free survival; SE=standard error

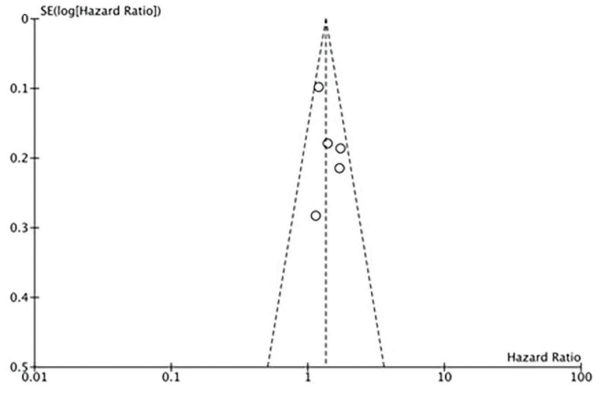

Figure 4. Funnel plots of HR of plasma fibrinogen according to the PFS in multivariate analyses (horizontal axis) and the SE for the HR (vertical axis). Each study is represented by one circle. The vertical line represents the pooled effect estimate. HR=hazard ratio; PFS=progression-free survival; SE=standard error

PFS. In subgroup analysis, a higher NLR was associated with shorter PFS in all stages of ovarian cancer (Figure 2b). Subgroup analysis based on the type of therapy administered revealed that patients with a higher NLR, both in those who underwent surgery and chemotherapy, had a lower PFS (Supplementary Figure 2).

Plasma fibrinogen level and OS

Multivariate analysis showed that plasma fibrinogen levels greater than the cut-off value were associated with a lower OS. According to the subgroup analysis, higher plasma fibrinogen levels were associated with lower OS in patients with ovarian cancer at all stages (Figure 3a) and in those who underwent surgical treatment (Supplementary Figure 3).

Plasma fibrinogen level and PFS

Fibrinogen levels greater than the cut-off were associated with lower PFS (Figure 3b) in patients who underwent surgical treatment (Supplementary Figure 4). In subgroup analysis, higher plasma fibrinogen levels were associated with lower PFS in patients with ovarian cancer at all stages.

Sensitivity analysis

A sensitivity analysis was performed to assess the effect of each study on the pooled HR. One study included in the pooled meta-analysis was omitted from each round of analysis. If the corresponding HR did not change significantly, this suggested that the meta-analysis results were credible (data not shown).

Publication bias

Funnel plots were used to evaluate publication bias. All NLR analyses exhibited asymmetric funnel plots, indicating a substantial publication bias. The funnel plots of the plasma fibrinogen analyses were asymmetric, except for the five-study analysis of plasma fibrinogen levels and PFS in ovarian cancer (Figure 4). Other funnel plots are shown in Supplementary Figures 5–7.

DISCUSSION

This meta-analysis pooled a large number of studies on the prognostic value of NLR and fibrinogen levels on OS and PFS in patients with ovarian cancer. Overall, higher NLR or plasma fibrinogen levels were associated with poor prognosis in patients with ovarian cancer. Patients with low NLR or plasma fibrinogen levels had higher OS and PFS despite heterogeneity. The prognostic effects of the NLR and plasma fibrinogen levels were reliable at all stages (FIGO stages I–IV) and advanced stages (FIGO stages III–IV). These results suggest that decreased NLR or plasma fibrinogen predicts a favorable prognosis in ovarian cancer, in agreement with a meta-analysis on pretreatment NLR or plasma fibrinogen and other cancer prognoses.[8,9,11,40,41] Analyses of sensitivity and publication bias indicated that our results were credible.

It is important to identify systemic inflammation status as the inflammatory pathway is known to play a role in many diseases, including cancer.[6] Inflammation is a hallmark of the development and progression of cancer.[42,43] Chronic inflammation has been suggested to cause the development of malignant tumors, which increases the probability of and accelerates mutations. Therefore, inflammation can affect the incidence, tumor stage, and development of cancer. Increasing evidence suggests an elevated systemic inflammatory response as an important indicator of cancer progression and prognosis.[44,45] Recent studies have shown that the interactions between tumor cells, immune cells, inflammatory cells, and interstitial components influence tumor metastasis.[43]

Various biochemical or hematological features routinely measured in general blood tests or as ratios derived from the measurements can be used to assess systemic inflammation. Previous studies have highlighted several ratios associated with morbidity and mortality, including NLR, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, C-reactive protein/albumin ratio, and systemic immune-inflammation index.[44–46] However, most of these studies examined them as prognostic markers in patients newly diagnosed with cancer, even though this ratio has been associated with cancer risk and mortality.[44]

Lymphocytes, the primary antitumor response effectors, have prognostic and predictive values in cancer treatment.[22–24] The role of neutrophils in cancer is controversial, as they can either impede or promote tumor growth.[26,27] NLR, a marker of disease burden, was hypothesized to be an independent prognostic factor after adjusting for disease stage, metastatic site, and tumor markers.[10–12] However, data on blood parameters and the mechanical basis for the prognostic value of NLR remain unclear.[23,47] NLR is an affordable and promising index for cancer prognosis; however, some studies have shown conflicting results.[7,8,47–49]

Other markers of inflammation, such as plasma fibrinogen, are associated with tumor development and poor prognosis in several patients with cancer.[10,50] For example, studies on hepatocellular carcinoma,[10] gastrointestinal cancers of different types,[11] and gastric cancer[12] have revealed that elevated plasma fibrinogen levels before treatment are independently associated with poor prognosis or survival. Tumor growth, invasion, and distant metastasis are associated with coagulation disorders. Several studies have discussed the role of fibrinogen in cancer pathogenesis.[12–14] Fibrinogens can act as a platform to bind to tumor cells and platelets when they detach from the primary focus into the circulation,[14] contributing to tumor cell adherence to distant organs and facilitating tumor angiogenesis.

Evidence has shown that fibrinogen supplies nutrients and exchanges gases for the proliferation of tumor cells. Fibrinogen promotes tumor cell migration and protects cells from the innate immune system by acting as an extracellular matrix.[13] Zheng et al[51] reported that fibrinogen can accumulate and form dense fibrin layers around tumor cells, protecting them from natural killer cell-mediated cytotoxicity. Gropp et al[52] also found that fibrinogen breakup products repress immune reactions.

Based on the present meta-analysis, patients with low NLR and low plasma fibrinogen serum levels had greater OS and PFS. In a subgroup study of patients with ovarian cancer at any stage who were simultaneously receiving surgical treatment, those with lower OS and PFS had higher NLR and plasma fibrinogen levels. Moreover, multivariate analysis showed that a higher NLR was associated with lower OS and PFS in patients with ovarian cancer receiving chemotherapy. These results are similar to those of another study involving 2,919 patients, in which lower OS and PFS were found in the group with high NLR rates in multivariate and univariate analyses.[53] Luo et al[39] also showed that high plasma fibrinogen levels were associated with poor PFS and OS.

In contrast to the present study, a study on preoperative NLR in high-grade serous ovarian cancer found that high NLR was an independent predictor for PFS ($p = 0.011$) but not for OS ($p = 0.148$) in multivariate analysis.[25] A retrospective study in patients with ovarian cancer receiving NACT also stated that a high NLR was significantly associated with poor median OS ($p = 0.012$) but not significantly associated with median PFS ($p = 0.128$).[54] However, there is marked variability in the cut-off values of NLR among ovarian cancer studies.[49,54] Patients with a low NLR in the population have minimal systemic inflammation and better prognostic features, which may be the main reason why NLR lost prognostic significance in multivariate analysis.[54]

Some studies have added other prognostic scores such as combined NLR and fibrinogen levels (F-NLR) for different tumors, including non-small cell lung cancer,[40] esophageal squamous cell carcinoma,[41] and ovarian cancer,[55] with interesting results. Marchetti et al[55] revealed that patients with high F-NLR (NLR ≥3.24 and fibrinogen ≥450 mg/dl) had a significantly shorter PFS ($p = 0.023$) in ovarian cancer than patients with low F-NLR (NLR <3.24 and fibrinogen <450 mg/dl).

This study had several limitations. The varied cut-off values of NLR and plasma fibrinogen in several studies led to high heterogeneity. Additionally, there was publication bias in the NLR and plasma fibrinogen analyses. Some studies did not explicitly state the variables included in the multivariate model, thus generating uncertainty in interpreting the independent prognostic value of the NLR. Furthermore, only English articles were included, leading to language and publication biases. Most of the included studies were retrospective; therefore, additional clinical trials and research are essential to draw more accurate conclusions.

In conclusion, NLR and plasma fibrinogen levels were reliable indicators of ovarian cancer prognosis. These affordable tests are widely available at hospitals. The F-NLR score could also be a prognostic blood marker. However, these indicators could be affected by factors such as disease burden, age, and systemic inflammation. Further research is needed to understand the association between prognostic value and the combination of NLR and plasma fibrinogen levels.

Conflict of Interest
The authors affirm no conflict of interest in this study.

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