

Prognostic role of pretreatment neutrophil to lymphocyte ratio in breast cancer patients

A meta-analysis

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Abstract

Background: Inflammation and cancer are closely related to each other. As a parameter that can reflect inflammation and host immune reaction, elevated blood neutrophil to lymphocyte ratio (NLR) has been confirmed to be correlated with poor prognosis in a variety of cancers. However, this remains controversial in breast cancer. Thus, we performed this updated meta-analysis to further clarify whether high NLR could be a predictor of survival in breast cancer patients.

Methods: We searched on PubMed Database and Cochrane Library. Overall survival (OS), disease-free survival (DFS), and cancer-specific survival were used as outcome events, and hazard ratio (HR) was chosen as the parameter to evaluate the correlation.

Result: Eighteen eligible studies were involved in this meta-analysis. The synthesized analysis demonstrated that elevated NLR was associated with poor DFS [HR = 1.72, 95% confidence interval (95% CI) = 1.30–2.27], OS (HR = 1.87, 95% CI = 1.41–2.48), and cancer-specific survival (HR = 2.09, 95% CI = 1.04–4.21). The correlation was stronger in triple-negative breast cancer (TNBC) (OS: HR = 2.58, 95% CI = 1.63–4.06; DFS: HR = 3.51, 95% CI = 1.97–6.24).

Conclusion: Higher NLR was correlated to poor prognosis of breast cancer patients. As a clinical parameter that we can easily obtain, NLR might be a potential predictor in patients' survival to assist with physicians' treatment decisions.

Abbreviations: CSS = cancer-specific survival, DFS = disease-free survival, HR = hazard ratio, NLR = neutrophil to lymphocyte ratio, OR = odds ratio, OS = overall survival, RFS = recurrence-free survival, RR = relative risk, TNBC = triple-negative breast cancer.

Keywords: breast cancer, meta-analysis, neutrophil to lymphocyte ratio, prognosis, survival

1. Introduction

Breast cancer has been the most common cancer in women all over the world, and 1.8 million women died of it in 2013.^[1–3] Five major subtypes of breast cancer (luminal A and B, Her2, basal, and normal-like) are very different in clinical characters and prognosis.^[4] Inflammation plays an important role in cancer. More and more studies have found that cancer and inflammation are closely related to each other. Not only inflammation results in

cancer but also cancer causes inflammation. Serum interleukin (IL)-6, IL-8 that are linked to inflammation and macrophages in the tumor microenvironment (TME) have been identified as unfavorable factors for cancer patients' survival.^[5,6] Furthermore, anti-inflammation agents such as aspirin have been put in a new height in cancer prevention and therapy.

As a parameter that can reflect inflammation and host immune reaction, blood neutrophil to lymphocyte ratio (NLR) has received much attention in predicting the prognosis of cancer. Large numbers of studies have demonstrated that high NLR is related to poor prognosis of malignant tumor, including breast cancer, lung cancer, gastric cancer, colorectal cancer, and prostate cancer.^[7–11] Most studies showed that elevated NLR could be a predictor of poor prognosis in breast cancer patients. However, some studies could not support this conclusion very well.^[12,13]

In the meta-analysis by Chen et al,^[14] only 8 earlier studies were enrolled. Therefore, we performed this meta-analysis in which we included the newest studies to further clarify the relationship between NLR and prognosis of breast cancer patients.

2. Materials and method

2.1. Search strategy and selection criteria

A selective literature search was performed by 2 reviewers (Liu and Qu) using PubMed Database and the Cochrane Library with following terms: “neutrophil-to-lymphocyte ratio” or “neutrophil to lymphocyte ratio” or “NLR” and “breast cancer” or

Editor: Jianxun Ding.

The authors report no conflicts of interest.

Supplemental Digital Content is available for this article.

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Medicine (2017) 96:45(e8101)

Received: 16 August 2016 / Received in final form: 25 May 2017 / Accepted: 29 August 2017

<http://dx.doi.org/10.1097/MD.00000000000008101>

“tumor” or “carcinoma” and “prognosis” or “outcome” or “survival”. This meta-analysis was conducted in accordance with the guidelines provided by the PRISMA statement.

We included publications of clinical research aimed to study the association between NLR and breast cancer prognosis. NLR of peripheral blood is tested before any treatment including surgery or neoadjuvant treatment. Meanwhile, those studies should choose disease-free survival (DFS) or overall survival (OS) or disease-specific mortality (DSS) as the outcome events. Each included study was approved by an ethics committee or institutional review board. Exclusion criteria were as follows: publications that we could not extract sufficient data that we were interested in; nonclinical research, abstracts, reviews, letters, case reports, meta-analyses, and proceedings; duplicate publications; and subgroup of the included articles.

2.2. Data extraction and quality assessment

The first author, publishing year, county of origin, stage of studying population, treatment, the number of patients included in the analysis, molecular subtype of the patients, end-point of follow-up including DFS, OS, DSS, and parameters to analyze the correlation between prognosis and NLR were extracted from each eligible study by 2 independent investigators. Disagreements were resolved by discussion or consensus with a third reviewer.

2.3. Data synthesis and analysis

The hazard ratio (HR), its 95% confidence interval (95% CI), or *P* value were extracted, respectively, and HR of high NLR group was finally synthesized into pooled analysis to estimate the correlation between NLR and survival. All analyses were performed by using STATA Statistical Software, version 12.0 (Stata Corp, College Station, TX). Cochran *Q* test was chosen to evaluate the heterogeneity and I^2 was carried out to estimate the degree of heterogeneity among the included studies. Fixed-effect model was used to calculate HR if $I^2 \leq 50\%$ and $P > 10\%$, and significant heterogeneities ($I^2 > 50$) among the studies were resolved with the random-effects model. Subgroup analysis was conducted to determine the source of heterogeneity. Sensitivity analyses were performed to determine the stability of the result. Publication bias was analyzed using Begg and Egger funnel plot. $P_{>|t|} \leq 10\%$ is considered to exist publication bias. Trim and fill method was used to assess the influence of publication bias on pooled results.

3. Results

3.1. Search result

According to our search strategy, a total of 107 publications were identified, and among them, 35 duplicated publications were excluded. Then, 42 unrelated publications were excluded by reviewing titles and abstracts. Further, we review the left 30 publications carefully, and find that among them, 6 studies did not provide enough data for our analysis, or did not measure NLR at initial treatment, studied chemotherapy response instead of survival, or publications were meta-analysis and review. The left 23 studies were eligible.^[9,12,13,15–34] However, when we perform a review of the 23 publications again, we find that patients in the study by Chen et al^[33] is a subgroup of Jia et al.^[20] As a result, the study by Chen et al^[33] was excluded finally. Regrettably, 2 publications by Azab et al^[25,34] reported a dose-response HR, as patients' NLR was divided into quartiles. To avoid heterogeneity in study method, these 2 were excluded.

Although 2 publications by Forget et al^[24,32] had different research aims, they all reported HR for DFS or OS in different neutrophil-to-lymphocyte ratios. Taking the number of patients and quality of the 2 studies into consideration, we chose one of them in our analysis. In addition, only 1 literature^[12] chose OR as a parameter to assess the correlation between NLR and breast cancer survival. Finally, 18 studies were conducted in our meta-analysis. Figure 1 is the flowchart that describes our literature search progress. Among these 18 studies, 12 publications reported HR for DFS and 11 for OS. Four publications provided the HR for cancer-specific survival (CSS). Table 1 presents some details of the 18 included studies.

3.2. NLR and DFS

Twelve studies with 5523 patients provided HR for OS. Among them, 6 studies came from East or Southeast Asia, and the others were located in Turkey, East Europe, or the USA, mainly recruiting Caucasian patients. We defined those with less than 200 patients as small number studies. Therefore, half of the 12 studies were categorized into small number group. Pooled results showed that higher pretreatment NLR patients are prone to get a poorer outcome in DFS (HR=1.72, 95% CI=1.30–2.27, $I^2=76\%$, $P_{\text{heterogeneity}} < .001$, Fig. 2). Deletion of any of these studies did not significantly alter our pooled result, but the heterogeneity changed obviously after exclusion of study by Suppan et al^[15] when sensitivity analysis was performed (Table 2, Supplementary Figure 3, <http://links.lww.com/MD/B924>). We predicted that the study by Suppan et al^[15] might be an origin of heterogeneity. Then subgroup analysis was conducted, and the result showed that high heterogeneity still existed in Caucasian and large number study group when the study by Suppan et al^[15] was present (Table 3). As Suppan et al^[15] depicted in their article, early breast cancer patients were chosen in his study, very different from others. Thus, another synthesized analysis was performed when this study was absent. As expected, all the subgroups manifested association between NLR and DFS without statistical heterogeneity (Supplementary Figure 2, <http://links.lww.com/MD/B924>). These indicated that this study played a critical role in heterogeneity of our pooled analysis.'

3.3. NLR and OS

Eleven studies comprising 7002 patients reported HR for OS. In the study by Ulas et al,^[13] HR of low NLR group for survival was reported rather than that of high NLR group. Therefore, we had to convert HR into data of high NLR group to keep consistent with others' reports. Pooled analysis demonstrated that high NLR significantly decreased OS (HR=1.87, 95% CI=1.41–2.48, $I^2=51\%$, $P_{\text{heterogeneity}} = .027$). In order to find out the origin of heterogeneity, we performed a subgroup analysis taking ethnicity, tumor stage, and the number of patients into consideration, respectively. Although adverse effect of higher NLR still existed in each subgroup, significant heterogeneity was also observed in Asian, small number, or all tumor stage subgroup) as summarized in Table 3. The study by Koh et al^[17] might be a common factor, as it was categorized to those subgroups with a high heterogeneity. However, sensitivity analysis indicated that the study by Koh et al^[17] did not significantly affect the stability of our result. Four of the eleven studies included single molecular subtype patients (1 luminal, 1 Her2 positive, 2 TNBCs) instead of all the subtype compared with the other 7. Thus, another pooled analysis excluding all these 4 studies presented accordant correlation between NLR and

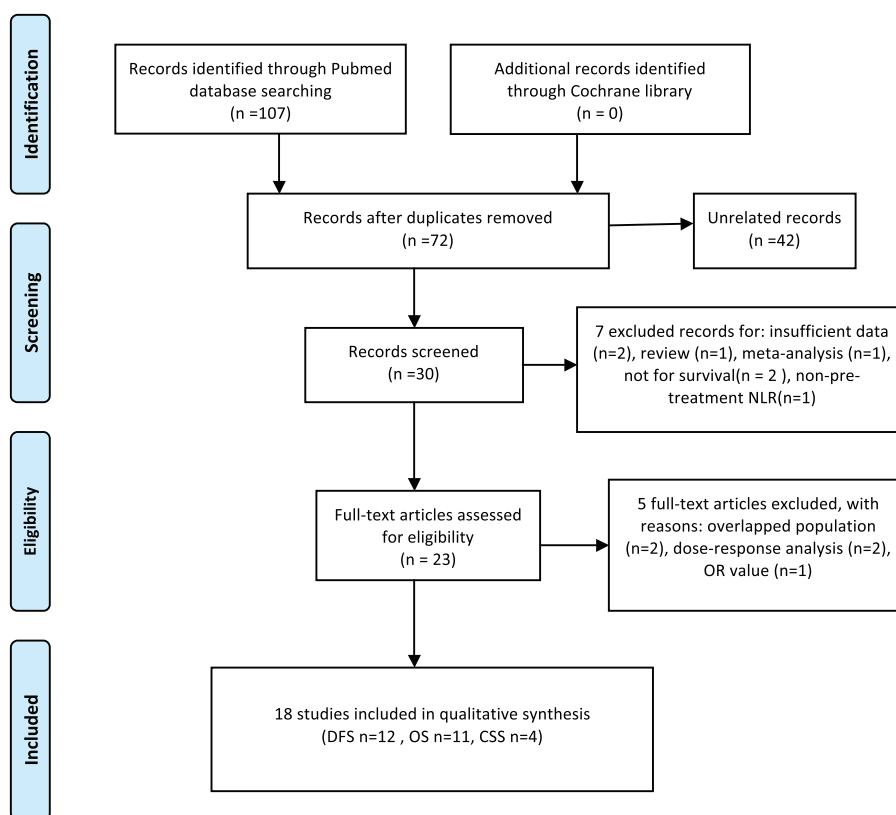


Figure 1. Flow graph of searching process.

OS without significant heterogeneity suggesting that these 4 studies potentially affected heterogeneity of total analysis (Supplementary Figure 1, <http://links.lww.com/MD/B924>).

3.4. NLR and triple-negative breast cancer

Triple-negative breast cancer (TNBC) is a heterogeneous and clinically aggressive disease with poorer prognosis compared

with Luminal or Her2 (+) subtype.^[35,36] We wanted to identify whether high NLR had adverse effects on the survival of TNBC. Fortunately, 3^[21,28,29] out of 18 studies were aimed to study NLR and survival in TNBC patients. Although all subtypes of breast cancer patients were included in the studies by Jia et al^[20] and Koh et al,^[9] HR for survival in TNBC was provided additionally in their report. Pooled analysis in which the above 5 studies were included demonstrated that NLR had a stronger association

Table 1
Main characteristics of 18 eligible studies.

| Author | Year | Country | Stage | Subtype | Number | Survival | Correlation | OS | DFS | CSS |
|--------------------------------|------|----------|----------|-------------|----------------|----------|-------------|---|---|-------------------|
| Kim et al ^[19] | 2016 | Korea | III | all | 220 | DFS OS | HR | | 3.93 (1.27–12.11) | |
| Lee et al ^[16] | 2015 | Korea | ≤III | all | 3116 | CSS | HR | | | 1.09 (0.94–1.26) |
| Koh et al ^[17] | 2014 | Korea | All | Luminal A/B | 157 | RFS OS | HR | 24.87 (3.07–201.30) | | |
| Zhang et al ^[18] | 2016 | China | ≤III | all | 162 | DFS OS | HR | 1.23 (0.59–2.36) | 1.44 (0.80–2.57) | |
| Jia et al ^[20] | 2015 | China | ≤III | all | 1570 (225TNBC) | DFS OS | HR | TNBC: 3.05 (1.08–8.61) All: 1.63 (1.07–2.49) | TNBC: 2.58 (1.23–5.42) All: 1.50 (1.14–1.97) | |
| Bozkurt et al ^[21] | 2015 | Turkey | ≤III | TNBC | 85 | DFS OS | HR | 2.86 (1.04–7.86)* | 5.46 (1.61–18.5) | |
| Ulas et al ^[13] | 2015 | Turkey | ≤III | Her2 (+) | 187 | DFS OS | HR | 0.84 (0.26–2.70) | 1.35 (0.61–2.99)* | |
| Suppan et al ^[15] | 2015 | Austria | early | all | 247 | DFS | HR | | 1.01 (0.96–1.06) | |
| Forget et al ^[24] | 2014 | Belgium | All | all | 720 | DFS OS | HR | 2.35 (1.02–5.43) | 1.99 (1.16–3.41) | |
| Nakano et al ^[22] | 2014 | Japan | ≤III | all | 167 | DFS CSS | HR | | 2.00 (0.90–4.10) | 2.70 (1.10–7.30) |
| Dirican et al ^[23] | 2015 | Turkey | All | all | 1527 | DFS OS | HR | 1.91 (1.31–2.79) | 1.46 (1.04–2.04) | |
| Noh et al ^[26] | 2013 | Korea | ≤III | all | 442 | CSS | HR | | | 4.08 (1.62–10.28) |
| Yao et al ^[27] | 2014 | China | ≤III | all | 608 | DFS OS | RR | 3.63 (1.60–8.26) | | |
| Koh et al ^[9] | 2015 | Malaysia | All | all | 1435 (208TNBC) | OS | HR | TNBC: 1.91 (1.00–3.65) All: 1.37 (1.08–1.74) | | |
| Pistelli et al ^[28] | 2015 | Italy | ≤IIIA | TNBC | 90 | DFS OS | HR | 6.16 (1.54–24.66) | 5.15 (1.11–23.88) | |
| Asano et al ^[29] | 2016 | Japan | IIA/IIIA | TNBC | 61 | DFS OS | HR | | 11.11 (0.35–354.69)† | |
| Rimando et al ^[30] | 2016 | USA | All | all | 461 | OS CSS | HR | 1.47 (0.73–2.96) | | 2.27 (1.02–5.08) |
| Hong et al ^[31] | 2016 | China | ≤III | all | 487 | DFS OS | HR | | 1.87 (1.16–3.02) | |

CSS=cancer-specific survival, DFS=disease-free survival, HR=hazard ratio, OS=overall survival, RFS=recurrence-free survival, TNBC=triple-negative breast cancer.

* HR of low NLR group for survival is provided in the study by Ulas et al, ^[13] original HR for DFS is 0.74 (P=.46), HR for OS is 1.19 (P=.77).

† The study by Asano et al^[29] included all molecular subtypes of patients, but only HR in TNBC was reported, original HR is for low NLR group: 0.09 (0.00, 2.89).

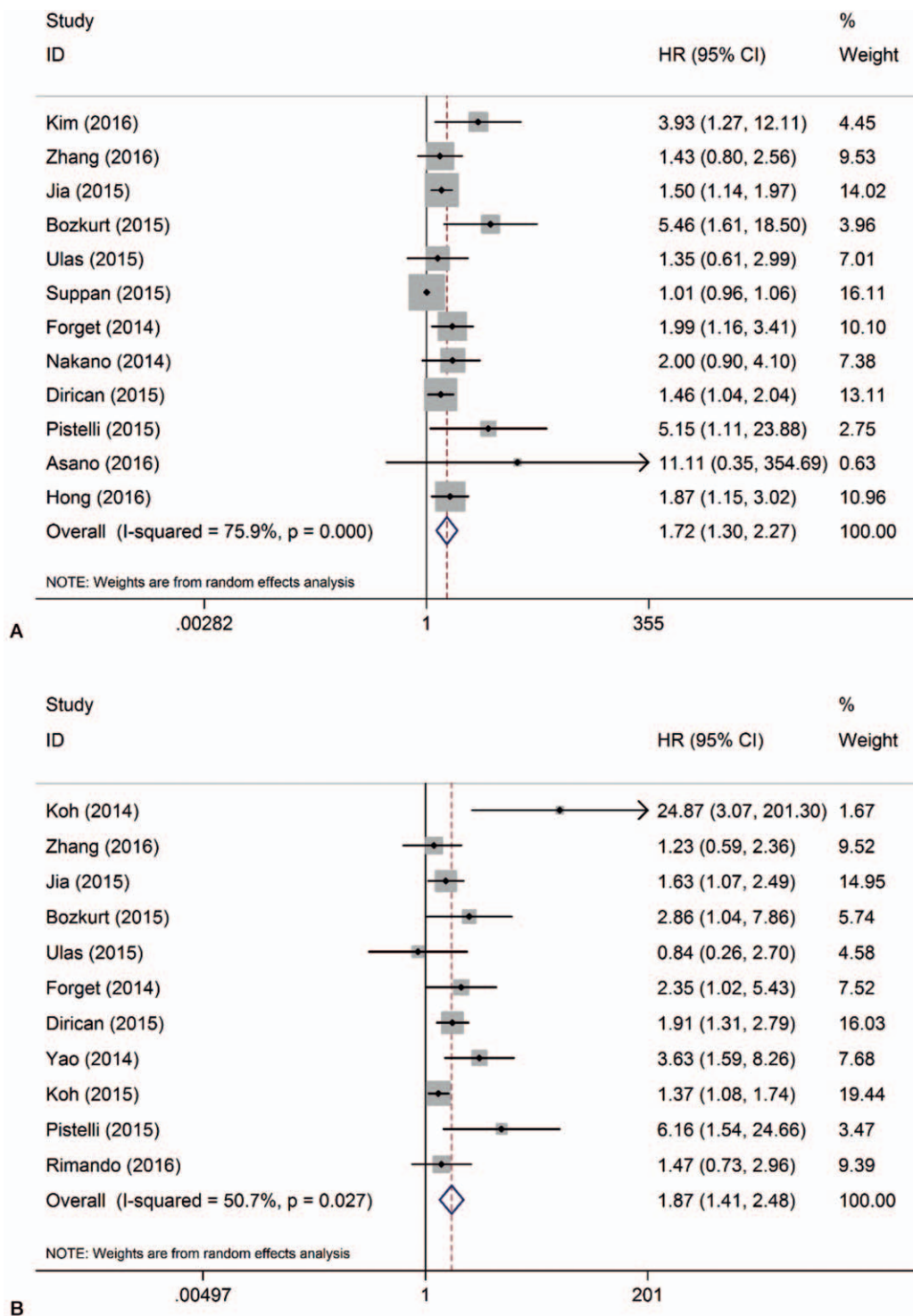


Figure 2. Forrest plots of survival: (A) HR for disease-free survival; (B) HR for overall survival.

with both OS (HR=2.58, 95% CI=1.63–4.06, $I^2 < 0.1\%$, $P_{\text{heterogeneity}} = .48$) and DFS (HR=3.51, 95% CI=1.97–6.24, $I^2 < 0.1\%$, $P_{\text{heterogeneity}} = .61$) in TNBC (Fig. 3).

3.5. NLR and CSS

Four studies involving 4186 patients estimated the association between NLR and CSS. Patients with higher NLR had

poorer CSS (HR=2.09, 95% CI=1.04–4.21) than those with lower NLR (Fig. 3), with a significant heterogeneity ($I^2 = 78\%$). Similarly, stability of the pooled result was influenced by the study by Lee et al^[16] in sensitivity analysis (Supplementary Figure 3, <http://links.lww.com/MD/B924>). As there were too few studies in this pooled analysis, we did not perform subgroup analysis and publication bias analysis.

Table 2**Result for sensitivity analysis of DFS and OS with random effect model.**

| Ref. | Initial treatment | Cut-off | Subtype | Analysis | HR | Heterogeneity | |
|--------------------------------|-------------------|---------|----------|----------|-------------------|--------------------|------|
| | | | | | | I ² (%) | P |
| OS | | | | | | | |
| Bozkurt et al ^[21] | All | 2 | TNBC | Multi | 1.83 (1.37, 2.45) | 53 | .02 |
| Dirican et al ^[23] | All | 4 | All | Multi | 1.91 (1.37, 2.68) | 54 | .02 |
| Forget et al ^[24] | Surgery | 3.3 | All | Multi | 1.85 (1.37, 2.50) | 54 | .02 |
| Jia et al ^[20] | All | 2 | All | Multi | 1.97 (1.41, 2.75) | 55 | .02 |
| Koh et al ^[17] | Neoadjuvant | 2.25 | Luminal | Multi | 1.74 (1.38, 2.21) | 34 | .13 |
| Koh et al ^[9] | All | 4 | All | Multi | 2.04 (1.47, 2.82) | 44 | .07 |
| Pistelli et al ^[28] | All | 3 | TNBC | Multi | 1.78 (1.36, 2.32) | 46 | .05 |
| Rimando et al ^[30] | All | 3.70 | All | Multi | 1.95 (1.43, 2.65) | 55 | .02 |
| Ulas et al ^[13] | Surgery | 2.38 | Her2 (+) | Uni | 1.95 (1.46, 2.60) | 52 | .03 |
| Yao et al ^[27] | Surgery | 2.57 | All | Multi | 1.75 (1.33, 2.31) | 46 | .06 |
| Zhang et al ^[18] | All | 1.81 | All | Uni | 1.97 (1.45, 2.67) | 54 | .02 |
| DFS | | | | | | | |
| Asano et al ^[29] | Neoadjuvant | 3 | TNBC | Multi | 1.69 (1.28, 2.24) | 77 | <.01 |
| Bozkurt et al ^[21] | All | 2 | TNBC | Multi | 1.62 (1.23, 2.11) | 74 | <.01 |
| Dirican et al ^[23] | All | 4 | All | Multi | 1.79 (1.30, 2.46) | 76 | <.01 |
| Forget et al ^[24] | Surgery | 3.3 | All | Multi | 1.68 (1.26, 2.25) | 75 | <.01 |
| Hong et al ^[31] | Surgery | 1.93 | All | Multi | 1.69 (1.26, 2.27) | 75 | <.01 |
| Jia et al ^[20] | All | 2 | All | Multi | 1.80 (1.30, 2.49) | 74 | <.01 |
| Kim et al ^[19] | Surgery | 3 | All | Multi | 1.64 (1.24, 2.16) | 75 | <.01 |
| Nakano et al ^[22] | All | 2.5 | All | Multi | 1.70 (1.27, 2.27) | 77 | <.01 |
| Pistelli et al ^[28] | All | 3 | TNBC | Multi | 1.65 (1.25, 2.18) | 76 | <.01 |
| Suppan et al ^[15] | Neoadjuvant | no | All | Multi | 1.72 (1.42, 2.08) | 14 | .31 |
| Ulas et al ^[13] | Surgery | 2.38 | Her2 (+) | Uni | 1.76 (1.31, 2.36) | 78 | <.01 |
| Zhang et al ^[18] | All | 1.81 | All | Multi | 1.76 (1.30, 2.38) | 76 | <.01 |

DFS=disease-free survival, HR=hazard ratio, multi=multivariate analysis, OS=overall survival, TNBC=triple-negative breast cancer, uni: univariate analysis.

3.6. Publication bias

Begg and Egger test (Fig. 4, supplementary Figure 4, <http://links.lww.com/MD/B924>) revealed obvious publication bias (OS: $P_{>|t|}=.034$; DFS: $P_{>|t|}<.001$). To determine the origin of this bias, the trim-and-fill method was applied. For DFS, there were 4 potential publications, and 2 hypothesized publications for OS. Recalculation of HR indicated that high NLR might be a risk factor for both OS (HR=1.72, 95% CI=1.25–2.36) and DFS

(HR=1.49, 95% CI=1.14–1.94) even though there existed heterogeneity.

4. Discussion

Although the mechanisms of the association between tumor and inflammation have not been fully understood, it is sure that tumor and inflammation interacts with each other.^[37,38] On the one

Table 3**Result for subgroup analysis.**

| Subgroup | HR | I ² | P | Effect model | Study number |
|-----------|-------------------|----------------|-------|--------------|--------------|
| OS | | | | | |
| Ethnicity | | | | | |
| Caucasian | 1.93 (1.46, 2.56) | 17% | 0.30 | Fixed | 6 |
| Asian | 1.88 (1.18, 2.98) | 68% | 0.02 | Random | 5 |
| Stage | | | | | |
| ≤III | 1.70 (1.33, 2.18) | 23% | 0.26 | Fixed | 6 |
| all | 1.82 (1.23, 2.69) | 60% | 0.04 | Random | 5 |
| Number | | | | | |
| Small | 2.65 (1.05, 6.66) | 68% | 0.01 | Random | 6 |
| Large | 1.61 (1.36, 1.90) | 30% | 0.21 | Fixed | 5 |
| DFS | | | | | |
| Ethnicity | | | | | |
| Caucasian | 1.65 (1.09, 2.50) | 77% | <0.01 | Fixed | 6 |
| Asian | 1.93 (1.46, 2.56) | 0% | 0.47 | Random | 6 |
| Number* | | | | | |
| Small | 1.90 (1.31, 2.75) | 30% | 0.21 | Fixed | 6 |
| Large | 1.55 (1.13, 2.12) | 82% | <0.01 | Random | 6 |

DFS=disease-free survival, HR=hazard ratio, OS=overall survival.

* Small number: the number of patients for final analysis in the study is less than 200; large number: the number of patients for final analysis in the study is more than 200.

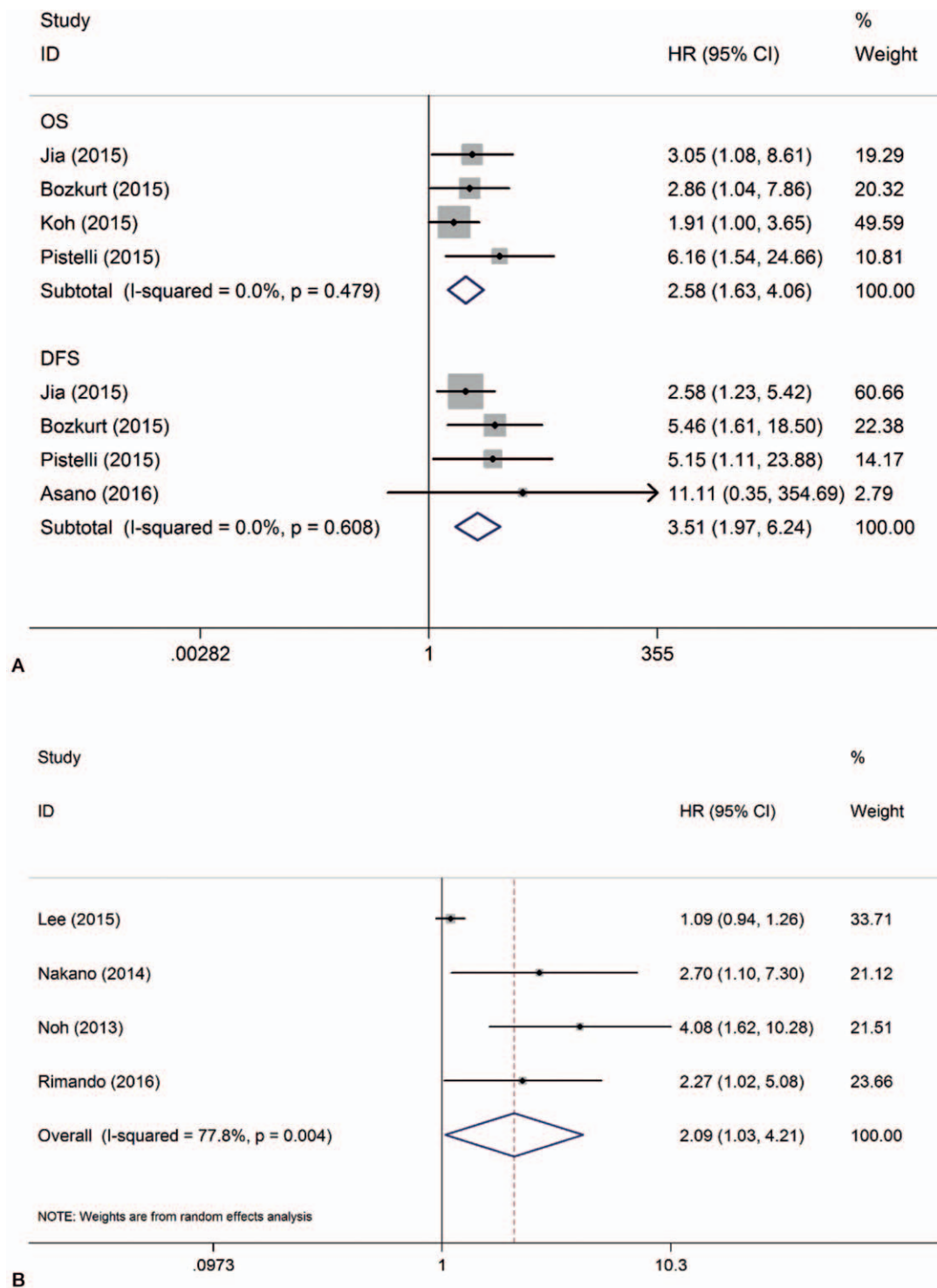


Figure 3. Forrest plots of survival: (A) HR for survival in TNBC; (B) HR for cancer-specific survival.

hand, regional hypoxia and reactive oxygen species (ROS) is considered to be a potential factor to drive inflammatory response in tumor.^[39–42] On the other hand, cancer-related inflammation plays a necessary role in the prognosis of cancer.^[38,43–46] According to that, several targets related to inflammation including cyclooxygenase, chemokine (C-C motif) ligand 2, CXC chemokine receptor 4 (CXCR4), nuclear factor kappa B, and so on have been established to apply in the

treatment of cancer.^[37,43,47–50] Besides, biomarkers associated with systemic inflammatory response such as neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and C-reactive protein were developed to predict the prognosis of cancer.^[51] Particularly in recent years, an increasing evidence demonstrated that pretreatment NLR could be a predictor of prognosis in variates of cancers.^[36,52–54] It could be mainly explained by TME and different functions of neutrophils and lymphocytes.

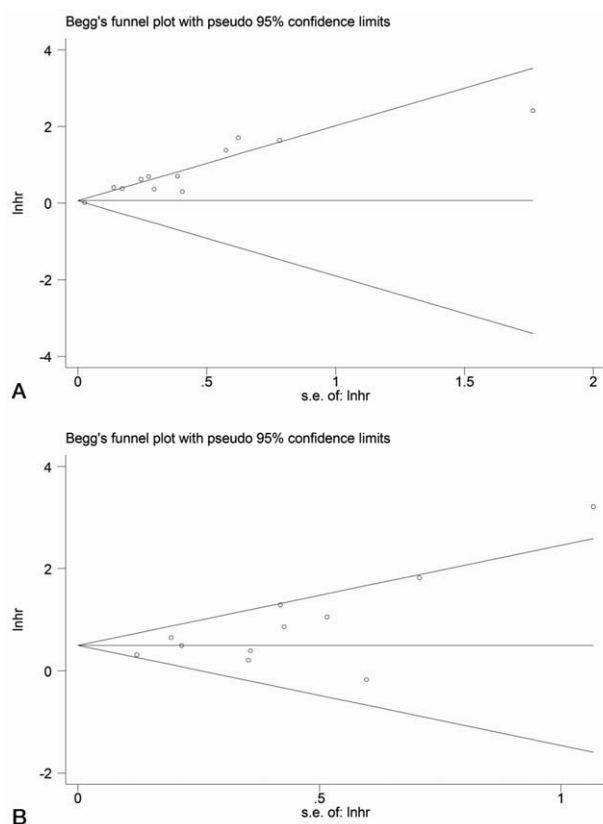


Figure 4. Begg funnel plot: (A) estimated publication bias in pooled analysis of disease-free survival; (B) estimated publication bias in pooled analysis of overall survival.

TME is defined as a complex tissue composed not only of tumor cells but also of stromal cells, inflammatory cells, vasculature, and extracellular matrices (ECMs).^[55] TME plays a critical role in regulating tumor immunity that is the basis of immunotherapy and further affects progression of cancer. Neutrophils in TME are divided into 2 types: N1 and N2. The former owns anti-tumor effect, while the later has immunosuppressive effect. Recruited neutrophils produce protein or chemokines such as CXCR, cytokines, vascular endothelial growth factor, or matrix metalloproteinase 9 to promote proliferation, invasion, and angiogenesis of tumor and more intratumoral neutrophil infiltration is associated with poorer prognosis in varieties of carcinoma.^[56,57] In contrast, lymphocytes are known to have the function of immunosurveillance and anti-tumor effects.^[58–60] Besides, pooled analysis indicates that a decreased number of tumor-infiltrating lymphocytes in breast cancer tissue predicts low pathology complete response rate to chemotherapy as well as shorter DFS and OS.^[61,62] Neutrophil-to-lymphocyte ratio might indirectly reflect immunosuppressive versus anti-tumor effect in cancer patients. Therefore, patients with an elevated NLR might be inclined to show a poorer outcome.

In this study, a system review with a meta-analysis of previous publications aimed to study correlations between pretreatment NLR and survival was performed. The result demonstrated that high NLR correlated with poor OS (HR=1.87, 95% CI=1.41–2.48), DFS (HR=1.72, 95% CI=1.30–2.27), and CSS (HR=2.09, 95% CI=1.04–4.21). We got stable results even though we excluded Suppan and Koh's study, which we identified as the

potential origin of heterogeneity in our pooled analysis. What is more, we found that the correlation was stronger in TNBC with a higher HR (OS: HR=2.58, 95% CI=1.63–4.06; DFS: HR=3.51, 95% CI=1.97–6.24).

Although there has been 1 meta-analysis examining the role of NLR in predicting survival of breast cancer patients so far, our study possessed the following several advantages: First, comparing with previous one that included only 8 studies, we included the newest publications from 2015 to 2016 in our analysis, which to date, contained the most study (18 publications) and patients number (5523 for DFS, 7002 for OS) to ensure the reliability of the conclusion. In particular, we involved 11 studies from Asian population. Second, we had a more strict inclusion criterion. For instance, we depleted studies came from the same center to avoid duplicated data in pooled analysis, while the previous meta-analysis used 2 studies by Azab et al.^[25,34] and Forget et al.^[24,32] In addition, we had chosen HR and relative risk (RR) (only 1 study) as the parameters of correlation in the synthesized analysis. By contrast, another meta-analysis included Cihan et al.^[12] that used OR to measure the association. Lastly, this is the first article to examine HR for DFS and OS in TNBC patients, and we also studied the influence of high NLR on CSS.

However, the following limitations must be considered when interpreting the findings in our study. First significant heterogeneity was observed in each pooled analysis. Aiming at this, we tried our best to find out the source of heterogeneity by subgroup and sensitivity analysis. What is more, those heterogeneous studies hardly altered pooled results. Second, there was publication bias in DFS and OS pooled analysis. However, trim-and-filled method demonstrated that the publication bias did not affect stability of the result. Third, all involved studies used different cut-off values that might affect extrapolation and operability of the results in predicting the survival of patients. Finally, there were only 4 studies in pooled analysis for CSS, and subgroup analysis was not performed.

5. Conclusion

Our meta-analysis suggested that high NLR was associated with poor prognosis in breast cancer patients. As an easily available clinical index, NLR could serve as a predictor of patients' survival to assist with treatment decisions. Thus, more high quality of perspective studies is necessary to be conducted to validate its role in breast cancer.

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