Original Paper

Prognostic Significance of Neutrophil-to-Lymphocyte Ratio in Ovarian Cancer: A Systematic Review and Meta-Analysis of Observational Studies

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Key Words

Ovarian cancer • Inflammatory • Neutrophil • Lymphocyte • Prognosis

Abstract

Background and Aims: Published data on the prognostic role of neutrophil-to-lymphocyte ratio (NLR) in ovarian cancer are controversial. We conducted this meta-analysis to obtain a more accurate assessment of prognostic significance of NLR in ovarian cancer. **Materials and Methods:** We conducted a systematic literature search using the electronic databases PubMed, Web of Science, and Embase up to May 2016. Hazard ratio (HR) and odd ratio (OR) with 95% confidence interval (95% CI) were calculated. Subgroup analyses were carried out to explore the source of heterogeneity. Statistical analysis was performed using Stata 10.0. **Results:** A total of 12 studies, consisting of 3,854 patients, which met our criterion were selected in this meta-analysis. Our pooled results showed that high pre-treatment NLR level was significantly associated with poorer overall survival (OS) (HR: 1.69, 95% CI 1.29-2.22) and shorter progression free survival (PFS) (HR 1.63, 95% CI 1.27-2.09). Additionally, increased NLR was also significantly correlated with advanced FIGO stage (OR 2.32, 95% CI 1.79-3.00), higher serum level of CA-125 (OR 3.33, 95% CI 2.43-4.58), more extensive ascites (OR 3.54, 95% CI 2.31-5.42) as well as less chemotherapeutic response (OR 0.53, 95% CI 0.40-0.70). The findings from most of subgroup meta-analyses were consistent with those from the overall meta-analyses. **Conclusions:** Elevated pre-treatment NLR could served as a predicative factor of poor prognosis for ovarian cancer patients

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Introduction

Ovarian cancer is one of the most common and lethal female malignancy, and there are over 200,000 estimated new cases and 150,000 deaths every year globally [1, 2]. After

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primary therapy including debulking surgery and platinum-based adjuvant chemotherapy, approximately half of the patients will relapse within 1 year, and the five-year overall survival rate is less than 50% [3-5]. Therefore, effective bio-markers for individualized prediction of therapy outcomes and prognosis are urgently warranted.

The associations between inflammation and tumor development have gained much interest in the past few decades [6]. Neutrophil to lymphocyte ratio (NLR), defined as the ratio of neutrophil to lymphocyte count, is a marker for evaluating the systemic potential balance between neutrophil-dependent pro-tumor inflammation and lymphocyte-associated anti-tumor immune response [7]. A higher level of NLR could represent a trend towards increased pro-tumor inflammation and decreased anti-tumor immune capacity.

Accumulating evidence demonstrates that NLR has prognostic significance in patients with various types of cancers [8-11], including gastrointestinal tract malignancies, pancreatic carcinoma, hepatocellular cancer, non-small-cell lung cancer as well as cervical carcinoma. Recently, several studies evaluated the prognostic significance of NLR in patients with ovarian cancer [12-25]. But the results of each individual studies were inconsistent. Therefore, the prognostic significance of NLR in ovarian cancer remained controversial. To clarify this issue, we performed this systematic review and meta-analysis to obtain a more reliable assessment of prognostic significance of NLR in patients with ovarian cancer.

Materials and Methods

This systematic review and meta-analysis was performed following the guidance provided in the Cochrane Handbook and was reported according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [26].

Search strategy

We conducted a systematic literature search using the electronic databases PubMed, Web of Science, and Embase up to May 2016. Search terms included “neutrophil to lymphocyte ratio”, “NLR”, “ovarian” and “tumor, cancer, neoplasm, carcinoma or malignancy”. The titles and abstracts of potential references were scanned carefully to exclude irrelevant articles. The remaining studies were assessed to identify the topic of interest, and full texts were then reviewed comprehensively.

Selection criteria

A study was included if it met the following criteria: (1) included patients with ovarian cancer diagnosed histopathologically; (2) provided pre-treatment and/or post-treatment NLR and cut-off values, (3) evaluated the associations between pre-treatment and/or post-treatment NLR and survival outcomes. Exclusion criteria were (1) review articles, editorial comments, letters, expert opinion, conference abstracts, or case reports; (2) insufficient data for estimating hazard ratios (HRs) and 95% confidence intervals (CIs); or (3) full text unavailable and non-English article.

All assessments were conducted independently by two reviewers to assure accuracy of inclusive studies. Multivariate data were preferred to univariate data if both were provided. However, univariate data were acceptable if no multivariate results were presented.

Data extraction

Two investigators independently gathered information from each eligible study. Data was extracted as follows: surname of first author, study country, year of publication, sample size, cancer stage, treatment method, cut-off value defining elevated NLR and hazard ratios (HRs) with 95% confidence intervals (CIs) for overall survival (OS) and progress-free survival (PFS)/recurrence-free survival (RFS). Disagreements in data extraction were resolved through discussion.

Assessment of methodological quality

Two independent investigators assessed the quality of each study included using the Newcastle-Ottawa Quality Assessment Scale (NOS) [27]. On a score scale from 0 to 9, a study with 7 or more stars was considered as high-quality.

Statistical analysis

The HR and and corresponding 95% CI were used to evaluate the prognostic efficiency of NLR on ovarian cancer. HRs and 95% CIs, either obtained directly from each articles or calculated from indirect data, were synthesized as the effective value. In addition, the relationship between NLR and clinical-pathological features were reported as odd ratios (ORs) and 95% CIs. Cochran's Q test and Higgins I-squared statistic were adopted to test the heterogeneity of pooled data. $I^2 < 50\%$ and $p > 0.1$ indicated no significant heterogeneity and fixed-effects model was applied to combine the effective value [28]. Otherwise, a random-effects model was adopted. All statistical analyses were performed using STATA 12.0 software (StataCorp LP, TX, USA).

Subgroup analyses were performed to investigate the associations of NLR with clinical features in relation to geographic area, statistical methods, sample size, cancer stage, lymph node involvement, NLR cut-off value, and follow-up duration. Moreover, a sensitivity analysis was performed to examine the robustness of the pooled results. We performed summary receiver operating characteristic to determine the NLR cut-off values as described [29, 30]. We used Youden index to further confirm our results [31].

Results

Selection and characteristics of included eligible studies

A flowchart for the selection of eligible studies is demonstrated in Fig. 1. A total of 359 studies was retrieved and screened by title and abstract. 296 studies were excluded after the initial assessment of title and abstract. Among the remaining 63 articles, 36 were further excluded because they were letters, comments, editorials, or reviews. The full texts of the remaining 27 articles were evaluated. A total of 13 full-text articles were excluded, including 9 without available data and 4 without NLR category.

The basic information of the selected studies was summarized in Table 1.

Association of pre-treatment NLR with overall survival

The association between NLR and OS was assessed in 12 studies consisting of 3,854 patients. The pooled estimate indicated that a significantly shorter OS in ovarian cancer patients with high NLR compared to those with low NLR (HR: 1.69, 95% CI 1.29-2.22) (Fig. 2). Because the heterogeneity test showed that significant heterogeneity ($I^2 = 68.3\%$, $P < 0.001$) exists between the studies, a random-effects model was used for the analysis.

Association of pre-treatment NLR with progression free survival

The association between NLR and PFS was evaluated in 5 studies including 2,071 patients. Those with high pre-treatment NLR had a significantly poorer PFS than those with low NLR (HR 1.63, 95% CI 1.27-2.09) (Fig. 3). Because significant heterogeneity was observed among these studies ($I^2 = 56.6\%$, $P = 0.024$), a random-effects model was used for the analysis.

Correlations between NLR and clinical-pathological features

The correlations between NLR and the clinical characteristics such as tumor grade of differentiation, serum level of CA-125, ascites, residual tumor size, FIGO stage, lymph node

Fig. 1. Flow diagram of the study selection process.

Table 1. Characteristics of all identified studies. HR: hazard ratio; CI: confidence interval; OS: overall survival; PFS: progression-free survival; DFS: disease-free survival; "—": not reported; EOC: epithelial ovarian cancer; OCCC: ovarian clear cell carcinoma; SOC: serous ovarian cancer; NEOC: non-epithelial ovarian cancer; HGSC: high-grade serous ovarian cancer; FIGO: International Federation of Gynecology and Obstetrics; Grade: 2.FIGO stage; 3.Ascites; 4.CA-125; 5.Cytoreductive; 6.Chemosensitivity; 7.Lymph node metastasis. The study performed by Wang et al. [17] contained different levels of NLR. # 1.86<NLR≤2.64; ##NLR>3.77

Study	Year	Country	Duration	Follow-up(m)	Multivariate analysis-HR(95%CI)	Univariate analysis-HR(95%CI)	Age(y)	Histologic type
Cho H [12]	2009	Korea	2003-2006	20.9	OS:8.42 (1.09-64.84)	OS:6.05 (1.77-20.71)	—	EOC
Thavaramara T [13]	2011	Thailand	2004-2009	60	OS:preoperative1.43(0.625-3.33) postoperative0.714(0.303-1.429) PFS:preoperative1.43(0.71-3.33) postoperative0.909(0.476-1.667)	—	49.6(37.1-61.1)	EOC
Asher V [14]	2011	UK	1988-1998	24.5	OS:0.865(0.521-1.437)	OS:1.686(1.231-2.310)	62(24-90)	EOC
Kim HS [15]	2016	Korea	1997-2012	46(62.1-192.9)	PFS:2.04 (1.01-4.00)	OS:3.45(1.47-7.70) PFS:2.94(1.50-5.60)	53(30-86)	OCCC
Williams KA [16]	2014	American	1992-2013	68.4(1-252)	OS:1.43 (1.13-1.81)	—	55	EOC
Wang Y [17]	2015	China	2009-2010	43(33-70.4)	OS#:1.877 (0.622-5.324) OS##:8.567 (2.808-26.136) PFS:3.554 (1.389-9.096)	OS#:2.403 (1.104-6.409) OS##:6.866 (2.797-16.851) PFS:3.191 (1.514-6.728)	50	SOC
Zhang WW [18]	2015	China	2000-2012	43(2-164)	—	OS:2.172 (1.545-3.054) PFS:2.012 (1.476-2.741)	50.6±11.1(24-76)	EOC
Nakamura K [19]	2016	Japan	2005-2013	25	mortality within 100 days: 14.128(1.207-165.400)	mortality within 100 days: 31.667 (3.887-257.963)	54.9(33-78)	EOC
Wang YQ [20]	2016	China	2006-2013	116	OS:3.37(1.39-8.15) PFS:2.20(1.03-4.70)	OS:2.90 (1.66-5.05) PFS:2.11 (1.29-3.46)	52.27(38.18-66.36)	EOC/NEOC
Feng Z [21]	2016	China	2005-2013	29(1-115)	OS:1.189 (0.940-1.504) (1.052-1.484)	PFS:1.250	56(30-90)	HGSC
Miao Y [22]	2016	China	2005-2010	72(61-97)	OS:1.616 (1.138-2.297) (1.225-2.453)	PFS:1.733	55(45-84)	EOC
Raungkaewmanee S [23]	2012	Thailand	2004-2010	28.3(6.1-94.4)	OS:0.85 (0.46-1.60) PFS:0.89 (0.48-1.64)	—	53(23-85)	EOC
Yildirim MA [24]	2014	Sultan	2006-2011	—	—	—	43	EOC/NEOC
Bakacak M [25]	2016	Turkey	2007-2015	—	—	—	53	EOC/NEOC

Study	Patient clinical parameters	Sample	Sampling time	NLR cut-off	Stage	End point	Treatment	Study-design	NOS
Cho H [12]	—	999	pretreatment	2.6	I-IV	OS/DFS	surgery	retrospective	8
Thavaramara T [13]	2,5	128	pre/postoperative	2.6	advanced	OS/ PFS	surgery/chemotherapy	retrospective	7
Asher V [14]	—	235	preoperative	4	I-IV	OS	surgery/chemotherapy	retrospective	7
Kim HS [15]	2,5,6	109	postoperative	2.8	I-IV	PFS	surgery/chemotherapy	retrospective	8
Williams KA [16]	1,2,3,5	519	pretreatment	3.6	I-IV	OS	surgery	retrospective	8
Wang Y [17]	1,2,3,4,5,6,7	126	preoperative	2.65	I-IV	OS/PFS	surgery/chemotherapy	retrospective	8
Zhang WW [18]	—	190	preoperative	3.4	I-IV	OS/PFS	surgery/chemotherapy	retrospective	6
Nakamura K [19]	—	30	pretreatment	3.91	advanced	mortality within 100 days	surgery/chemotherapy	retrospective	7
Wang YQ [20]	2,4,7	143	preoperative	3.43	I-IV	OS/PFS	surgery	retrospective	7
Feng Z [21]	2,3,4,5,6	875	preoperative	3.24	I-IV	OS/PFS	surgery	retrospective	8
Miao Y [22]	6	334	pretreatment	3.02	I-IV	OS/ PFS	surgery/chemotherapy	retrospective	8
Raungkaewmanee S [23]	1,2,3	166	pretreatment	2.6	I-IV	OS/ PFS	surgery	retrospective	6
Yildirim MA [24]	2	316	pre/postoperative	2.11	I-IV	OS	surgery	retrospective	5
Bakacak M [25]	2	218	preoperative	3.47	—	—	surgery	retrospective	7

involvement, chemotherapeutic response are presented in Table 2. Increased pre-treatment NLR was significantly correlated with advanced FIGO stage (OR 2.32, 95% CI 1.79-3.00), higher serum level of CA-125 (OR 3.33, 95% CI 2.43-4.58), more extensive ascites (OR 3.54, 95% CI 2.31-5.42) as well as less chemotherapeutic response (OR 0.53, 95% CI 0.40-0.70). Four, two and one studies were available for the pooled analysis with regard to residual tumor size, lymph node metastasis and tumor grade of differentiation. No significant correlations between NLR with the abo-

Fig. 2. Forest plot of the correlation between NLR and OS in ovarian cancer patients.

ve-mentioned clinical-pathological features were observed.

Subgroup analysis

Subgroup analyses are conducted to explore the possible sources of heterogeneity. Results of subgroup meta-analyses are summarized in Table 3.

Publication bias analysis

The funnel plots showed a low probability of publication bias (Fig. 3 A&B). Consistently, the Egger's and Begger's regression tests demonstrated little evidence of publication bias for OS ($P = 0.061$; $P = 0.150$) and for PFS ($P = 0.203$; $P = 0.536$), respectively.

Sensitivity analysis

To assess the stability of every pooled result in our meta-analysis, we performed a sensitivity analysis for every analysis by sequential omission of the individual study. The pooled HRs for OS and PFS were not significantly changed, which suggested the robustness of the results.

Discussion

Accumulating evidence demonstrates that inflammation exerts an essential role in cancer formation, development and progression through facilitating angiogenesis, proliferation and preventing tumors from apoptosis [7]. Previous studies demonstrate that hematological inflammatory markers (including C-reactive protein, albumin, neutrophils and so on) could help predicting survival in patients with various types of cancers [12–15]. Among these predictors, NLR is a reproducible and widely available laboratory hematological marker in our routine clinical practice. Neutrophils have been considered to be the primary

source of circulating VEGF, which play a critical role in tumor-associated angiogenesis [13–15]. In addition, neutrophils could enhance the producing of many inflammatory cytokines such as tumor necrosis factor, interleukin 1, interleukin 6, and therefore provide a favorable

Fig. 3. Forest plot of the correlation between NLR and PFS in ovarian cancer patients.

Table 2. Correlation between high NLR and clinical parameters

Clinical parameters	N	OR	LCI	HCI	I ²
FIGO stage	7	2.32	1.79	3.00	41.4%
CA-125	3	3.33	2.43	4.58	0.0%
Ascites	2	3.54	2.31	5.42	40.2%
Chemosensitivity	3	0.53	0.40	0.70	22.7%
Residual tumor size	4	1.70	0.93	3.10	51.7%
Lymph node metastasis	2	0.86	0.08	9.20	94.2%
Tumor grade of differentiation	1	1.21	0.60	2.44	0.0%

Table 3. Result of the meta-analysis on predictive value of NLR in ovarian cancer patients. *Six studies [12, 14, 17, 19, 20, 22] analyzed correlation between NLR and overall survival using both univariate and multivariate analysis. Four studies [15, 17, 20, 22] analyzed correlation between NLR and disease-free survival using both univariate and multivariate analysis. #The study performed by Wang et al. [17] contained different levels of NLR. For overall survival: $1.86 < \text{NLR} \leq 2.64$, HR 1.877, 95% CI (0.662–5.324); $\text{NLR} > 3.77$, HR 8.567, 95% CI (2.808–26.136)

	Overall survival				Progression free survival			
	N	HR	LCI	HCI	N	HR	LCI	HCI
Overall	12	1.69	1.29	2.22	8	1.63	1.27	2.09
Geographic area								
1.Asian	10	1.98	1.39	2.82	8	1.63	1.27	2.09
2.non-Asian	2	1.17	0.72	1.90	0	-	-	-
Statistical methods*								
1.Univariate	8	3.33	2.15	5.15	5	2.91	1.82	4.46
2.Multivariate	10	1.51	1.14	2.01	7	1.38	1.20	1.59
Sample size								
1.<300	8	2.01	1.23	3.29	6	1.83	1.46	2.29
2.≥300	4	1.37	1.18	1.59	2	1.42	1.04	1.94
NLR standard								
1.<3	5	1.85	0.95	3.58	4	1.64	0.94	2.86
2.≥3	8#	1.74	1.27	2.39	4	1.65	1.32	2.21
Follow-up								
1.<60	8	1.85	1.17	2.92	5	1.61	1.12	2.31
2.≥60	4	1.54	1.28	1.85	3	1.75	1.30	2.34

micro-environment for tumor survival and proliferation [8]. Conversely, lymphocytes exert a critical role in cancer-specific immune response [32]. It has been shown that the increased infiltration of lymphocytes in tumor tissue is associated with good prognosis [33].

In the present study, we aimed to investigate the prognostic value of NLR in patients with ovarian cancer. Our results indicated that an elevated NLR was associated with poorer OS and shorter PFS in ovarian cancer patients, which was in accordance with the results from studies with several other cancer types.

Previous studies reported that NLR level was significantly associated with patient clinical characteristics [34, 35]. For instance, Yodying et al. [34] evaluated the prognostic role of NLR in esophageal cancer and indicated that NLR was associated with tumor invasion and lymph node metastasis. Xue et al. [35] observed that NLR was associated with vascular invasion in hepatic carcinoma. In this study, we also explored the correlations between NLR and clinical-pathological features in ovarian cancer patients. Our results showed that higher NLR was positively correlated with an advanced FIGO stage, an increased CA125 level and more extensive ascites in ovarian cancer patients. Therefore, we proposed that NLR might reflect ovarian cancer burden and inflammatory severity and significantly affect intrinsic tumor characteristics in patients with ovarian cancer. Moreover, our pooled results suggested that greater proportions of the ovarian cancer patients with chemo-resistance had higher NLR levels compared with those of chemo-sensitive, which suggested the potential application of NLR to predict chemotherapy response in ovarian cancer patients. Our meta-analysis also investigated the association between NLR level and tumor grade of differentiation, residual tumor size after cytoreduction and lymph node involvement. However, since limited studies were available, we still cannot draw a robust conclusion currently.

There were several limitations should be clarified in this study. First, most of the studies selected in this meta-analysis were retrospective, observational studies, and no prospective cohort study was identified. Therefore, it may be more susceptible to bias in data analysis. Second, a previous systemic review demonstrated that increased NLR predicted poor PFS with prostate cancer only in Asians, but not in Caucasians, which could be attributed to the ethnicity heterogeneity [36]. In this meta-analysis, majority of included articles came from Asian countries. Therefore, our current conclusions may be not suitable to be applied to other populations. Third, heterogeneity was observed in this meta-analysis. This heterogeneity may be partially caused by geographic area, statistical methods, sample size, NLR cut-off value, and the follow-up duration. For instance, studies with significant results are easier to be published than those with null or insignificant results. Thus the pooled HR may be potentially overestimated. Moreover, dichotomized cut-off values of NLR differed significantly among the studies. The further subgroup analyses showed that a pre-treatment $\text{NLR} \geq 3$ was significantly associated with poorer overall survival, and the predictive value were not significant when $\text{NLR} < 3$. Thus, a higher NLR cut-off may increase the specificity for predicting a poor prognosis. However, significant heterogeneity was observed in these subgroups, and a random-effect model was employed to produce more conservative results. In the future, more prospective, original research is required to determine the most suitable cut-off value of NLR in ovarian cancer patients.

Despite the limitations, our meta-analysis also has some strengths. To the best of our knowledge, this meta-analysis is the first to evaluate the prognostic role of a pre-treatment peripheral blood NLR in ovarian cancer. Moreover, our results showed that a significantly positive correlations between NLR and the clinical features of ovarian cancer, such as advanced FIGO stage, more extensive ascites as well as less chemotherapeutic response. Thus, NLR could have a wider clinical application regarding the prognostic assessment of ovarian cancer and might be useful in stratifying patients and in determining individual treatment plans in the future.

In conclusion, our meta-analysis of currently available clinical evidence demonstrates that a high pre-treatment NLR is associated with a poor prognosis in ovarian cancer patients. NLR could serve as a promising prognostic marker because it is available from blood routine test in daily clinical practice, which are convenient, low cost, and reproducible. In addition,

considering that NLR level is associated with several pathological features of ovarian cancer including tumor staging, ascites and chemotherapy response rates, it would be interesting to explore whether decreasing the inflammatory conditions, such as lowering NLR level could serve as an adjuvant therapy and prolong the survival of ovarian cancer patients in the near future.

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Disclosure Statement

The authors have no competing interests to declare.

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