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Review

Integrated analysis of the prognostic role of the lymph node ratio in node-positive gastric cancer: A meta-analysis

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ABSTRACT

Background: The lymph node ratio (LNR) as a prognostic parameter for gastric cancer has yet to be fully validated in the current tumor node metastasis staging system. We assessed the prognostic role of LNR in lymph node-positive gastric cancer through a meta-analysis.

Materials and methods: PubMed and EMBASE were searched for relevant studies up until December 2016. The effect measure for meta-analysis of primary outcomes was the hazard ratio (HR) for overall survival. Pooled HRs and 95% confidence intervals were calculated using random effects models. The I^2 statistic was used to measure heterogeneity. Subgroup analysis and meta-regression were chosen to illustrate the potential heterogeneity of the risk factors of outcomes. Publication bias was assessed using Egger's test and Begg's funnel plots. Sensitivity analysis was applied to evaluate the origin of the heterogeneity.

Results: We included 27 studies in this meta-analysis. Higher LNRs were significantly associated with a shorter overall survival (OS). High heterogeneity among the studies was identified (I^2 = 85.6), and the publication bias was moderate. Subgroup analysis showed similar results, and elevated LNR was associated with late-stage gastric cancer and indicative of a worse prognosis. Univariate meta-regression analysis of OS indicated that both treatment type and ethnicity may be causes of heterogeneity in patients with gastric cancer (p values were 0.005 and 0.008, respectively).

Conclusion: LNR was associated with a significantly poorer OS and LNR was an independent predictor of survival in patients with gastric cancer. LNR should be added as one of the parameters to be used in future tumor staging classification systems.

1. Introduction

Gastric cancer is the fourth most common cancer and the third leading cause of cancer-related death throughout the world [1]. Surgery is the main treatment in gastric cancer, and lymph node metastasis is the most effective predictor of postoperative survival [2]. Therefore, lymph node status is considered to be one of the key prognostic factors in gastric cancer.

The AJCC (UICC TNM classification) staging system of malignant tumors showed that proper pathological lymph node staging (pN stage) requires at least 15 lymph nodes to be cleared [3]. Certain factors have led to an insufficient number of lymph nodes being dissected in clinical practice. Increasing the number of lymph nodes dissected has been found to affect the number of metastases detected based on standard pN staging, which may result in a change in the TMN classification of a cancer that can affect the accuracy of the prognostic prediction [4–6].

The classic staging system for gastric cancer is the TNM staging system. However, the TNM staging system is not used when checking for tumor-free lymph nodes. Thus, the lymph node ratio (LNR) is considered to be an essential prognostic factor and a suitable staging method for patients with positive lymph nodes [7]. However, its use as a prognostic factor is controversial because of conflicting LNR results and differences in study design and sample size used in previous studies. Previous systematic reviews suggested that LNR can be used as a prognostic factor for gastric cancer and colorectal cancer [8,9]. Nevertheless, to date there has been no formal meta-analysis focused on

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the prognostic significance of LNR in gastric cancer. In this study, the first comprehensive systematic review was conducted to investigate the prognostic role of LNR in patients with lymph node-positive gastric cancer, and the results demonstrated that an increased LNR correlated with poor overall survival (OS) in gastric cancer patients.

2. Materials and Methods

2.1. Search strategy

A comprehensive, computerized literature search was conducted in PubMed and Embase for relevant studies up to December 2016. The search was performed using the following text words and corresponding medical subject heading terms: ((gastric cancer) OR (stomach cancer) OR (gastric carcinoma) OR (stomach carcinoma) OR (gastric neoplasm) OR (stomach neoplasm) OR (lymph node ratio)) AND ((LNR) OR (lymph positive node ratio) OR (lymph metastatic node ratio)). The search strategy was repeatedly performed until no new relevant articles were found. In addition, we reviewed references in the retrieved articles to search for additional relevant studies. All articles were evaluated by two authors based on the eligibility criteria we designed.

2.2. Study selection

First, we checked titles and abstracts of articles that were searched using keywords to exclude irrelevant articles. Next, all retained studies were screened according to inclusion and exclusion criteria. The following conditions were used to evaluate whether the study was included: (a) all patients were diagnosed with gastric cancer using pathology; (b) patients underwent radical surgery (R0 resection); (c) the outcome of interest was disease-free survival (DFS) and OS; and (d) hazard ratios (HRs) and 95% confidence intervals (CIs) used to evaluate prognosis could be extracted from the original literature, including direct acquisition or approximation by calculation. Exclusion criteria were defined as follows: (a) gastric cancer patients with other tumors or patients with distant metastases (TNM IV staging); (b) articles including patients undergoing tumor-related neoadjuvant chemotherapy before surgery; (c) articles consisting of letters, meeting summaries, commentary articles, and posters; and (d) studies could not provide outcome data and did not calculate the necessary results.

2.3. Data extraction

Data were extracted independently by two researchers and any discrepancies in the data were settled by consensus. If necessary, a third researcher was expected to participate in the discussion and make a decision. The main data extracted from each study included: first author, publication year, number of patients, country of the study population, study design, duration of follow-up, patient age, gender, number of checked nodes, type of study, cut-off value of the LNR and the definition of stratification, and HRs and 95% CIs. The primary goal of this meta-analysis was to compare the predictive effect of LNR for survival time in gastric cancer patients.

2.4. Data synthesis and statistical analysis

This meta-analysis was undertaken to obtain the association of survival time with LNR in gastric cancer patients. It was performed using pooled HRs and 95% CIs to assess prognosis in gastric cancer. We used a more conservative random effects model to balance the random effects of different studies rather than a fixed effects model [10]. We chose I^2 and Q statistics to evaluate statistical heterogeneity. I^2 was calculated to obtain the difference in total variance between the observed trials, in which $I^2 < 25\%$ was considered low heterogeneity, while $I^2 > 75\%$ was considered high heterogeneity [11]. Sensitivity analysis was used to assess the robustness and stability of the results, calculating the heterogeneity in each situation in which a single study was removed in turn in order to evaluate the effect of a single study on the overall outcome. Subgroup analysis was performed according to each parameter including year, race, treatment, sample size, ratio of patients with stage I/II and stage III/IV gastric cancer, and number of lymph nodes. We compared the pooled HR estimates from different subgroups using an interaction test. A meta-regression model was developed to explore the potential impact of different factors on heterogeneity, and to assess the effect of year, race, treatment, and other risk factors or potential confounding factors on outcome. Finally, Begg's test and Egger's test were used to assess publication bias. In addition, a bias risk test chart was made to assess the risk of various biases and the bias of each article using Revman 5.2 software [12,13]. Statistical analysis was performed using STATA12.0 software, according to the Cochrane Collaboration Organization and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines. A p value < 0.05 indicated a statistically significant difference.

3. Results

3.1. Study selection and characteristics

A flow diagram of the literature selection process used in this study is shown in Fig. 1. A total of 1208 articles were initially retrieved from PubMed and EMBASE according to particular keywords. After manually screening and filtering these, 27 articles were eventually chosen that included a total of 11,441 patients. Characteristics of the included studies are summarized in Table S1 and Table S2. All patients underwent radical surgery, and the median age of patients in the studies ranged from 54 to 72 years old. Of these studies, 17 involved Asian patients and 10 involved non-Asian patients. Lymph node data and survival time of patients were also retrieved. Median follow-up time in the studies ranged from 52 to 75.3 months.

HRs and 95% CIs obtained from all articles are listed in Table 1. HRs and 95% CIs of OS could be directly obtained from 12 studies. The other 15 studies did not provide HRs and 95% CIs directly; therefore, we used relative data such as Kaplan–Meier curves and the total number of survivors to calculate HRs and 95% CIs [14].

3.2. Primary outcomes and sensitivity analysis

Using a random effects model, pooled results of HR and OS statistics from 27 studies indicated that there was a significant association between the LNR and OS in patients with gastric cancer. The survival rate was significantly higher in patients with lower LNRs (HR = 1.99; 95% CI 1.74–2.27; $p < 0.001$) (Fig. 2). The results also showed that there was high heterogeneity among studies ($I^2 = 85.6\%$; $p < 0.001$).

Subsequently, sensitivity analysis was performed to evaluate the stability of the model by omitting each individual study and calculating new HRs. Results showed that HRs were relatively stable and that study heterogeneity was still apparent (Fig. 3).

3.3. Subgroup and meta-regression analyses

To identify factors involved in the heterogeneity, we used meta-regression and subgroup analyses. Subgroup analysis was conducted using variables that included race (Asian vs. non-Asian), treatment (R0 surgery + adjuvant therapy (AT) vs. R0 surgery), sample size, ratio of patients with stages I/II and III/IV gastric cancer, and lymph node numbers. Data in Table S3 shows that in nearly all subgroup analyses, higher LNRs also correlated with poor OS in gastric cancer patients. Taking treatment as an example, R0 surgery + AT results were similar to those studies in which treatment was only R0 surgery (HR = 2.15; 95% CI 1.64–2.83; $p < 0.001$ vs. HR = 1.82; 95% CI 1.59–2.09; $p < 0.001$). The heterogeneity I^2s of the two groups were 79.5% and 79.5%, respectively. In Asian patients, HR = 1.88 (95% CI 1.61–2.20;