Clinica Chimica Acta 484 (2018) 1–6

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Review

Preoperative lymphocyte-to-monocyte ratio predicts breast cancer outcome: A meta-analysis

Ru-jin Hu[1], Qin Liu[1], Jian-ying Ma[1], Jing Zhou, Gang Liu*

Department of Breast surgery, Thyroid surgery, Pancreatic surgery, Huangshi Central Hospital of Edong Healthcare Group, Hubei Polytechnic University, No.141, Tianjin Road, Huangshi, Hubei, China

ARTICLE INFO

Keywords:
Breast cancer
Lymphocyte-to-monocyte ratio
Disease-free survival
Overall survival
Meta-analysis

ABSTRACT

Aim: To assess the prognostic value of the preoperative lymphocyte-to-monocyte ratio (LMR) in patients with breast cancer (BC).

Methods: Relevant studies were systematically retrieved from the online Cochrane, MEDLINE, EMBASE and CNKI databases published until February 2018. The end points were overall survival (OS), disease-free survival (DFS), and clinicopathological parameters. Meta-analysis was performed using hazard ratios (HRs) or odds ratios (ORs) and their 95% confidence intervals (CIs) as effect measures.

Results: Ten studies with 5667 individuals were included. The synthesized analysis demonstrated that that low LMR was significantly associated with poor OS (HR: 0.65, 95% CI: 0.47–0.90, $p = .009$) and DFS (HR: 0.60, 95% CI: 0.49–0.74, $p < .001$). Subgroup analyses revealed that the negative prognostic impact of low LMR on OS outcomes remained substantial in Asian populations, triple-negative patients, and patients with non-metastatic and mixed stage. However, low LMR was not significantly related to clinicopathological features.

Conclusion: The preoperative LMR might be a predictive factor of poor prognosis for BC patients.

1. Introduction

Breast cancer is the most frequent malignancy in women worldwide. It is a complex and heterogeneous disease, and is categorized into three major subtypes: luminal A and B, human epidermal growth factor 2 (HER2), basal, and normal-like enriched, which exhibit distinct clinical features and prognosis [1–3]. In order to conduct appropriate risk stratification and select appropriate treatments, the determination of prognostic factors remains the subject of intense investigation in breast cancer. Several factors affect the prognosis of the breast cancer, including clinicopathological features (such as tumor size, stage, histological grade, lymph node status) and receptor status [4]. However, most of these factors are usually achieved after surgical resection, and the discriminant efficiency of them is still lack of accuracy. Therefore, easily available and efficient prognostic parameters are desirable.

It is generally recognized that the prognosis of breast cancer patient depends on both tumor characteristics and patient-related factors. Accumulating evidence has highlighted the role of inflammation as a critical component in tumor development and progression [5]. System inflammation factors, such as plasma fibrinogen, C-reactive protein (CRP), prognostic nutritional index (PNI), neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR) have been explored as prognostic biomarkers in multiple malignancies [6–10]. A low preoperative LMR, defined as the absolute lymphocyte count divided by the absolute monocyte count, has been reported to be associated with poor survival in patients with BC [11,12]. Moreover, LMR tests are easy to perform, less expensive, and readily available. However, some studies failed to find the correlation between the LMR and the prognosis of patients with BC [13–15]. We therefore conducted a meta-analysis to evaluate the impact of LMR on clinicopathologic parameters and oncologic outcomes in patients with breast cancer.

2. Materials and methods

2.1. Search strategies

An electronic search of MEDLINE, EMBASE, Cochrane Library, and China National Knowledge Infrastructure (CNKI) was performed for relevant articles using the following terms: “lymphocyte-to-monocyte ratio” or “LMR” or “lymphocyte to monocyte ratio” or “lymphocyte monocyte ratio” and “breast cancer” or “tumor” or “carcinoma” or

* Corresponding author at: Department of Breast surgery, Thyroid surgery, Pancreatic surgery, Huangshi Central Hospital of Edong Healthcare Group, Hubei Polytechnic University, China.
E-mail address: gangliu2017@126.com (G. Liu).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.cca.2018.05.031
Received 23 March 2018; Received in revised form 9 May 2018; Accepted 14 May 2018

"neoplasms" and "prognosis" or "outcome" or "survival". The deadline for the date of publication was February 2018. The bibliographies cited in the selected articles were also examined to identify other relevant studies.

2.2. Study selection

The criteria for inclusion were as follows: (1) the diagnosis of BC established by pathological examination; (2) studies evaluated the prognostic role of preoperative LMR on survival outcome; (3) reported a cut-off value for LMR; 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) case-reports, letters, or conference abstracts; (2) studies with insufficient data; and (3) duplicate publication.

2.3. Data extraction and quality assessment

The two investigators independently reviewed the studies and extracted data from each study: the first author, country, ethnicity, publication year, number of patients, age, menopause status, time of follow-up, histology, ER status, PR status, HER2 status, molecular subtype, tumor size, tumor grade, TNM stage, and lymph node status,cut-off values, survival analysis methods,clinicopathological parameters, and HRs and associated 95% CIs for OS or DFS.

The Quality Assessment of Newcastle-Ottawa Scale (NOS) was adopted to evaluate the methodological quality of included studies [16]. This scale consists of three parameters: selection (0–4 points), comparability (0–2 points), and outcome assessment (0–3 points). The NOS scores ≥ 6 are considered as high-quality studies. Validity of included studies was assessed by two independent reviewers.

2.4. Statistical analysis

The meta-analysis was conducted using Review Manager 5.3 software (Cochrane Collaboration, Copenhagen, Denmark). HRs and 95% CIs for OS and DFS were directly obtained from individual articles or calculated from indirect data according to the methods illustrated by Tierney and Parmar [17,18]. Odds ratios (ORs) and their 95% CIs were applied to estimate the association between LMR and clinicopathological features. Cochran's Q test was chosen to evaluate the heterogeneity and Higgins I-squared statistics was carried out to estimate the degree of heterogeneity among the included studies. The result was defined as heterogeneous when the I^2 was > 50% or the *P*-value was < 0.1 for the Q test. A fixed-effect model was used in the absence of significant heterogeneity; otherwise, a random-effect model was used. Subgroup analyses were conducted for ethnicity, disease stage, subtype, analysis method, and the cut-off value. Sensitivity analyses were performed to determine the stability of the result. $P < .05$ indicated a statistically significant result.

3. Results

3.1. Study characteristics

Initially, 57 records were identified from electronic databases. After we removed the duplications, 35 articles were left. Of these, 14 were excluded on the basis of title and abstract review, leaving 21 potentially relevant full-text articles. Ultimately, after reading all 21 articles, 10 eligible studies with a combined 5667 patients were included [11–15,19–23]. A flow diagram of the literature search is shown in Fig. 1.

All included studies were published between 2014 and 2017. Of the ten studies, seven studies were from China, one was from Spain, one was from Japan, and one was from Czech Republic. The sample sizes ranged from 92 to 2000 subjects. There were seven studies for OS, and six for DFS. The cut-off values for LMR ranged from 3.8 to 5.83; All included studies were divided into high and low LMR group. Quality assessment results of the studies are shown in Table 1 using the NOS. The quality of the included studies varied from moderate to high. Characteristics of included studies are described in Table 1.

3.2. Meta-analysis

3.2.1. Overall survival

Seven studies reported data on the prognostic value of the LMR on OS in BC patients. Overall, patients with low LMR had shorter OS outcomes (HR: 0.65, 95% CI: 0.47–0.90, $p = .009$), with significant heterogeneity ($p = .01$, $I^2 = 73\%$; Fig. 2). We also conducted subgroup analysis for further investigation (Table 2). The results showed that LMR was still an indicator for poor OS in Asian populations (HR = 0.56; 95% CI = 0.37–0.84; $P = .005$). In the exploratory subgroup analyses stratified by subtype, a low LMR significantly predicted shorter OS in triple-negative breast cancer (TNBC) patients (HR = 0.55; 95% CI = 0.39–0.78; $P < .001$). When stratified by analysis method, a low LMR have a prognostic effect in multivariate analysis (HR = 0.69; 95% CI = 0.54–0.89; $P = .003$). Pooled HRs for OS were stratified by disease stage, the negative effect of low LMR on OS was observed in patients with non-metastatic (HR = 0.42; 95% CI = 0.19–0.95; $P < .001$) and mixed (HR = 0.69; 95% CI = 0.50–0.96; $P = .03$). In addition, subgroup analyses suggested that low LMR predicted worse OS in patient with BC, regardless of the cut-off value for LMR (< 5.0 and ≥ 5.0).

3.3. Disease-free survival

Six studies comprising 3047 patients reported HRs for DFS. In comparison with a high LMR, a low LMR was significantly correlated with worse DFS (HR = 0.60; 95% CI = 0.49–0.74; $P < .001$; Fig. 3), without significant heterogeneity ($I^2 = 0\%$; $P = .71$).

3.4. Sensitivity analysis

Each study was successively deleted to assess the influence of individual studies on the pooled HR. The results of the sensitivity analyses revealed that the corresponding pooled HRs were not radically changed, which indicates the robustness of our findings.

3.4.1. LMR and clinicopathological features

The correlations between LMR and clinicopathological parameters are presented in Table 3. Several studies were available for the pooled analysis with regard to age, menopause status, histology, ER status, PR status, HER2 status, molecular subtype, tumor size, tumor grade, TNM stage, and lymph node status. The results indicated no significant correlation between LMR and clinicopathological features.

4. Discussion

In the present study, we identified 10 studies that involved 5667 patients, and we investigated the clinical relevance and prognostic value of preoperative LMR in patients with BC. In this meta-analysis, we found that patients with low LMR had shorter OS and DFS outcomes. Subgroup analyses showed that the negative prognostic effect of low LMR on OS outcomes remained substantial in Asian populations, TNBC patients, and patients with non-metastatic and mixed stage. Additionally, low LMR predicted poor OS in patients with BC, regardless of the cut-off value (< 5.0 and ≥ 5.0). When we further analyzed the associations between preoperative LMR and clinicopathological features, we found that no significant correlation between LMR and clinicopathological features. Taken together, the preoperative LMR could serve as a convenient and reliable facoter for BC prognostication.

The actual mechanism between the low LMR and poor outcome of breast cancer remained unclear. Tumor-promoting inflammation is an