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Review

Clinicopathological and prognostic significance of lymphocyte to monocyte ratio in patients with gastric cancer: A meta-analysis

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ABSTRACT

Background: Recently, the lymphocyte-to-monocyte ratio (LMR) has been reported to be a prognostic factor in multiple malignancies. The current study was designed to assess the prognostic value of pretreatment LMR in gastric cancer (GC).

Methods: MEDLINE, EMBASE, Cochrane, and CNKI databases were searched until April 2017. Eligible articles were defined as studies assessing the prognostic role of pretreatment LMR in GC. Pooled hazard ratios (HRs) for overall survival (OS), disease-free survival (DFS), and recurrence-free survival (RFS) were calculated using fixed-effects or random-effects models.

Results: A total of six studies comprising 4908 patients were included in the study. Pooled results showed that low LMR was significantly associated with decreased OS (HR: 0.66, 95% confidence interval [CI]: 0.54–0.82, $p < .001$), but not with poor DFS/RFS (HR: 0.71, 95% CI: 0.38–1.32, $p = .004$). The unfavorable prognostic impact of low LMR on OS was observed in patients of different disease stages and cut-off values. Moreover, low LMR was significantly related to age (> median), gender (male), CEA (> 5 ng/ml), tumor size (> 3 cm), TNM stage (III-IV), lymph node metastasis, and distant metastasis.

Conclusions: Low pretreatment LMR may be a significant prognostic biomarker for poor OS in patients with GC.

1. Introduction

Although incidences have declined in recent decades, gastric cancer (GC) is still the fifth most common malignancy and ranks as the third leading cause of cancer-related death worldwide [1]. Radical resection without residual tumor is the most effective therapy for the majority of patients. Nevertheless, the benefits of surgery are greatly limited because patients with GC are usually diagnosed at advanced stages [2,3]. Despite significant recent developments in surgical techniques and adjuvant therapy, the overall prognosis of GC remains poor [4,5]. Currently, the prognosis for GC mainly relies on the tumor-node-metastasis staging classification; however, precise pathologic tumor-node-metastasis staging is usually achieved after surgical resection. Therefore, it is vital to identify easily accessible biomarkers that predict prognosis and help clinicians implement better therapeutic strategies.

It is well known that inflammation can largely influence tumor development and progression [6]. Several inflammatory factors, such as plasma fibrinogen, C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) have been identified as useful biomarkers for predicting the prognosis in renal cell carcinoma, ovarian cancer, and pancreatic cystic neoplasms [7–10]. Recently, the pretreatment lymphocyte to monocyte ratio (LMR), which also reflects the degree of systemic inflammation, has been found to be linked to prognosis in patients with GC [11–13]. Nevertheless, the prognostic value of LMR in GC has not yet been fully elucidated. Furthermore, there has been no report of a systematic review or meta-analysis to determine the reliability and degree of its prognostic value. We therefore conducted a meta-analysis to assess the prognostic effect of pretreatment LMR as well as determine the associations between LMR and clinicopathological features of patients with GC.

2. Materials and methods

2.1. Search strategies

We performed a comprehensive literature search of MEDLINE, EMBASE, Cochrane, and CNKI databases from inception to April 2017. The following MeSH terms and text words were used in combination: “gastric cancer” or “gastric carcinoma” or “gastric adenocarcinoma” or “stomach tumor” or “stomach neoplasms” and “LMR” or “lymphocyte-

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to-monocyte ratio" or "lymphocyte to monocyte ratio" or "lymphocyte monocyte ratio". The references of eligible studies, relevant systematic reviews and meta-analyses in this field were manually retrieved. Detailed search strategies refer to file S1.

2.2. Study selection

The criteria for inclusion of studies were as follows: (1) GC was pathologically confirmed; (2) studies assessed the prognostic value of pretreatment LMR on OS, DFS/RFS; (3) the cut-off value of LMR was reported; and (4) studies supplied sufficient information for calculating the hazard ratio (HR) and 95% confidence interval (CI). The exclusion criteria were as follows: (1) reviews, letters, case reports, and comments; (2) studies lacking essential information for calculating HR and 95% CI; and (3) overlapping or duplicate data.

2.3. Data extraction and quality assessment

The two reviewers independently reviewed all eligible studies and extracted data. Any disagreement was resolved by discussions among all coauthors. The following information was collected: first author's name, year of publication, country, number of patients, ethnicity, tumor stage, outcome measures (HRs for OS, DFS/RFS, and their 95% CIs), and clinicopathological features, survival analysis methods, cut-off values, and time of follow-up. HRs were extracted from multivariate or univariate analyses or estimated from Kaplan-Meier survival curves [14].

The quality of each study was assessed in accordance with the Newcastle-Ottawa Scale (NOS) [15], which included an assessment of subject selection, comparability of groups, and clinical outcome. A total of 9 items were extracted, and each item was scored 1. The total scores ranged from 0 to 9. If scores were ≥7, the study was considered to be high quality.

2.4. Statistical analyses

HRs and their 95% CIs were searched in the original articles or extrapolated using methods described by Tierney and Parmar [14,16]. The log HR and standard error (SE) were used for aggregation of the survival results [16]. The associations between LMR and clinicopathologic features were expressed as odds ratios (ORs) and its 95% CIs. Heterogeneity of the HR of each study was quantified using Cochran's Q test and Higgins-I^2 statistic. A p-value < .1 for the Q-test or I^2 > 50% was considered statistically significant, and the random-effects model was used, otherwise, the fixed-effects model was applied. Subgroup analyses were conducted based on the area of sample size, disease stage, and the cut-off value. Sensitivity analyses were carried out to evaluate result stability excluding each study. If the number of included studies was more than 11, the publication bias was performed using the Begg's funnel plots and Egger's tests [17,18]. All statistical analyses were conducted by Review Manager 5.3 software (Cochrane Collaboration, Copenhagen, Denmark). Statistical significance was reached when P values < 0.05.

3. Results

3.1. Study characteristics

Our search strategy yielded 133 potentially relevant citations. 92 remained to be screened after exclusion of duplicated data. Of these, 78 were excluded through titles and abstracts, leaving 14 articles for further evaluation. Subsequently, 8 articles did not meet the inclusion criteria and were therefore excluded. As a result, 6 eligible studies, comprising a total of 4908 patients, were included in the quantitative synthesis [11–13,19–21]. The selection process was shown in Fig. 1.

All included studies were from China and were published between 2014 and 2017. The sample sizes ranged from 188 to 1621. Six study explored the prognostic role of LMR in OS, and two studies investigated the prognostic impact of LMR in DFS/RFS. The cut-off values for LMR ranged from 3.15 to 5.15. All included studies consisted of two groups: high and low LMR. HR and 95% CI was extracted directly from the six studies. In methodological quality of studies, the NOS scores of all included studies were ≥7. Table 1 lists the detailed study characteristics.

4. Meta-analysis

4.1. Impact of LMR on OS

Six studies involving 4908 patients reported data on LMR and OS in GC. Overall, low LMR had an association with decreased OS (HR: 0.66, 95% CI: 0.54–0.82, p < .001). However, excessive heterogeneity existed between studies (p = .001, I^2 = 75%). Thus, the random-effects model was used (Fig. 2). To detect potential heterogeneity, subgroup analyses were stratified based on sample size, disease stage, and the cut-off value. As shown in Table 2, low LMR significantly predict poor OS in studies with sample sizes ≥500 (HR = 0.60; 95% CI = 0.46–0.77; P < .001). However, no prognostic effect was observed in patients with sample sizes < 500 (HR: 0.76, 95% CI: 0.57–1.02, p = .07). Exploratory subgroup analysis, based on disease stage, revealed that low LMR predicted decreased OS, in patients with non-metastatic (HR = 0.69; 95% CI = 0.52–0.91; P = .01), mixed (HR = 0.67; 95% CI = 0.50–0.89; P = .006), and metastatic disease subgroups (HR = 0.60; 95% CI = 0.38–0.96; P = .03). In addition, subgroup analyses suggested that low LMR predicted decreased OS in patient with GC, regardless of the cut-off value for LMR (< 4.0, 4.0–5.0, or ≥ 5.0).

In order to assess the influence of single studies on the overall estimate, sensitivity analysis was performed. When the sensitivity analysis was restricted to Lin et al.'s study, the heterogeneity significantly diminished (p = .13, I^2 = 43%), but the results did not significantly change, indicating the robustness of our findings.

4.2. Impact of LMR on DFS/RFS

Two studies reported data for the association between LMR and DFS/RFS in GC. A combined analysis demonstrated that LMR did not influence DFS/RFS (HR: 0.71, 95% CI: 0.38–1.32, p = .004), with significant heterogeneity between studies (p < .001, I^2 = 91%; Fig. 3).

4.3. LMR and clinicopathological features

To explore the impact of LMR on clinical features, we identified 10 clinical factors in GC. The pooled analysis demonstrated that low LMR was significantly correlated with age (> median vs. < median; HR = 1.97, 95% CI: 1.65–2.35, P < .001), gender (male vs. female; HR = 1.67, 95% CI: 1.42–1.97, P < .001), CEA (> 5 ng/ml vs. < 5 ng/ml; HR = 1.92, 95% CI: 1.44–2.55, P < .001), tumor size (> 3 cm vs. < 3 cm; HR = 1.78, 95% CI: 1.02–3.11, P = .04), TNM stage (III-IV vs. I-II; HR = 1.73, 95% CI: 1.08–2.78, P = .02), lymph node metastasis (pos vs. neg; HR = 2.17, 95% CI: 1.58–2.97, P < .001), and distant metastasis (pos vs. neg; HR = 2.19, 95% CI: 1.24–3.88, P = .007). No significant association was found between LMR and other clinicopathological parameters such as tumor differentiation, CA199, and vascular invasion. The correlation between LMR and clinicopathological parameters of GC is shown in Table 3.

5. Discussion

In the present study, we identified 6 studies involving 4908 patients that investigate the prognostic value of pretreatment LMR in patients with GC. This meta-analysis demonstrated that low LMR is an independent predictor of worse OS. However, LMR did not influence