Introduction

Despite the incidence of gastric cancer is decreasing, it remains one of the most frequent causes of cancer-related death worldwide [1]. The incidence of gastric cancer varies widely in different regions and is particularly common in East Asia [2]. In China, where gastric cancer is endemic, more patients are diagnosed in middle or late stage, which is reflected by poor overall survival rates. Although there have been great improvements in diagnostic and treatment technologies, most of the gastric patients still have either regional or distant metastatic disease with the 5-year overall survival less than 10% [3]. Therefore, it is important to identify prognostic factors for these patients in order to select patients for tailor treatment. Up to now, the prognosis significance of lymph node status [4], depth of tumor invasion [5] and macroscopic tumor size [6] are well known in GC. In addition, elevations of serum tumor markers can also be an independent predictor of adverse prognosis [7]. However, none of these have been demonstrated to be sufficiently effective for clinical use. More recently, established systemic inflammation-based prognostic scores have been explored extensively, such as NLR and serum C-reactive protein (CRP). CRP is an acute-phase response protein, which has been proven to be an independent prognostic factor for survival in malignancy [8]. However, CRP is not routinely measured in many hospitals, and CRP level displays nonspecific change after treatment [9]. NLR can be suggested as the balance between pro-tumor inflammatory status and anti-tumor immune status. Patients with elevated NLR have a relative lymphocytopenia and neutrophil leukocytosis in favor of protumor inflammatory response, which gained its prognostic value in patients with colorectal cancer [10], lung cancer [11], pancreatic ductal adenoma [12], etc. Elevated level of NLR in GC patients may predict poorer clinical outcome [13], while some authors did not agree with the former results [14]. The aim of this study was to comprehensively and quantitatively summarize the global results to evaluate its prognostic value for patients with GC.

Methods

Search strategy and eligibility criteria

This meta-analysis was executed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15]. A systematic literature search of relevant studies was conducted in PubMed and EMBASE up to June 2014. We used the following search terms without restrictions: “NLR”, “neutrophil to lymphocyte ratio”, “neutro-
phil lymphocyte ratio”, “prognosis” and “gastric cancer” or “GC”. Moreover, reference lists of retrieved articles were also reviewed to identify any studies that were not identified from the preliminary literature searches. Studies were included if they met the following criteria: (1) patients with gastric cancer in the studies were histopathologically confirmed (2) neutrophil-lymphocyte ratio values were reported (3) they evaluated the correlation between neutrophil lymphocyte ratio and the survival outcome of GC and (4) if studies’ hazard ratios (HRs) were not directly reported, estimation of the HR could be reconstructed by other data. Articles were excluded from the meta-analysis based on the following criteria: (1) letters, conference abstracts, editorials, review articles, not full text in English, studies on cancer cell line and animal model and irrelevant studies (2) studies had overlapping or duplicate data (3) studies failed to present the cut-off value for elevated HR. 

**Quality Assessment**

The quality of studies was assessed according to Newcastle-Ottawa Quality Assessment Scale (NOS) [16] by two reviewers (Xi Z and Wei Z). This scale includes three aspects of evaluation: selection, comparability, and outcome between the case group and control group. Studies that scored ≥6 were assigned as high-quality studies. Any disagreement was resolved by discussion.

**Data extraction**

Two investigators independently evaluated and extracted the data. All studies were double-checked by both authors and disagreements were resolved by consensus. The extracted data elements of this review included the following: (1) publication details, including first author’s last name, publication year, and origin of the studied population (2) characteristics of the studied population, including sample size, age, and stage of disease and (3) HR of NLR for OS, DFS and PFS as well as their 95% CIs and p values and (4) follow-up time (5) cut-off values for elevated HR. If data for HR was not available, we extracted the total numbers of observed deaths and
Table 2. Quality Assessment of included studies based on the Newcastle-Ottawa Scales.

| Study                  | How representative was the exposed Cohort | Selection of non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Of cohorts on basis of design or analysis | Assessment of outcome | Follow up Long enough for outcomes to occur | Adequacy of cohort follow-up |
|-----------------------|------------------------------------------|--------------------------------|---------------------------|-----------------------------------------------------------------------|------------------------------------------|-----------------------|---------------------------------------------|--------------------------------|
| Lee et al.(2013)      | Somewhat representative of GC patients    | Drawn from the same community as exposed cohort | Written self-report       | Yes                                                                   | Study controls for multiple covariate   | confirmation of the outcome by reference to secure records | Yes                           | No description                            |
| Wang et al.(2012)     | Somewhat representative of GC patients    | Drawn from the same community as exposed cohort | From structured interview | Yes                                                                   | Study controls for multiple covariate   | confirmation of the outcome by reference to secure records | Yes                           | No description                            |
| Jeong et al.(2012)    | Somewhat representative of GC patients    | Drawn from the same community as exposed cohort | Secure record             | Yes                                                                   | Study controls for multiple covariate   | confirmation of the outcome by reference to secure records | Yes                           | Complete follow-up                        |
| Jung et al.(2011)     | Somewhat representative of GC patients    | Drawn from the same community as exposed cohort | Secure record             | Yes                                                                   | Study controls for multiple covariate   | confirmation of the outcome by reference to secure records | Yes                           | No description                            |
| Shimada et al.(2010)  | Representative of GC patients             | Drawn from the same community as exposed cohort | From structured interview | Yes                                                                   | Study controls for multiple covariate   | confirmation of the outcome by reference to secure records | Yes                           | No description                            |
| Jin et al.(2013)      | Somewhat representative of GC patients    | Drawn from the same community as exposed cohort | Secure record             | Yes                                                                   | Study controls for multiple covariate   | confirmation of the outcome by reference to secure records | No                            | No description                            |
| Aurello et al.(2014)  | Representative of GC patients             | Drawn from the same community as exposed cohort | From structured interview | Yes                                                                   | Study controls for multiple covariate   | confirmation of the outcome by reference to secure records | Yes                           | Complete follow-up                        |
| Cho et al.(2014)      | Somewhat representative of GC patients    | Drawn from the same community as exposed cohort | Secure record             | Yes                                                                   | Study controls for multiple covariate   | confirmation of the outcome by reference to secure records | Yes                           | No description                            |
| Jiang et al.(2014)    | Somewhat representative of GC patients    | Drawn from the same community as exposed cohort | Secure record             | Yes                                                                   | Study controls for multiple covariate   | confirmation of the outcome by reference to secure records | Yes                           | No description                            |
| Dirican et al.(2013)  | Somewhat representative of GC patients    | Drawn from the same community as exposed cohort | Secure record             | Yes                                                                   | Study controls for multiple covariate   | confirmation of the outcome by reference to secure records | No                            | No description                            |
the numbers of patients in each group to calculate HR. Data were extracted from the graphical survival plots when data were only available as Kaplan-Meier curves [17]. If several estimates were reported in the same article, we chose the most powerful one (multivariate analysis was superior to univariate analysis).

Statistical Analysis

HRs and their 95% CIs from each study were used to calculate pooled HRs. The heterogeneity of the combined HRs was performed using Cochran’s Q test and Higgins’ I-squared statistics. A P value <0.05 was considered significant. We used the random effects model (Der Simonian and Laird method) if heterogeneity was observed (P<0.05). The fixed effects model was applied in the absence of between-study heterogeneity (P>0.05) [18]. Publication bias of literature was evaluated using Begg’s funnel plot and the Egger’s linear regression test and a p<0.05 was considered significant. Statistical analyses were carried out using the statistical software Stata (version 12.0).

Results

Literature search

A flow diagram of our literature search is shown in Figure 1. We identified 15 potentially relevant articles concerning NLR and prognosis of gastric cancer. Three studies were excluded as HR can’t be calculated by the described method [19–21] and 2 studies were excluded as failed to present NLR specific data for OS or DFS and PFS [22–23]. A total of 10 articles [13–14,24–31] that met the inclusion and exclusion criteria were retrieved. Of these reports selected for further evaluation, 10 investigated the prognostic role of NLR for OS, 3 for DFS and 2 for PFS, respectively.

Study Characteristics

The characteristics of the included studies were summarized in Table 1. We collected the data from 10 studies, which involved a total of 2,952 patients from the Korea, China, Japan, Italy and Turkey. Treatment methods for nine studies were surgery and chemotherapy. Patients of one study were treated by multiple-therapy. Four studies enrolled less than 200 patients and six studies...
Table 3. Summary of the subgroup meta analysis results for OS.

| Subgroup                  | N  | Random-effects model HR(95%CI) | Fixed-effects model HR(95%CI) | Heterogeneity |
|---------------------------|----|-------------------------------|------------------------------|---------------|
|                           |    |                               |                              | $I^2(\%)$     | $P$ Value     |
| Treatment method          |    |                               |                              |               |               |
| Surgery                   | 5  | 1.59(1.30–1.95)               | 1.59(1.30–1.95)              | 0             | 0.808         |
| Chemotherapy              | 4  | 1.82(1.48–2.23)               | 1.82(1.53–2.15)              | 21            | 0.284         |
| Sample size               |    |                               |                              |               |               |
| Sample size <200          | 4  | 1.94(1.52–2.47)               | 1.97(1.58–2.46)              | 7.3           | 0.357         |
| Sample size ≥200          | 6  | 1.79(1.46–2.20)               | 1.77(1.54–2.05)              | 44.4          | 0.11          |
| Cut-off value             |    |                               |                              |               |               |
| Cut-off value ≥3          | 4  | 2.01(1.44–2.80)               | 2.14(1.70–2.70)              | 42.7          | 0.157         |
| Cut-off value ≤3          | 6  | 1.72(1.49–1.99)               | 1.72(1.49–1.99)              | 2.9           | 0.398         |
| Geographic region         |    |                               |                              |               |               |
| Eastern countries         | 8  | 1.74(1.53–1.99)               | 1.74(1.53–1.99)              | 0             | 0.625         |
| Western countries         | 2  | 1.80(0.65–4.97)               | 2.46(1.80–3.38)              | 74.5          | 0.048         |
| TNM stage                 |    |                               |                              |               |               |
| (III+IV)/All=100%         | 4  | 1.57(1.31–1.87)               | 1.57(1.31–1.87)              | 0             | 0.936         |
| (III+IV)/All<100%         | 6  | 2.03(1.65–2.21)               | 2.09(1.77–2.47)              | 28.7          | 0.220         |

HR: hazard ratio; CI: confidence interval; All: all patients.

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Subgroup analyses was conducted for OS. Subgroup analyses by treatment methods showed that elevated NLR predicted poor prognosis in patients treated with both surgery and chemotherapy [HR = 1.59, 95%CI: (1.30–1.95); HR = 1.82, 95%CI: (1.53–2.15)]. Stratification by sample size, we found the pooled HRs was 1.77, 95%CI: (1.54–2.05) for studies with more than 200 cases and 1.97, 95%CI: (1.58–2.46) for studies with less than 200 cases. The results revealed that high NLR remained to be a worse prognostic marker regardless of sample size. Stratification by cut-off value ≥3.0 and cut-off value < 3.0, it was found that the pooled HRs was still a poor predictor for GC [HR = 1.72, 95%CI: (1.49–1.99)] for cut-off value ≤3.0 and [HR = 2.14, 95%CI: (1.70–2.70)] for cut-off value >3.0. In the subgroup analyses by geographic region, we found that elevated NLR was still a poor predictor for eastern patients [HR = 1.74, 95%CI: (1.53–1.99)] but not for western patients [HR = 1.80, 95%CI: (0.65–4.97)]. When per-
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Publication Bias

We applied funnel plots and Egger's test to evaluate publication bias of the included studies. As shown in Figure 3, the funnel plot was symmetrical. There was no evidence for significant publication bias for OS and DFS, since their p values for Egger were more than 0.1.

Discussion

Our results from this meta-analysis including 10 studies with 2952 cases showed that elevated NLR was associated with OS, DFS and PFS. Subgroup analyses revealed that poor OS with high NLR could be found in patients treated with both surgery and chemotherapy. Elevated NLR was a significant prognostic marker to predict poor OS regardless of sample size and cut-off values. When subgroup was analyzed by geographic region, we found that elevated NLR was still a poor OS predictor for eastern patients but not for western patients. Moreover, when the prognostic significance of elevated NLR was evaluated by TNM stage, NLR might be a more crucial prognostic factor for early TNM stage patients.

Chronic inflammation is known to promote carcinogenesis contributing to the onset or progression of cancer [32]. Tumors can not only develop at the sites of inflammation, such as Helicobacter pylori infection is recognized as a causative agent for gastric cancer [33], but they can also trigger regional immune response and release inflammatory factors around the tumor which result in the formation of an inflammatory microenvironment. Inflammatory processes always accompany with progression of cancer, which can contribute to tumorigenesis by supplying cytokines, such as vascular endothelial growth factor (VEGF), interleukin-18 and matrix metalloproteinases [34–36] to the tumor microenvironment that promotes angiogenesis, and thus promotes tumor growth and metastasis.

In recent decades, a variety of predictors have been identified and applied for predicting GC outcomes. CEA, Her-2 are currently used in routine pathological assessment of GC. Ki-67, caspase-3 and p53 have also been reported associated with GC survival [37]. In addition, it is well known today that miRNAs have very important regulatory functions in cancer. Up to now, accumulating studies have investigated the diagnostic and prognostic values of miRNAs in GC. For example, Ueda T found that microRNAs are expressed differentially in gastric cancers and unique microRNAs are associated with progression and prognosis of GC [38]. However, the above-mentioned biomarkers should be examined in cancerous tissues. Thus it is impossible to monitor their levels continuously throughout disease progression. In contrast, NLR as an indicator of inflammation can be easily assayed in plasma or serum, which may be widely applied in the clinic.

NLR is known to possess prognostic value in cancer population. There are a number of possible mechanisms by which NLR is associated with worse outcome in patients with cancer. Firstly, the antitumor responses of natural killer cells and activated T cells may be suppressed by increased number of neutrophils around the tumor [39]. A high NLR reflects both a heightened neutrophil-dependent inflammatory response and a decreased lymphocyte mediated antitumor immune reaction, which may weaken the lymphocyte-mediated anti-tumor cellular immune response and contribute to aggressive tumor biology, cancer progression and poor prognosis. Secondly, circulating neutrophils contributes to tumor growth and progression by producing cytokines, such as tumor necrosis factor (TNF), IL-1, IL-6, and angiogenic factor vascular endothelial growth factor (VEGF) [40]. Thirdly, a reduced number of lymphocytes may weaken the lymphocyte-mediated anti-tumor cellular immune response. The neutrophil count alone may not reflect the prognostic information of a decreased lymphocyte mediated immune response, and a low lymphocyte count alone may not reflect the neutrophil driven tumor growth process. Hence, it is likely that the combined effects of neutrophilia and lymphocytopenia lead to a high NLR which may reflect the combined prognostic information of these two processes, and be a stronger predictor of outcome than either alone.

There are some limitations in this study. First, there is some heterogeneity of subjects for NLR in the OS group. Heterogeneity might be caused by characteristics of the patients, such as age, differentiation or disease stage, cut-off values, treatment they might have received, the duration of follow-up, and adjustments for other cofactors. Moreover, our results are likely to be affected by the wide range of cutoff values for elevated NLR, which may affect the positive associations between NLR and GC prognosis. For example, cut-off scores of NLR were defined as 1.44, 2.5, 3.0, 4.0 or 5.0 by analyzing the ROC curve, median value or based on previous studies, however, subgroup analyses stratified by cut-off values showed that the NLRs prognostic value was not affected substantially. Second, the NLR is usually regarded as a prognostic marker in several diseases which are related to survival, such as cardiovascular diseases [41]. Thus, we cannot consider NLR as a “predictor” for survival unless the involved patients don’t have other severe diseases related to NLR. Finally, only English studies were included in this analysis and small studies with null results tended not to be published, which may cause potential publication bias.

Conclusions

In conclusion, our meta-analysis, including a quantified synthesis of all published studies, showed that elevated NLR was a poor predictor for survival in patients with gastric cancer. The critical role of NLR in cancer prognosis may contribute to its clinical utility. Considering the limitations of the present meta-analysis, further research with large-scale and standard investigations should be conducted.

Supporting Information

Checklist S1  PRISMA checklist. (DOC)
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Author Contributions

Conceived and designed the experiments; XZ, WZ, LJF. Performed the experiments: XZ, WZ, LJF. Analyzed the data; XZ. Contributed reagents/materials/analysis tools: XZ. Wrote the paper: XZ.