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Prognostic value of neutrophil-to-lymphocyte ratio in breast cancer

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ABSTRACT

Inflammation is an essential component of pathogenesis and progression of cancer. A high neutrophil-to-lymphocyte ratio (NLR) is considered as a prognostic indicator for breast cancer. This meta-analysis was conducted to establish the overall accuracy of the NLR test in the diagnosis of breast cancer. A comprehensive search of the literature was conducted by using PubMed, Web of Science and China National Knowledge Infrastructure (CNKI). Published studies dating up to July 2014 and 4,293 patients were enrolled in the present study. In order to evaluate the association between NLR and overall survival (OS), disease-free survival (DFS), recurrence-free survival (RFS) or cancer specific survival (CSS), the hazard ratios (HRs) and their 95% confidence intervals (CIs) were extracted. OS was the primary outcome. The results suggested that increased NLR was a strong predictor for OS with HR of 2.28 (95% CI = 1.08–4.80, $P_{heterogeneity} < 0.001$). Stratified analyses indicated that a high NLR appeared to be a negative prognostic marker in Caucasian populations (HR = 4.53, 95% CI = 3.11–6.60, $P_{heterogeneity} = 0.096$), multivariate analysis method (HR = 2.10, 95% CI = 1.52–2.89, $P_{heterogeneity} = 0.591$), and mixed metastasis (HR = 4.53, 95% CI = 3.11–6.60, $P_{heterogeneity} = 0.096$). Elevated NLR was associated with a high risk for DFS (HR = 1.38, 95% CI = 1.09–1.74, $P_{heterogeneity} = 0.050$) and in subgroups of multivariate analysis (HR = 1.64, 95% CI = 1.25–2.14, $P_{heterogeneity} = 0.545$) and mixed metastasis (HR = 1.99, 95% CI = 1.28–3.09, $P_{heterogeneity} = 0.992$). In summary, NLR could be considered as a predictive factor for patients with breast cancer.

1. Introduction

Breast cancer is a common malignancy that affects the health of women worldwide. One in eight women will be diagnosed with breast cancer in their lifetime [1]. 5–7% of women are diagnosed before the age of 40, and the highest frequency is found in the age group 25 to 39 [2–5]. With the rapid advancement of early diagnosis and treatment in breast cancer, more than four fifths of patients are now successfully treated [4] and the mortality has recently declined in young women [6]. However, a large proportion of patients were still suffered from breast cancer due to heterogeneity of diagnosis and treatment. Therefore, it is crucial to understand causes contributing to breast carcinogenesis, invasion and metastasis and to identify effective early-diagnostic and prognostic biomarkers that help to diagnose, evaluate treatment efficacy and prognosis and follow-up schedule [7].

It has been demonstrated that the inflammatory response plays an important role in the development and progression of various cancers, including breast cancer [8–10]. The cancer-related inflammatory response helps proliferation and survival of malignant cells, angiogenesis and metastasis of breast cancer, and it subverts adaptive immune responses and alters responses to chemotherapeutic agents. Severe inflammatory responses result in a weaker adaptive immune response, leading to an imbalance of immune response and malignant cancer to promote cancer progression and poor OS.

Biomarkers such as neutrophils, lymphocytes, neutrophil-to-lymphocyte ratio (NLR), mean platelet volume, red cell distribution width, circulating tumor cells and gamma-glutamyl transferase have been proposed as potential prognostic factors for cancer [11–15]. There is accumulating evidence for the association of NLR with survival of patients with many kinds of

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; DFS, disease-free survival; RFS, recurrence-free survival; CSS, cancer specific survival; HR, hazard ratio; CI, confidence interval

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cancers, including breast cancer [16–23]. However, the published results are inconsistent. Some studies reported that NLR was significantly associated with shorter DFS and OS in breast cancer patients [24,25], while others showed that NLR could not be considered as an independent prognostic factor for breast cancer [26,27].

In order to obtain an objective and consistent conclusion, we therefore conducted this comprehensive systematic review and meta-analysis of the association between NLR and survival of breast cancer.

2. Materials and methods

2.1. Search strategy

This meta-analysis was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and methods [28,29]. A comprehensive literature search was carried out using search terms of "neutrophil-to-lymphocyte ratio (NLR)", "breast cancer or tumor or carcinoma" and "prognosis or outcome or survival" in databases of PubMed, Web of Science and CNKI dating up to July 2014. Hand searches were performed to obtain substantial relevant study by reviewing all references within all relevant articles. All selected literatures were journal articles in Chinese and English. This study was approved by the institution ethics committee of Nanjing Normal University.

2.2. Selection criteria

In the meta-analysis, studies were considered eligible if they met the following criteria: (1) study investigated the association between NLR and clinical prognosis in patients with breast cancer; (2) study provided sufficient data for estimating hazard ratio (HR) with 95% confidence interval (CI). Meanwhile, studies were excluded based on the following criteria: (1) duplicate publications; (2) insufficient data for further analysis; (3) letters, reviews, meeting abstracts, editorials, and case reports; (4) other topics.

2.3. Data extraction

The following data, the first author, year of publication, name of journal, county of origin, ethnicity of the study population, type of specimen, metastasis, cut-off value, follow-up period, number of patients included in analysis, and HR with its 95% CI for overall survival (OS), disease-free survival (DFS), recurrence-free survival (RFS) or cancer specific survival (CSS) were extracted from each eligible study by two independent investigators (JC, QWD). If there was any disagreement, it solved by discussion to reach a consensus.

2.4. Statistical analysis

HR and its 95 % CI were selected as common measurements to assess the strength of the association between NLR and prognosis in breast cancer. Cochran's Q test was chosen to evaluate the heterogeneity and Higgins I-squared statistic was carried out to estimate the degree of heterogeneity of pooled results. The random-effect and fixed-effect models were used to calculate the pooled HR and its 95% CI. If $P_H < 0.05$, the random-effect model (DerSimonian–Laird method) was applied to calculate the pooled HRs [30]. Otherwise, the fixed-effect model (Mantel–Haenszel method) was employed [31]. The HR is commonly and conveniently estimated via a Cox proportional hazards model, which can include potential confounders as covariates. HR > 1 reflects that elevated NLR is associated with the corresponding variate, while HR < 1 has the opposite meaning. Furthermore, subgroup was performed to explore the heterogeneity among studies which stratified by ethnicity, analysis method and metastasis. Sensitivity analysis was conducted to check whether individual study influenced the results by sequential omission of each study in this meta-analysis. Additionally, Begg's funnel plot and Egger's linear regression test were used to assess the extent of publication bias in the meta-analysis and $P_E < 0.05$ was considered as statistically significant. Statistical analysis was performed by Stata 11.0 software (STATA Corporation, College Station, TX, USA).

3. Results

3.1. Included studies

A total of 45 potentially relevant articles were retrieved. 14 papers were defined duplicate publications according to their titles. Then 20 articles were excluded because of obvious lack of relevance. A careful review of the remaining 11 studies revealed that 3 studies did not provide sufficient information. Finally, 8 studies were included in the meta-analysis (Fig. 1) [16,22–25,27,32,33].

3.2. Study characteristics

The main features of eligible studies were shown in Table 1. The eligible studies were published in a period of 2012 to 2014 and contained a total of 4,293 patients. In total, 8 studies were enrolled and 4 studies were conducted in Asian and Caucasian population, respectively. 5 studies were involved in mixed metastasis and the others without metastasis. The cut-off values applied in the studies were not consistent and it was not provided in one study [16]. Among them, 5, 4, 1 and 1 studies investigated the relationship of NLR and OS, DFS, RFS, and CSS, respectively. The useful data of HRs and 95% CIs were obtained from multivariate analysis in 5 studies and univariate analysis in 3 studies, respectively.

3.3. Overall survival

The pooled analysis was conducted in 5 studies including 3,350 patients that reported HR for OS. The main results of this meta-analysis were listed in Table 2 and Fig. 2. The results showed that elevated NLR was associated with a worse outcome for OS with the pooled HR of 2.28 (95% CI = 1.08–4.80, $P_H < 0.001$). Subgroup analyses showed that the prognostic effect of NLR was found only in Caucasian population (HR = 4.53, 95% CI = 3.11–6.60, $P_H = 0.096$) and it was examined to be was a strong prognostic factor in multivariate analysis (HR = 2.10, 95% CI = 1.52–2.89, $P_H = 0.591$). When metastasis was taken into consideration, increased NLR was associated with a poor prognosis for OS in mixed metastasis (HR = 4.53, 95% CI = 3.11–6.60, $P_H = 0.096$).

From sensitivity analysis we found that the result was not obviously impacted by an included study conducted by Cihan et al. [27]. The HR for it was 3.08 (95% CI = 1.59–5.96, $P_H = 0.002$). The shape of funnel plots showed no evidence of publication bias in the analysis (Fig. 3) and the result was further supported by Egger's tests ($P_E = 0.896$).

3.4. Disease-free survival

4 studies comprising 2,764 patients were included to assess the association between NLR and DFS in breast cancer (Table 2). Overall, elevated NLR was associated with a high risk for DFS