Prognostic Role of Neutrophil to Lymphocyte Ratio in Ovarian Cancer: A Meta-Analysis

Gaowen Chen, MS¹, Lin Zhu, MBBS², Yulu Yang, MBBS², Yusheng Long, MBBS², Xiangyuan Li, MS³, and Yifeng Wang, MD¹

Abstract

Objective: The aim of the study was to investigate the prognostic role of neutrophil to lymphocyte ratio in ovarian cancer. Growing number of articles reported the relationship between neutrophil to lymphocyte ratio and prognosis in ovarian cancer, but the results remains inconclusive. The meta-analysis was conducted to analyze the association of pretreatment neutrophil to lymphocyte ratio with overall survival and progression-free survival. Methods: We performed a systematic literature research of PubMed, EMBASE, Medline, and Cochrane library for relevant studies up to October 8, 2017. The quality of included studies was assessed by the Newcastle-Ottawa Quality Assessment Scale. The hazard ratio and corresponding 95% confidence intervals were calculated. We checked the heterogeneity by the Q test and Higgins I-squared statistic. Begg funnel plot and Egger linear regression test were also applied for ascertain publication bias. All of the statistical analyses were performed using STATA version 12.0. Results: A total of 12 studies with 4046 patients were included in our study. The results indicated that depressed neutrophil to lymphocyte ratio was significantly correlated with higher overall survival (hazard ratio = 1.409, 95% confidence intervals = 1.112-1.786, P = .005) and progression-free survival (hazard ratio = 1.523, 95% confidence intervals = 1.187-1.955, P = .001) in ovarian cancer. Subgroup analysis by ethnicity of overall survival and progression-free survival showed that the prognostic effect of neutrophil to lymphocyte ratio was found both in Asians and Caucasians. Conclusion: Patients with depressed neutrophil to lymphocyte ratio had a higher overall survival and progression-free survival in ovarian cancer. This meta-analysis provided neutrophil to lymphocyte ratio as an available predictor of overall survival and progression-free survival for patients with ovarian cancer.

Keywords
neutrophil to lymphocyte ratio, ovarian cancer, prognosis, overall survival, progression-free survival, meta-analysis

Abbreviations
95% CI, 95% confidence intervals; CCOC, clear cell ovarian carcinoma; FIGO, International Federation of Obstetricians and Gynecologists; HR, hazard ratio; NLR, neutrophil to lymphocyte ratio; OS, overall survival; PFS, progression-free survival.

Received: August 29, 2017; Revised: April 20, 2018; Accepted: June 22, 2018.

Introduction

As the most lethal gynecologic malignancy, ovarian cancer is the seventh leading cause of cancer death in women worldwide.¹ Ovarian cancer accounted for 14,080 deaths in United States alone in 2017.² The early diagnosis of ovarian cancer is difficult because of insidious onset. Sixty percent of patients are diagnosed at the distant stage with survival of only 29%.² In addition to the high-mortality rate, the recurrence rate of ovarian cancer is as high as 80%.³ Thus, it is imperative to run some tests to predict prognosis.

¹ Department of Obstetrics and Gynecology, Zhujiang Hospital, Southern Medical University, Guangzhou, Guangdong, China
² Zhujiang Hospital, Southern Medical University, Guangzhou, Guangdong, China
³ Department of Reproductive Medical Center, Women and Children Hospital of Guangdong Province, Guangzhou, Guangdong, China

Corresponding Author:
Yifeng Wang, MD, Department of Obstetrics and Gynecology, Zhujiang Hospital, Southern Medical University, Guangzhou, Guangdong 510282, China.
Email: wyf2015@163.com

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (http://www.creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).
Prognostic variables in ovarian cancer include age at diagnosis, International Federation of Obstetricians and Gynecologists (FIGO) tumor stage, histological type, tumor grade, and presence of residual disease after initial surgery. Ovarian cancer’s gene detection is also a way to predict the prognosis, including BRCA1, BRCA2, CYP1B1, ARID1A, and p53, but it is expensive and time consuming.

Systemic inflammation is associated with tumor progression. Recent epidemiological investigations showed that chronic inflammation, including infection, is involved in 15% and 20% of all human malignancies. Inflammation activity is an important risk factor for the prognosis of patients with cancer. The state of inflammation can be reflected by the corresponding biological indicators such as CA-125, soluble cytokeratin, serum human kallikreins, serum cytokines, serum vascular endothelial growth factor, plasma D-dimer, and so on. The neutrophil to lymphocyte ratio (NLR) has also been suggested as a simple index of inflammatory response in patients with cancer. Massive studies supported that elevated inflammatory markers such as NLR and the platelet lymphocyte ratio are associated with poor prognosis in patients with different malignancies. In recent years, several researches revealed the relationship between NLR and prognosis of ovarian cancer, but the conclusions are inconsistent. Therefore, we performed this meta-analysis to examine the prognostic role of NLR in ovarian cancer.

**Materials and Methods**

**Search Strategy**

We conducted a systematic literature retrieval on PubMed, EMBASE, Medline, and Cochrane library for relevant studies up to October 8, 2017. The following search terms were used: (“neutrophil to lymphocyte ratio” OR “neutrophil-to-lymphocyte ratio” OR “neutrophil-lymphocyte ratio” OR NLR) AND (“ovarian cancer” OR “ovary cancer” OR “ovarian tumor” OR “ovary tumor”) AND (“ovarian cancer” OR “ovary cancer” OR “ovarian tumor” OR “ovary tumor”). Besides, references listed in the retrieved articles were reviewed to trace additional relevant studies missed by the search.

![Flow diagram of the included studies.](https://example.com/Figure1.png)
Inclusion and Exclusion Criteria

All articles were identified independently by 2 investigators. Included studies satisfied all of the following criteria: (1) studies in ovarian cancer reporting the prognostic value of the peripheral blood NLR; (2) studies investigated correlation of pretreatment NLR with overall survival (OS) or progression-free survival (PFS); and (3) sufficient data to estimate hazard ratio (HR) with 95% confidence interval (95% CI). Excluded studies met any of the following criteria: (1) overlapping or duplicate publications; (2) abstracts, reviews, letters, case reports, case series, editorials, and commentaries; (3) non-English articles; (4) nonhuman research; (5) unpublished trials; (6) insufficient data to assess HR with 95% CI; and (7) without full text.

Data Extraction

Data were extracted independently by 2 investigators. For each study, the following characteristics were collected: first author, publication year, study type, country of the study, sample size, age, FIGO stage, treatment, cutoff value, survival analysis data including OS and PFS, duration, and follow-up time.

Quality Assessment of Primary Studies

The quality of included studies was assessed by 2 reviewers independently using the Newcastle-Ottawa Quality Assessment Scale (NOS).\textsuperscript{19} Newcastle-Ottawa Quality Assessment Scale scores of $\geq 6$ were considered to be of high quality. Discrepancies were resolved by consensus after discussion.

Statistical Analysis

We assessed the relationship between NLR and prognosis (OS and PFS) using pooled HR and 95% CIs based on methods of Parmar et al.\textsuperscript{20} The significance of the pooled HRs was determined using a Z test, and the level of statistical significance was established as $P < .05$. The heterogeneity among studies was checked by the Q test and Higgins I-squared statistic.\textsuperscript{21,22} If the $P$ value for the heterogeneity test was $>.05$, we performed the Mantel-Haenszel method-based fixed effects model to calculate the pooled HR.\textsuperscript{23} Otherwise, the DerSimonian and Laird method-based random effects model was performed.\textsuperscript{24} An Egger linear regression test was also applied ($P < .05$ was considered a significant publication bias).\textsuperscript{25} All of the statistical analyses were carried out using a software program, STATA version 12.0 (Stata, College Station, Texas).

Results

Extraction Process and Study Characteristics

A total of 190 full-text articles were identified according to the search strategy. Our initial search and the process of study selection are summarized in Figure 1. Eventually, 12 studies published from 2009 to 2017 were included in our
meta-analysis, containing 4046 patients. The main characteristics of included studies are shown in Table 1.

### Neutrophil to Lymphocyte Ratio and OS in Ovarian Cancer

There were 12 cohorts presenting the data of pretreatment NLR and OS in ovarian cancer. Our results revealed that patients with depressed NLR were expected to have higher OS after treatment ($HR = 1.409$, $95\% CI = 1.112-1.786$, $P = .005$; Figure 2). Subgroup analysis showed that the prognostic effect of NLR for OS was found both in Asian population ($HR = 1.807$, $95\% CI = 1.084-3.014$, $P = .023$) and in Caucasians ($HR = 1.205$, $95\% CI = 1.014-1.432$, $P = .035$). Remarkable heterogeneity ($Ph = 0.000$, $I^2 = 81.3\%$) was observed in the overall study. After subgroup analysis, we determined that Asian studies contribute to substantial heterogeneity because heterogeneity was significantly decreased in Caucasian ($Ph = 0.066$, $I^2 = 58.3\%$) but not in Asian ($Ph = 0.000$, $I^2 = 84.6\%$). The test of Galbraith Plot showed that the studies by Wang et al.\textsuperscript{29} and Kim et al.\textsuperscript{37} could contribute to substantial heterogeneity. The results also reminded us that ethnicity may be one of the reasons for significant heterogeneity.

### Neutrophil to Lymphocyte Ratio and PFS in Ovarian Cancer

Three cohorts presented the data of pretreatment NLR and PFS in ovarian cancer. The pooled HR demonstrated a significant association between depressed pretreatment NLR and higher PFS after treatment ($HR = 1.523$, $95\% CI = 1.187-1.955$, $P = .001$; Figure 3) with significant heterogeneity ($P = .000$, $I^2 = 78.8\%$). Subgroup analysis showed that the combined HR was $1.628$ ($95\% CI = 1.160-2.284$, $P = .005$) in Asian population, with significant heterogeneity ($P = .000$, $I^2 = 79.4\%$). With only 1 study included in Caucasian subgroup, there was no need to combine HRs and assess heterogeneity in this group. The test of Galbraith Plot indicated that the study by Wang et al.\textsuperscript{29} and Kim et al.\textsuperscript{37} could contribute to substantial heterogeneity.

### Sensitivity Analyses

Sensitivity analyses were performed to assess the influence of each individual study on the pooled HRs. A single study involved in the pooled meta-analysis was excluded each round of analysis, and the corresponding HRs were not changed considerably, suggesting that the results of this meta-analysis are credible (data also not shown).
Publication Bias

Begg funnel plot (Figures 4 and 5) and Egger test were performed to assess the publication bias of the included studies. Funnel plot shapes did not reveal any obvious evidence of asymmetry. The P value for Egger test in the NLR and OS was .161, respectively. The P value for Egger test in the NLR and PFS was .230. Thus, the results above suggest that publication bias was not evident in this meta-analysis.

Discussion

Inflammation plays a crucial role in the occurrence and development of cancer, providing a favorable microenvironment for...
tumor initiation, invasion, and metastasis.\textsuperscript{10,38,39} Inflammatory cells and cytokines promote tumor development by facilitating cancer cells’ proliferation, angiogenesis, and apoptosis inhibition, and in turn the tumor-induced inflammation creates a “snowball” effect.\textsuperscript{40,41} Inflammation infiltration can be evaluated by performing laboratory examinations. As one of representative inflammatory parameters, NLR is a promising index to predict the prognosis of cancer. Neutrophil to lymphocyte ratio is accessed easily from peripheral blood test results and relatively inexpensive. A growing number of studies show the correlation between high pretreatment NLR and poor prognosis in different cancer types.\textsuperscript{42-46}

This study aimed at exploring the prognostic significance of pretreatment NLR in ovarian cancer, including 12 studies with 4046 patients. According to the results, we found that patients with depressed NLR had higher OS and PFS although with heterogeneity. Both in Asian and in Caucasian population, the prognostic effect of NLR is dependable. The results indicated that reduced NLR predicted good prognosis in ovarian cancer, in accordance with meta analyses of pretreatment NLR and other cancer types. Sufficient ovarian cancer types were included. Sensitivity analyses and publication bias showed that our results were credible. Therefore, NLR is a reliable and satisfactory indicator to predict prognosis of patients with ovarian cancer. Neutrophil to lymphocyte ratio assessing is an ideal prognostic test of ovarian cancer, which is widely available in all hospitals and saves money for patients.

We checked out sources through subgroup analysis and Galbraith Plot test. Subgroup analysis indicated that heterogeneity of OS significantly decreased in Caucasian but not in Asian, which meant the Asian studies were the primary cause of heterogeneity. The Galbraith Plot test revealed that the studies of Wang et al and Kim et al contribute to substantial heterogeneity, which are both Asian studies. It also reminds us that ethnicity may be one of the reason for heterogeneity. As for PFS, Galbraith Plot test revealed that the studies of Wang and Kim et al could contribute to substantial heterogeneity. There could be 3 reasons through analysis about Wang’s study. First, the strict exclusion criteria were most likely the major cause. Wang excluded patients with malignancies or multiple primary malignancies, hematological disease, inflammatory disease, hematology, influenced drugs use, missing preoperative complete blood cell count prior to surgery or prior chemotherapy or radiotherapy. Second, the study object was serous ovarian cancer, which had a high malignant potential. Third, the sample size of this study was only 126, which may cause the result not accurate enough like the studies of large sample size. As for the study of Kim, first, their inclusion criteria were strict, and Kim only included patients with clear cell ovarian carcinoma (CCOC) who did not have any inflammatory conditions except endometriosis and underwent primary debulking surgery. As we all know, CCOC is a unique histologic type of epithelial ovarian cancer, which is characterized by being a more aggressive histologic subtype\textsuperscript{47,48} and has poor response rate to platinum-based chemotherapies.\textsuperscript{49} Second, the sample size of Kim study was the smallest in 12 studies.

All of the 12 included studies treated NLR as a categorical variable. However, the cutoff values of NLR are different in these studies due to different methods. For instance, 7 of the included studies optimized NLR cutoff values for overcoming Receiver Operating Curve (ROC) values from 2.6 to 4.0.\textsuperscript{26,30,31,34-37} In contrast, one study used a median level (3.24),\textsuperscript{32} one used the log-rank test (4),\textsuperscript{27} and one used an interquartile level (1.86-3.77, from the lowest to highest category).\textsuperscript{29} We didn’t find enough evidence to prove which method provides the most accurate value. Further researches are needed to clarify which cutoff method is the best one to assess the prognosis risk of patient with ovarian cancer.

Some limitations exist in this meta-analysis. First, the number of articles meeting our criteria was only 12, causing limited data for analysis. Second, the cutoff values of NLR in 12 studies were not the same, which may be the major cause to the heterogeneity. Third, only English articles were involved, leading to language bias and publication bias. Fourth, only 2 included articles were cohort studies. We need more prospective studies to confirm our conclusion. More scientifically designed clinical trials and further investigation are imperative to draw accurate conclusions.

In summary, our study demonstrated that depressed NLR was associated with higher OS and PFS in patients with ovarian cancer by meta-analysis. The association was both dependable in Asians and Caucasians. The findings could provide suggestions for clinical management of patients with ovarian cancer.

Authors’ Note
Gaowen Chen, Lin Zhu, and Yulu Yang contributed equally to this work.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article. The work was supported by the Science and Technology program of Guangdong province, China (2013B021800307), the National Natural Science Foundation of China (81773291), the Natural Science Foundation of Guangdong Province, China (2015A030313308), and the Wu Jieping Medical Foundation (320.6755.15010).

ORCID iD
Lin Zhu, MBBS \(\text{http://orcid.org/0000-0002-6909-1655} \)

References
1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69-90.
2. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67(1):7-30.
3. Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a...
Chen et al

Gynecologic Oncology Group Study. J Clin Oncol. 2003;21(17):3194-3200.

Gadducci A, Cosio S, Tana R, Genazzani AR. Serum and tissue biomarkers as predictive and prognostic variables in epithelial ovarian cancer. Crit Rev Oncol Hematol. 2009;69(1):12-27.

Prowse AH, Vanderveer L, Milling SW, et al. OVCA2 is downregulated and degraded during retinoid-induced apoptosis. Int J Cancer. 2002;99(2):185-192.

Schultz DC, Vanderveer L, Berman DB, Hamilton TC, Wong AJ, Godwin AK. Identification of two candidate tumor suppressor genes on chromosome 17p13.3. Cancer Res. 1996;56(9):1997-2002.

Hall JM, Lee MK, Newman B, et al. Linkage of early-onset familial breast cancer to chromosome 17q21. Science (New York, NY). 1990;250(4988):1684-1689.

Miki Y, Swensen J, Shattuck-Eidens D, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science (New York, NY). 1994;266(5182):66-71.

Wooster R, Neuhausen SL, Mangion J, et al. Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. Science (New York, NY). 1994;265(5181):2088-2090.

Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420(6917):860-867.

Gambhir S, Vyas D, Hollis M, Aekka A, Vyas A. Nuclear factor kappa B role in inflammation associated gastrointestinal malignancies. World J Gastroenterol. 2015;21(11):3174-3183.

Ozdemir Y, Akin ML, Sucullu I, Balta AZ, Yucel E. Pretreatment neutrophil/lymphocyte ratio as a prognostic aid in colorectal cancer. Asian Pac J Cancer Prev. 2014;15(6):2647-2650.

Azab B, Shah N, Radbel J, et al. Pretreatment neutrophil/lymphocyte ratio is superior to platelet/lymphocyte ratio as a predictor of long-term mortality in breast cancer patients. Med Oncol. 2013;30(1):432.

Szkandera J, Absenger G, Liegl-Atzwanger B, et al. Elevated preoperative neutrophil/lymphocyte ratio is associated with poor prognosis in soft-tissue sarcoma patients. Br J Cancer. 2013;108(8):1677-1683.

Urrejola GI, Bambs CE, Espinoza MA, et al. An elevated neutrophil/lymphocyte ratio is associated with poor prognosis in stage II resected colon cancer. Rev Medica Chil. 2013;141(5):602-608.

Gondo T, Nakashima J, Ohno Y, et al. Prognostic value of neutrophil-to-lymphocyte ratio and establishment of novel preoperative risk stratification model in bladder cancer patients treated with radical cystectomy. Urolology. 2012;79(5):1085-1091.

Xu J, Ni C, Ma C, et al. Association of neutrophil/lymphocyte ratio and platelet/lymphocyte ratio with ER and PR in breast cancer patients and their changes after neoadjuvant chemotherapy. Clin Transl Oncol. 2017;19(8):989-996.

Tomita M, Shimizu T, Ayabe T, Yonei A, Onitsuka T. Preoperative neutrophil to lymphocyte ratio as a prognostic predictor after curative resection for non-small cell lung cancer. Anticancer Res. 2011;31(9):2995-2998.

Wells GA, Shea BJ, O’Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis. Appl Eng Agric. 2014;18(6):727-734.

Parnar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med. 1998;17(24):2815-2834.

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-560.

Cochran WG. The combination of estimates from different experiments. Biometrics. 1954;10(1):101-129.

Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959;22(4):719-748.

DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials. 2015;45:139-145.

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-634.

Cho H, Hur HW, Kim SW, et al. Pre-treatment neutrophil to lymphocyte ratio is elevated in epithelial ovarian cancer and predicts survival after treatment. Cancer Immunol Immunother. 2009;58(1):15-23.

Asher V, Lee J, Innamaa A, Bafi A. Preoperative platelet lymphocyte ratio as an independent prognostic marker in ovarian cancer. Clin Transl Oncol. 2011;13(7):499-503.

Williams KA, Labidi-Galy SL, Terry KL, et al. Prognostic significance and predictors of the neutrophil-to-lymphocyte ratio in ovarian cancer. Gynecol Oncol. 2014;132(3):542-550.

Wang Y, Liu P, Xu Y, et al. Preoperative neutrophil-to-lymphocyte ratio predicts response to first-line platinum-based chemotherapy and prognosis in serous ovarian cancer. Cancer Chemother Pharmacol. 2015;75(2):255-262.

Zhang WW, Liu KJ, Hu GL, Liang WJ. Preoperative platelet/lymphocyte ratio is a superior prognostic factor compared to other systemic inflammatory response markers in ovarian cancer patients. Tumour Biol. 2015;36(11):8831-8837.

Badora-Rybicka A, Nowara E, Starzycczy-Slota D. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio before chemotherapy as potential prognostic factors in patients with newly diagnosed epithelial ovarian cancer. ESMO Open. 2016;1(2):e00039.

Feng Z, Wen H, Bi R, et al. Preoperative neutrophil-to-lymphocyte ratio as a predictive and prognostic factor for high-grade serous ovarian cancer. Plos One. 2016;11(5):e0156101.

Li Z, Hong N, Robertson M, Wang C, Jiang G. Preoperative red cell distribution width and neutrophil-to-lymphocyte ratio predict survival in patients with epithelial ovarian cancer. Int J Gynecol Cancer. 2016;26:763.

Miao Y, Yan Q, Li S, Li B, Feng Y. Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio are predictive of chemotherapeutic response and prognosis in epithelial ovarian cancer patients treated with platinum-based chemotherapy. Cancer Biomark. 2016;17(1):33-40.

Wang YQ, Jin C, Zheng HM, et al. A novel prognostic inflammation score predicts outcomes in patients with ovarian cancer. Clin Chim Acta. 2016;456:163-169.

Komura N, Nabuchi S, Yokoi E, et al. Comparison of clinical utility between neutrophil count and neutrophil-lymphocyte ratio
in patients with ovarian cancer: a single institutional experience and a literature review. *Int J Clin Oncol*. 2017;23(1):104-113.

37. Kim HS, Choi HY, Lee M, et al. Systemic inflammatory response markers and CA-125 levels in ovarian clear cell carcinoma: a two center cohort study. *Cancer Res Treat*. 2016;48(1):250-258.

38. Shalapour S, Karin M. Immunity, inflammation, and cancer: an eternal fight between good and evil. *J Clin Invest*. 2015;125(9):3347-3355.

39. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet (London, England)*. 2001;357(9255):539-545.

40. Munn LL. Cancer and inflammation. *Wiley Interdiscip Rev Syst Biol*. 2017;9(2):13.

41. Lin WW, Karin M. A cytokine-mediated link between innate immunity, inflammation, and cancer. *J Clin Invest*. 2007;117(5):1175-1183.

42. Gu XB, Gao XS, Li XY, et al. Prognostic significance of neutrophil-to-lymphocyte ratio in prostate cancer: evidence from 16,266 patients. *Sci Rep*. 2016;6:22089.

43. Yin YM, Wang J, Wang XD, et al. Prognostic value of the neutrophil to lymphocyte ratio in lung cancer: a meta-analysis. *Clinics*. 2015;70(7):524-530.

44. Koh CH, Bhoo-Pathy N, Ng KL, et al. Utility of pre-treatment neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as prognostic factors in breast cancer. *Br J Cancer*. 2015;113(1):150-158.

45. Cheng H, Long FW, Jaiswar M, Yang L, Wang C, Zhou ZG. Prognostic role of the neutrophil-to-lymphocyte ratio in pancreatic cancer: a meta-analysis. *Sci Rep*. 2015;5:11026.

46. Li MX, Liu XM, Zhang XF, et al. Prognostic role of neutrophil-to-lymphocyte ratio in colorectal cancer: a systematic review and meta-analysis. *Int J Cancer*. 2014;134(10):2403-2413.

47. Jenison EL, Montag AG, Griffiths CT, et al. Clear cell adenocarcinoma of the ovary: a clinical analysis and comparison with serous carcinoma. *Gynecol Oncol*. 1989;32(1):65-71.

48. Sugiyama T, Kamura T, Kigawa J, et al. Clinical characteristics of clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy. *Cancer*. 2000;88(11):2584-2589.

49. Chan JK, Teoh D, Hu JM, Shin JY, Osann K, Kapp DS. Do clear cell ovarian carcinomas have poorer prognosis compared to other epithelial cell types? A study of 1411 clear cell ovarian cancers. *Gynecol Oncol*. 2008;109(3):370-376.