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Review Article

Is the neutrophil-to-lymphocyte ratio prognostic of survival outcomes in gynecologic cancers? A systematic review and meta-analysis

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HIGHLIGHTS

- High neutrophil-to-lymphocyte ratio (NLR) is associated with adverse survival outcomes.
- This association was maintained in studies of ovarian, endometrial and cervical cancer.
- In cervical cancer, NLR was most prognostic in those treated with chemotherapy and radiation.

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ABSTRACT

Background. Presence of a high neutrophil-to-lymphocyte ratio (NLR) has been associated with increased mortality in several malignancies. Here, we quantify the effect of NLR on survival in patients with gynecologic cancers, and examine the effect of clinico-pathologic factors on its prognostic value.

Methods. A systematic search of electronic databases was conducted to identify publications exploring the association of pre-treatment blood NLR with overall survival (OS) and event-free survival (EFS) among patients with ovarian, endometrial and cervical cancers. Data from studies reporting a hazard ratio (HR) and 95% confidence interval (CI) or a p-value (*P*) were weighted by generic inverse-variance and pooled in a random effects meta-analysis. Subgroup analyses were conducted according to primary tumor type. Meta-regression was performed to evaluate the influence of clinico-pathologic factors on the HR for OS and EFS. All statistical tests were two-sided.

Results. Twenty-six studies comprising 10,530 patients were included. Studies used different cut-offs to classify high NLR (range 0.89 to 5.03). The median cut-off for high NLR was 2.95 among twenty-six studies reporting a HR for OS, and 2.79 in seventeen studies reporting EFS outcomes. NLR greater than the cut-off was associated with worse OS (HR 1.65, 95% CI = 1.44 to 1.89; $P < 0.001$) and EFS (HR 1.57, 95% CI = 1.35 to 1.82; $P < 0.001$). This association was present in all tumor types. Most studies were comprised of patients with both early-stage and advanced disease. In cervical cancer, significant associations between NLR and OS were observed in studies of early- and mixed-stage patients and regression analysis showed a greater magnitude of effect in patients with locally advanced disease and in those who received both chemotherapy and radiation.

Conclusions. High NLR is associated with an adverse OS and EFS in patients with gynecologic malignancies.

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1. Background

Systemic inflammation has been shown to be an important manifestation of malignancy development and progression [1]. This often manifests as neutrophilia, thrombocytosis and relative lymphocytopenia in the peripheral blood, with the potential for use as accessible preoperative prognostic markers [2–4]. Additionally, alterations in antitumor immunity are thought to be important in the pathogenesis of gynecologic malignancies including ovarian, endometrial and cervical cancers [5,6]. In ovarian and cervical cancers, pre-clinical data has shown that neutrophils may have immune deregulating effects, potentially contributing to progression and metastatic potential of tumor cells [7,8]. The presence of certain types of tumor infiltrating lymphocytes (TILs) and tumor-associated neutrophils has also been associated with improved outcomes [9–12]. However, it is unclear whether systemic inflammatory markers are prognostic in gynecologic cancers.

The presence of an elevated peripheral neutrophil-to-lymphocyte ratio (NLR) has been identified as a poor prognostic indicator in various cancers. In a previous meta-analysis of one hundred studies of patients with unselected solid tumor malignancies, increased NLR was associated with decreased overall survival (OS) (hazard ratio [HR] 1.81; 95% confidence interval [CI] = 1.67 to 1.97; p-value [P] < 0.001) [13]. This effect was observed in all disease sites, subgroups and stages. However, its prognostic value in ovarian, cervical and endometrial cancers is unclear, as the previous study included few studies performed in patients with gynecologic malignancies and did not examine the effect of NLR specifically in these subgroups.

In this study, we aimed to quantify the effect of peripheral blood NLR on OS and event-free survival (EFS) in adult women with ovarian, cervical and endometrial cancers. We also examined the effect of clinico-pathologic factors on the prognostic value of NLR.

2. Methods

2.1. Data sources and searches

This analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14]. The search strategy developed by Templeton et al. was used with the addition of "ovarian neoplasms", "endometrial neoplasms", "uterine cervical neoplasms" and synonymous gynecologic cancer-specific terms [13]. An electronic search of the following databases was performed: Medline (host: OVID), Medline in Process, Medline Epub Ahead of Print (host: OVID), EMBASE (host: OVID), and Cochrane Database of Systematic Reviews. All databases were searched from January 2013 to April 2016, supplementing the initial systematic review that searched databases until different time points in 2013. The search was updated in November 2016. Citation lists of retrieved articles were screened manually to ensure sensitivity of the search strategy. The full search strategy is described in Appendix 1.

2.2. Study selection

The following eligibility criteria were utilized: 1) studies of adult women with ovarian, endometrial or cervical cancer reporting on the prognostic impact of the peripheral blood NLR; 2) NLR collected prior to all treatment (surgery and/or systemic therapy and/or radiotherapy); 3) reporting of a HR for OS, and/or EFS defined as disease-free survival (DFS) or progression-free survival (PFS), and corresponding 95% CI and/or p-value; 4) available as full-text publication; 5) clinical trials, cohort or case-control studies; and 6) English language publication. Case reports, conference proceedings and letters to editors were excluded. Corresponding authors were contacted on four occasions to clarify missing or ambiguous data,

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