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Review

Prognostic significance of pretreatment neutrophil-to-lymphocyte ratio in melanoma patients: A meta-analysis

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ABSTRACT

Introduction: Recently, the prognostic value of the neutrophil-to-lymphocyte ratio (NLR) has been widely evaluated in many cancers. Here we assessed the prognostic value of pretreatment NLR in melanoma.

Methods: A range of online databases was systematically searched up to March,2018 for identify available studies which assessed the prognostic significance of NLR. Data from studies reporting a hazard ratio (HR) and 95% confidence interval (CI) were weighted by generic inverse-variance and pooled in random effects meta-analysis.

Results: Twelve studies with 4593 individuals were included. Patients with elevated NLR had a significantly shorter overall survival (OS) (HR: 1.56, 95% CI: 1.28–1.90, $p < .001$) and disease-free survival (DFS)/progression-free survival (PFS) (HR = 1.86; 95% CI = 1.24–2.80; $P = .003$). Subgroup analyses showed that the negative prognostic effect of elevated NLR on OS remained substantial in North American and Europen populations and patients with non-metastatic and metastatic stage. Additionally, elevated NLR was related to worse OS in patients with melanoma, regardless of the sample size and the cut-off value.

Conclusion: Our findings suggest that elevated pretreatment NLR was associated with poor prognosis in melanoma patients, suggesting NLR might be a prognostic factor in patients with melanoma.

1. Introduction

Melanoma is a highly aggressive skin cancer, characterized by rapid progression and late recurrence [1]. Based on data from the American Cancer Society, it is estimated that approximately 91,270 new diagnosed cases and 9320 deaths of cancer occur in the United States in 2018. The vast majority of patients are diagnosed with localized potentially curable melanoma. However, the clinical behavior of melanoma is not always predictable on the basis of conventional histopathological criteria [2, 3], and life expectancy is significantly reduced in patients diagnosed with distant metastatic disease, with 5-year survival rates of 16% [4].

It is clear that systemic inflammation plays an important role in tumor development, progression, and metastasis [5]. Inflammatory responses in tumor microenvironment have been reflected by some common markers in peripheral blood, for example, some cytokines, leucocytes and their subtypes [6]. Various inflammatory factors, such as the plasma fibrinogen, C-reactive protein (CRP), Glasgow prognostic score (GPS), and the neutrophil-to-lymphocyte ratio (NLR) have been investigated in a variety of solid tumors [7–10]. A high pretreatment NLR, calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, has been reported to be related to poor survival in patients with melanoma [11–13]. Moreover, NLRtests are easy to perform, less expensive, and readily available. However, the prognostic value of NLR in melanoma has not yet been fully elucidated. Thus, we aimed to quantify the prognostic effect of NLR on survival in patients with melanoma.

2. Materials and methods

2.1. Search strategies

An electronic search of MEDLINE, EMBASE, and Cochrane Library was performed for relevant articles with the deadline of March 4, 2018. Keywords used in the search strategy were: “neutrophil lymphocyte ratio” or “NLR” and “melanoma” and “prognosis” or “outcome” or “survival”. The bibliographies cited in the selected articles were also examined to identify other relevant studies. The comprehensive databases searching was carried out by the two authors independently.

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2.2. Study selection

The following eligibility criteria were utilized: (1) the diagnosis of melanoma was pathologically confirmed; (2) studies investigated NLR and survival in melanoma; (3) reported a cut-off value for NLR; and (4) sufficient data were provided to calculate the hazard ratio (HR) and 95% confidence interval (CI). Studies were excluded if they meet the following criteria: (1) studies were reviews, case reports, letters, or conference abstracts; (2) studies with insufficient data; and (3) duplicate publication.

2.3. Data extraction and quality assessment

All eligible studies were reviewed and extracted independently by two reviewers. We extracted data including: the first author, area, publication year, number of patients, age, time of follow-up, treatment, TNM stage, cut-off values, survival analysis methods, and HRs and associated 95% CIs for OS or DFS/PFS.

The Quality Assessment of Newcastle-Ottawa Scale (NOS) was adopted to evaluate the methodological quality of included studies [14]. This scale consists of three parameters: selection, comparability, and outcome assessment. The NOS scores ≥6 are considered as high-quality studies. Validity of included studies was assessed by two independent reviewers.

2.4. Statistical analysis

Extracted data were pooled using Stata 13.0 statistical software (StataCorp, College Station, TX, U.S.A.). HRs and 95% CIs were directly extracted from included studies or calculated based on methods by Tierney and Parmar [15, 16]. The heterogeneity among studies was evaluated (with I square as the test level). If I square < 50%, we used the fixed-effect model to analyse. Otherwise, a random-effect model was used. Subgroup analyses were conducted for area, disease stage, sample size, and the cut-off value. To validate the credibility of the result, sensitivity analyses were performed by removing each study. $P < .05$ indicated a statistically significant result.

3. Results

3.1. Study characteristics

After systematically retrieving in selected databases, 212 relevant records were initially retrieved. 134 records were left after duplicates removed. Of these, 94 were excluded by reviewing titles and abstracts, leaving 40 potentially relevant full-text articles. Finally, 12 studies with a combined 4593 patients met the criteria and were enrolled into the meta-analysis [11–13, 17–25]. A flowchart demonstrating the process of study selection is illustrated in Fig. 1.

All included studies were published between 2016 and 2018. Of the twelve studies, four studies were conducted in USA, three in France, two in Italy, one in China, one in Canada, and one in Mexico. The sample sizes ranged from 49 to 1431 subjects. A total of 10 and 6 studies performed analyses on OS, DFS/PFS, respectively. Most of the included studies used multivariate analysis method. Quality assessment results of the studies are shown in Table 1 using the NOS. The quality of the included studies varied from 6 to 9, with average 7.3. Table 1 presents details of included studies.

3.2. Meta-analysis

3.2.1. Overall survival

Ten studies reported data on the prognostic value of the NLR on OS in melanoma patients. Overall, elevated NLR had an association with poor OS (HR: 1.56, 95% CI: 1.28–1.90, $p < .001$), with excessive heterogeneity ($p = .06$, $I^2 = 90.9\%$; Fig. 2). We also performed

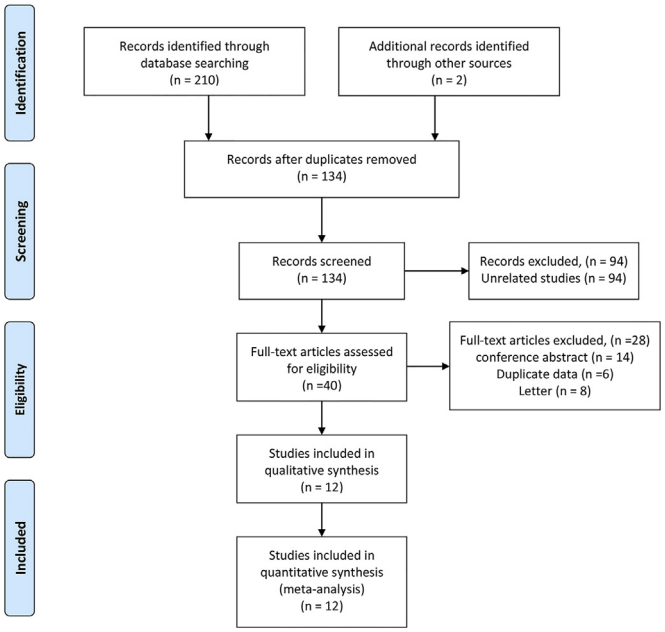

Fig. 1. Flow diagram of the study selection process.

subgroup analyses to detect potential sources of heterogeneity among several related clinical features of the included studies for OS (Table 2). The results showed that elevated NLR predicted poor prognosis for patients both in North America (HR = 1.27; 95% CI = 1.10–1.47; P = .001) and Europe country (HR = 1.56; 95% CI = 1.28–1.90; P = .001). In the exploratory subgroup analyses stratified by disease stage, the negative effect of elevated NLR on OS was observed in patients with non-metastatic (HR = 1.56; 95% CI = 1.28–1.90; P = .01) and metastatic disease subgroups (HR = 1.58; 95% CI = 1.23–2.01; P < .001). Moreover, subgroup analyses demonstrated that elevated NLR predicted worse OS in patient with melanoma, regardless of the sample size (≥200 or < 200), and the cut-off value for NLR (> 3.0 and ≤3.0).

3.2.2. Disease-free survival/progression-free survival

Six studies comprising 1386 patients reported HRs for DFS/PFS. The combined data showed that elevated NLR was significantly correlated with worse DFS/PFS (HR = 1.86; 95% CI = 1.24–2.80; P = .003; Fig.3). The heterogeneity between included studies was significant ($I^2 = 89.8\%$; P < .001).

3.3. Sensitivity analysis and publication bias

We also performed sensitivity analyses for the OS by removing one study at a time to determine whether an individual study influenced the results; there was no significant influence by any single study (Fig. 4). The results showed that the results were not radically changed, which indicates the robustness of our results. There was significant publication bias in OS (P = .474 for Begg's test and P = .004 for Egger's test, Fig. 5), while no significant publication bias was observed for DFS/PFS (P = 1.000 for Begg's test and P = .088 for Egger's test, Fig. 6).

4. Discussion

In this meta-analysis, we combined the outcomes of 4593 patients from 12 studies, indicating that elevated NLR is significantly associated with poor OS and DFS/PFS. We also performed subgroup analyses, the results showed that the negative prognostic effect of low NLR on OS remained substantial in North American and Europen populations and patients with non-metastatic and metastatic stage. Additionally,