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Review

The prognostic role of neutrophils to lymphocytes ratio and platelet count in gastric cancer: A meta-analysis

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HIGHLIGHTS

- Inflammation plays an important role in the development of gastric cancer.
- Both inflammatory markers predicted poor survival in patients with gastric cancer.
- The results may provides some useful evidence for the clinical application.

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ABSTRACT

Background: Systemic inflammatory response was reported to be associate with a poor survival in gastric cancer. However, these results remain inconsistent. The purpose of this meta-analysis was to evaluate the prognostic role of neutrophils to lymphocytes ratio (NLR) and platelet count in gastric cancer.
Methods: Relevant studies were identified by searching PubMed, Embase and Cochrane Library. Data was pooled using a fixed-effects models or random-effects models.
Results: A total of 29 studies were included for meta-analysis (19 for NLR, 10 for platelet count). Elevated NLR and platelet count were associated with an increased lymph node metastasis and serosal invasion (T3 + T4) risk with individual ORs being 1.70 (95% CI: 1.05–2.75) and 2.93 (95% CI: 2.27–3.78), 1.62 (95% CI: 1.08–2.42) and 2.09 (95% CI: 1.57–2.77), respectively. The incidence of stage (III + IV) in elevated NLR group was higher than in normal NLR group (OR = 1.87, 95% CI: 1.48–2.35). The disease-free survival in patients with elevated NLR was markedly shorter (HR = 1.61; 95% CI: 1.28–1.94). For the overall survival, both indicators were strong predictors with individual HRs being 1.65 (95% CI: 1.47–1.83), 1.61 (95% CI: 1.35–1.86), respectively.
Conclusions: This meta-analysis suggests that elevated NLR and platelet count predict poor survival in patients with gastric cancer, and may provides some useful evidence for the clinical application of the two prognostic indicators in gastric cancer.

1. Introduction

Gastric cancer (GC) is a very common tumor in the world, and still remains a major public health problem and a leading cause of cancer death. Surgical resection remains the only option for the patients with gastric cancer, but at least about 50% patients receiving curative resection die within 5 years of diagnosis [1]. Although preoperative tumor stage is useful to select the appropriate therapeutic strategy for patients with gastric cancer, clinical tumor stage alone cannot predict patient's postoperative complication and prognosis. Therefore, it is necessary to find some reliable prognostic markers that could predict the survival of patients at high risk of recurrence and help these patients to choose additional

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treatment, such as chemotherapy, radiotherapy.

In the recent years, the relationship between inflammation and cancer has been explored extensively in the clinical trials [2–4]. Inflammation in the tumor microenvironment plays an important role in the proliferation and survival of malignant cells. Several inflammatory markers have been used in cancer patients to quantify the worse outcomes, such as platelet count, C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR) and platelet -lymphocyte ratio (PLR) [4–6].

Among these inflammatory markers, NLR and platelet count in particular have gained notable interest. NLR calculated as neutrophil count divided by lymphocyte count, is suggested as a marker for survival outcomes in a variety of cancers due to its performance and availability [4]. It is thought that an elevated level of NLR reflects increased systemic inflammatory changes in the host, which may associated with poorer survival in GC [7–9]. Additionally, a number of studies indicated that platelets played an important role in the process of distant dissemination [10–12]. Some evidence revealed that platelets protect tumor cells against immune system and facilitate tumor cells adhesion to vascular endothelium through the formation of tumor thrombus and interactions between tumor cells and platelet ligands [13]. Thrombocytosis has been reported to have worse prognostic significance in patients with colorectal cancer, lung cancer, endometrial cancer, ovarian cancer, esophageal cancer and breast cancer [14,15].

To date, evidence from individual studies suggests elevated NLR and platelet count are associated with poorer survival [2,4,14]. Due to the variance in study design and sample size, these results remain inconsistent. In the present study, we performed a meta-analysis based on relevant studies to evaluate the prognostic role of elevated NLR and platelet count in gastric cancer.

2. Methods and materials

2.1. Search strategy

PubMed, Embase, and Cochrane Library were searched systematically for all articles without any restriction. The literature investigating the prognostic value of NLR and platelet count were searched using the following terms: (“neutrophil-lymphocyte ratio” OR “neutrophil-to-lymphocyte ratio” OR NLR) OR (thrombocytosis OR thrombocythemia OR “platelet count”) AND (“gastric cancer” OR “gastric adenocarcinoma” OR “stomach neoplasms” OR “gastric carcinoma”). The search strategy was performed repeatedly until no new relevant article was found.

Additionally, in order to identify the relevant publications, the reference lists of the found articles were also scanned. Overlapping articles or duplicate data were excluded by examining the authors' names and affiliations of each publication. All searches were conducted independently by two authors. The results were compared, and any discrepancies or questions were resolved through iteration and consensus. The selection process of the articles was shown in Fig. 1.

2.2. Inclusion and exclusion criteria

The data was included if the studies met the following criteria: (i) evaluating the prognostic role of preoperative NLR or platelet count in gastric cancer; (ii) the diagnosis of GC was made based on pathological examination and (or) the current clinical practice guidelines; (iii) providing sufficient data (HR and 95%CI on overall survival or the number of cases in different depth of tumor invasion or the number of cases with or without lymph node metastasis). Exclusion criteria were as followed: (i) the studies without sufficient data; (ii) studies reporting the prognostic value of inflammatory markers without specific data concerning NLR or platelet count; (iii) abstracts, letters, editorials, expert opinions, reviews, case reports; (vi) nonhuman research. Two authors independently evaluated the quality of each study using the 9-star Newcastle-Ottawa Scale (NOS) [16].

2.3. Data extraction

Data was abstracted independently by two investigators, and disagreement was resolved by discussion. For each study, the following information were extracted: year of publication; first author' name; country of origin; study design; the total number of cases and the number of cases with elevated platelet count or NLR; the age of subjects (mean or median); the data of HR and 95%CI; the number of cases with or without lymph node metastasis, with different depth of tumor invasion and different tumor stage.

2.4. Statistical analysis

For this meta-analysis, the fixed-effects model or the random-effects model were considered according to heterogeneity. Data were measured as odds ratio (OR) or hazard ratio (HR) and their associated 95% confidence intervals (CI). The I^2 statistic was used to evaluate heterogeneity. I^2 values > 50% represented the possibility of substantial heterogeneity. If no obvious heterogeneity existed, the OR and HR were calculated by the fixed-effects model. Otherwise, the random-effects model was used. Finally, publication bias was assessed by Begg's and Egger's test. $P < 0.05$ was considered statistically significant. All statistical analyses were performed with STATA (version 9.0; Stata Corp, College Station, TX).

3. Results

3.1. Literature searches and study characteristics

The search strategy generated 240 references: Pubmed (n = 71), Embase (n = 153), Cochrane Library (n = 16). Only a total of 41 potentially eligible studies were identified by literature search. We excluded 7 studies that failed to report available data, and 5 were just reviews. Finally, we identified 29 full-text articles that met the inclusion criteria (19 for NLR, 10 for platelet count). The search process and summary of 29 articles were detailed in Fig. 1 and Table 1. All the 29 studies were cohort studies (prospective:7, retrospective:22). The included studies were published between 2002 and 2014.

3.2. The prognostic value of neutrophils to lymphocytes ratio

Of the 19 studies, 8 reported the link between NLR and lymph node metastasis [4,8,12–14,17–19]. Elevated NLR had a positive association with the incidence of lymph node metastasis (OR = 1.70, 95% CI: 1.05–2.75, $P < 0.001$) (Fig. 2A). Data for investigating the correlation between NLR and depth of tumor invasion (serosal invasion: positive (T3 + T4) and negative (T1 + T2)) were available from 3 studies [8,13,14], the pooled analysis demonstrated that elevated NLR had a positive association with the incidence of serosal invasion (T3 + T4) (OR = 2.93, 95%CI 2.27–3.78, $P < 0.001$) (Fig. 2B). Six articles reported the data for evaluating the link between NLR and tumor stage (stage (I + II) and stage (III + IV)) [2,4,8,12,14,18]. The pooled analysis revealed that the incidence of stage (III + IV) in elevated NLR group was higher than in normal NLR group (OR = 1.87, 95%CI 1.48–2.35, $P < 0.001$) (Fig. 2C).

A total of 18 studies provided the available data for evaluating the correlation between NLR and the overall survival of patients with gastric cancer [2–5,7,9,12–14,17–25], the HR in patients with