Pretreatment neutrophil-to-lymphocyte ratio predicts the benefit of gastric cancer patients with systemic therapy

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ABSTRACT

Pretreatment neutrophil-to-lymphocyte ratio (NLR) has been reported to be associated with the prognosis of inoperable gastric cancer patients with systemic therapy. However, no consensus on the association has been reached. In this study, we mainly evaluated whether pretreatment NLR predicted the benefit of inoperable gastric cancer patients with systemic therapy, including chemotherapy, targeted therapy and immunotherapy. PubMed, Embase and Cochrane Library databases were systematically searched from inception up to September 16th, 2020. A total of 36 studies including 8614 patients were involved in the meta-analysis. Pooled data revealed that high pretreatment NLR was significantly associated with poor outcomes of OS (HR = 1.78, 95% CI = [1.59, 1.99]) and PFS (HR = 1.63, 95% CI = [1.39, 1.91]) in gastric cancer. Subgroup analyses stratified by country, study type, case load, analysis of HR, cutoff of pretreatment NLR, or treatment types arrived at the same conclusion. Pooled data based on different effect models and sensitivity analyses did not change the conclusion. Overall, high pretreatment NLR predicts the poor prognosis of inoperable gastric cancer patients with systemic therapy. Measurement of pretreatment NLR will assist clinicians with patient counseling and clinical treatment guiding accordingly.

INTRODUCTION

Gastric cancer is one of the most common malignant tumors, ranking the third highest mortality worldwide [1]. Although its morbidity is declining in most countries, the increase of incidence in the under-50 population could reverse the overall decline in gastric cancer [2, 3]. Moreover, though advances in diagnosis and surgical treatment have reduced mortality for early-stage gastric cancer [4], many patients were often initially diagnosed at advanced stages [5], which highlights the importance of effective systemic therapy.

Systemic therapy consists of chemotherapy, targeted therapy, and immunotherapy [6]. Chemotherapy is a relatively traditional therapy mainly based on fluoropyrimidine and platinum agents. It is the first-line
treatment for metastatic gastric patients with human epidermal growth factor receptor-2 (HER-2)-negative expression in accordance with the latest international guidelines [7–9]. While, targeted therapy with trastuzumab is recommended to treat gastric cancer patients with HER2 overexpression [10, 11]. Usually, those patients are treated with trastuzumab as well as the first-line chemotherapy [7, 8, 12]. Immunotherapy has emerged as a powerful treatment for chemoresistant gastric cancer [2]. Chemotherapy combined with immunotherapy might achieve better therapeutic efficacy compared with chemotherapy alone [2]. Overall, systemic therapy has revolutionized the treatment and improved the prognosis of patients with inoperable gastric cancer. Therefore, identifying novel biomarkers is of great significance to predict the outcome of inoperable gastric cancer patients with systemic therapy.

Neutrophil-to-lymphocyte ratio (NLR) is well-known as a systemic inflammation biomarker, which could be assessed from blood routine easily. Previous meta-analyses showed that NLR was a prognostic biomarker of gastric cancer, especially after gastrectomy [13–15]. Moreover, increasing studies demonstrated the correlation between pretreatment NLR and the gastric cancer prognosis after systemic therapy [16–51]. However, there is a lack of meta-analysis to comprehensively evaluate the association between pretreatment NLR and the outcomes of systemic therapy for inoperable gastric cancer.

Therefore, from the above and with the introduction of systemic therapy for advanced inoperable gastric cancer patients, it is timely to systematically review the association between pretreatment NLR and therapeutic efficacy of gastric cancer patients with systemic therapy, including chemotherapy, targeted therapy and immunotherapy.

RESULTS

Literature search and studies characteristics

A flow chart of study selection was presented in Figure 1. The initial searching retrieved 947 relevant records identified through database searching (n = 947) Additional records identified through other sources (n = 0) Records after duplicates removed (n = 682) Records screened (n = 682) Records excluded through title and abstract scanning (n = 532) Full-text articles assessed for eligibility (n = 150) Studies included in qualitative synthesis (n = 36) Full-text articles excluded, with reasons (n = 124): - No relevant outcomes (n = 97) - Outcomes were not available (n = 6) - Treatment was not clarified (n = 14) - Review and meta-analysis (n = 3) - Duplicates (n = 4) Studies included in quantitative synthesis (meta-analysis) (n = 36)
Table 1. Characteristics of eligible studies.

| First author | Year | Country | Study type | Cases | Age (years) | Sex (male %) | Cutoff | Treatment | Variables | NOS scores | References |
|--------------|------|---------|------------|-------|-------------|-------------|--------|-----------|-----------|------------|------------|
| Yamana | 2007 | Japan | Multi-center | 1220 | – | 869 (71.2%) | 2.5 | Chemotherapy | OS* | 8 | [16] |
| Jeong | 2012 | Korea | Single-center | 104 | 52 ± 10.7 | 69 (66.3%) | 3 | Chemotherapy | OS*, PFS | 8 | [17] |
| Lee | 2013 | Korea | Single-center | 174 | – | 114 (65.5%) | 3 | Chemotherapy | OS*, PFS | 8 | [18] |
| Cho | 2014 | Korea | Single-center | 268 | 55.4 ± 12.5 | 175 (65.3 %) | 3.06 | Chemotherapy | OS*, PFS | 9 | [19] |
| Dogan | 2015 | Turkey | Single-center | 109 | 53.9 ± 9.1 | 80 (73.4%) | 2.5 | Chemotherapy | OS, PFS | 7 | [20] |
| Liu | 2015 | China | Single-center | 135 | 61.1 ± 12.1 | 79 (58.5%) | 4 | Chemotherapy | OS | 7 | [21] |
| Wang | 2015 | China | Single-center | 120 | 66.9 ± 9.7 | 75 (62.2%) | 4.62 | Chemotherapy | OS, PFS | 7 | [22] |
| Zhang | 2015 | China | Multi-center | 99 | – | 76 (76.8%) | 4.558 | Chemotherapy | OS | 7 | [23] |
| Hsieh | 2016 | China | Single-center | 256 | 59.7 ± 10.5 | 176 (68.8%) | 3 | Chemotherapy | OS* | 9 | [24] |
| Musi | 2016 | Turkey | Single-center | 143 | 59.0 ± 12.0 | 103 (72.0%) | 3.34 | Chemotherapy | OS, PFS | 7 | [25] |
| Wang | 2016 | China | Single-center | 310 | 57.7 ± 9.6 | 213 (68.7%) | median | Chemotherapy | OS* | 9 | [26] |
| Giampieri | 2017 | Italy | Single-center | 103 | – | 71 (68.9%) | 0.4 | Chemotherapy | OS, PFS | 7 | [27] |
| Gonda | 2017 | Japan | Single-center | 100 | 65.2 ± 9.0 | 56 (56.0%) | 3 | Chemotherapy | OS* | 9 | [28] |
| Manikhas | 2017 | Russia | Single-center | 32 | 60.5 | – | 3 | Chemotherapy | OS* | 8 | [29] |
| Marshall | 2017 | Japan | Single-center | 143 | – | – | 3.11 | Chemotherapy | OS* | 7 | [30] |
| Ock | 2017 | Korea | Single-center | 745 | 59.8 ± 11.0 | 534 (71.7 %) | 2.42 | Chemotherapy | OS* | 9 | [31] |
| Huang | 2018 | China | Single-center | 136 | 55.1 ± 10.9 | 82 (60.3%) | 3.04 | Chemotherapy | PFS | 9 | [32] |
| Hwang | 2018 | Korea | Single-center | 73 | 61.7 ± 14.0 | 61 (83.6%) | 3 | Chemotherapy | OS* , PFS | 9 | [33] |
| Kim | 2018 | Korea | Single-center | 502 | 57.7 ± 10.1 | 300 (59.8%) | 3 | Chemotherapy | OS*, PFS | 9 | [34] |
| Kondoh | 2018 | Japan | Single-center | 50 | 65.2 ± 9.4 | 29 (58.0%) | 3.5 | Chemotherapy | OS* | 9 | [35] |
| Migita | 2018 | Japan | Single-center | 177 | 67.6 ± 11.3 | 124 (70.1%) | 2.2 | Chemotherapy | OS* | 9 | [36] |
| Ogata | 2018 | Japan | Multi-center | 26 | 64.3 ± 10.6 | 19 (73.1%) | 5 | Immunotherapy | OS, PFS | 7 | [37] |
| Ryu | 2018 | Korea | Multi-center | 236 | 58.8 ± 10.0 | 185 (78.4%) | 2.08 | Chemotherapy | OS*, PFS | 9 | [38] |
| Bozkurt | 2019 | Turkey | Single-center | 194 | 58.7 ± 9.4 | 129 (66.5%) | 2.6 | Chemotherapy | OS* , PFS | 8 | [39] |
| Mitani | 2019 | Japan | Multi-center | 112 | 61.4 ± 10.6 | 84 (75.0%) | 3 | Chemotherapy | OS* | 7 | [40] |
| Murakami | 2019 | Japan | Single-center | 92 | – | 73 (79.3%) | 2.83 | Chemotherapy | OS* | 8 | [41] |
| Namikawa | 2019 | Japan | Single-center | 262 | 68.1 ± 12.4 | 171 (65.3%) | 3.9 | Chemotherapy | OS* | 9 | [42] |
| Sugimoto | 2018 | Japan | Single-center | 141 | 71.9 ± 10.6 | 98 (69.5%) | 4 | Chemotherapy | OS* | 9 | [43] |
| Cipriano | 2020 | Portugal | Single-center | 55 | 62.0 ± 9.2 | 43 (73.2%) | 5 | Chemotherapy | OS* | 9 | [44] |
| Kim | 2020 | Korea | Single-center | 1156 | 57.3 ± 12.3 | 738 (63.8%) | 3 | Chemotherapy | OS* | 9 | [45] |
| Namikawa | 2020 | Japan | Single-center | 21 | 70.2 ± 9.1 | 19 (65.5%) | 2.5 | Immunotherapy | OS, PFS | 7 | [46] |
| Ota | 2020 | Japan | Single-center | 98 | 65.1 ± 10.2 | 68 (69.4%) | 3 | Immunotherapy | OS*, PFS | 8 | [47] |
| Shigeto | 2020 | Japan | Single-center | 109 | 69.1 ± 5.9 | 85 (78.0%) | 3.15 | Chemotherapy | OS* | 7 | [48] |
| Wang | 2020 | China | Single-center | 466 | 59.8 ± 11.3 | 327 (70.2%) | 2.8 | Chemotherapy | OS*, PFS | 8 | [49] |
| Zhao | 2020 | China | Single-center | 110 | – | 84 (76.4%) | 2.48 | Chemotherapy | OS* | 8 | [50] |
| Zhou | 2020 | China | Single-center | 537 | 55.0 ± 9.5 | 321 (59.8%) | 2.610 | Chemotherapy | OS*, PFS | 9 | [51] |

*Variables are calculated by multivariable analysis. Abbreviations: OS, overall survival; PFS, progression-free survival; NOS, Newcastle-Ottawa Scale.

Studies. After the removal of duplicated studies, 682 studies remained, of which 532 studies were ruled out after a scanning of the titles and abstracts. Full-test article evaluation for eligibility were implemented in 150 studies, among which 124 studies were removed owing to 97 studies with no relevant outcomes, six with unavailable outcomes, 14 without clarifying treatment types, three being review or meta-analyses, and four duplicates. Eventually, a total of 36 studies were of eligibility and enrolled into the meta-analysis [16–51].

Table 1 summarized the characteristics of eligible studies published between 2007 and 2020, and from four different regions including Japan, China, Korea, or Europe. Among them, there were five multi-center studies and 30 single-center studies. The cutoffs of NLR were not consistent in these studies, ten of which used three as the cutoff of high versus low pretreatment NLR. In terms of systemic treatment, 20 studies assessed the prognostic significance of pretreatment NLR in chemotherapy, 13 studies in chemo/targeted therapy, and 3 studies in immunotherapy. All studies reported on overall survival (OS) and 17 studies reported on progression-free survival (PFS). The Newcastle-Ottawa Scale (NOS) was adopted to evaluate the methodological quality of eligible studies for observational studies [52]. All studies were identified as high quality with stars above six on the basis of quality assessment. The response of each individual study to NOS was exhibited in Table 2.
Table 2. Methodological quality of studies included in the meta-analysis based on Newcastle-Ottawa Scale.

| First author | Year | Selection | Comparison | Exposure/Outcome | Total score | References |
|--------------|------|-----------|------------|------------------|-------------|------------|
| Yamanaka     | 2007 | ****      | *          | ***              | 8           | [16]       |
| Jeong        | 2012 | ****      | *          | ***              | 8           | [17]       |
| Lee          | 2013 | ****      | *          | ***              | 8           | [18]       |
| Cho          | 2014 | ****      | **         | ***              | 9           | [19]       |
| Dogan        | 2015 | ****      | –          | ***              | 7           | [20]       |
| Liu          | 2015 | ****      | –          | ***              | 7           | [21]       |
| Wang         | 2015 | ****      | –          | ***              | 7           | [22]       |
| Zhang        | 2015 | ****      | –          | ***              | 7           | [23]       |
| Hsieh        | 2016 | ****      | **         | ***              | 9           | [24]       |
| Musri        | 2016 | ****      | –          | ***              | 7           | [25]       |
| Wang         | 2016 | ****      | **         | ***              | 9           | [26]       |
| Giampieri    | 2017 | ****      | –          | ***              | 7           | [27]       |
| Gonda        | 2017 | ****      | **         | ***              | 9           | [28]       |
| Manikhas     | 2017 | ****      | *          | ***              | 8           | [29]       |
| Marshall     | 2017 | ****      | –          | ***              | 7           | [30]       |
| Ock          | 2017 | ****      | **         | ***              | 9           | [31]       |
| Huang        | 2018 | ****      | **         | ***              | 9           | [32]       |
| Hwang        | 2018 | ****      | **         | ***              | 9           | [33]       |
| Kim          | 2018 | ****      | **         | ***              | 9           | [34]       |
| Kondoh       | 2018 | ****      | **         | ***              | 9           | [35]       |
| Migita       | 2018 | ****      | **         | ***              | 9           | [36]       |
| Ogata        | 2018 | ****      | –          | ***              | 7           | [37]       |
| Ryu          | 2018 | ****      | **         | ***              | 9           | [38]       |
| Bozkurt      | 2019 | ****      | *          | ***              | 8           | [39]       |
| Mitani       | 2019 | ****      | –          | ***              | 7           | [40]       |
| Murakami     | 2019 | ****      | *          | ***              | 8           | [41]       |
| Namikawa     | 2019 | ****      | **         | ***              | 9           | [42]       |
| Sugimoto     | 2018 | ****      | **         | ***              | 9           | [43]       |
| Cipriano     | 2020 | ****      | **         | ***              | 9           | [44]       |
| Kim          | 2020 | ****      | **         | ***              | 9           | [45]       |
| Namikawa     | 2020 | ****      | –          | ***              | 7           | [46]       |
| Ota          | 2020 | ****      | *          | ***              | 8           | [47]       |
| Shigeto      | 2020 | ****      | –          | ***              | 7           | [48]       |
| Wang         | 2020 | ****      | *          | ***              | 8           | [49]       |
| Zhao         | 2020 | ****      | *          | ***              | 8           | [50]       |
| Zhou         | 2020 | ****      | **         | ***              | 9           | [51]       |

Correlation between pretreatment NLR and OS

Thirty-six studies comprising of 8614 gastric cancer patients reported the association between pretreatment NLR and OS. With great heterogeneity ($I^2 = 80.3\%, P < 0.001$), we utilized random effect model to analyze the pooled hazard ratio (HRs) and results showed that higher pretreatment NLR was correlated with a poorer OS (HR = 1.78, 95% confidential interval (CI) = [1.59, 1.99]) (Figure 2). Analysis with fixed effect model showed a consistent conclusion (Figure 2). The conclusion also remained unchanged with sensitivity analysis (Supplementary Figure 1A).

Considering the existence of heterogeneity, univariate meta-regression analysis was performed and indicated that case load and cutoff of pretreatment NLR could be the possible significant moderators (Table 3). Then we adopted subgroup analyses following these clinical parameters. Notably, higher pretreatment NLR was
correlated with poorer OS from multi-center studies (HR = 1.60, 95% CI = [1.32, 1.94]) and multivariate analysis (HR = 1.72, 95% CI = [1.51, 1.95]). Moreover, subgroup analysis on the basis of the NLR cutoff values demonstrated that the prognostic value of pretreatment NLR consisted in all the NLR groups (<3 HR = 1.67, 95% CI = [1.39, 2.01]; = 3 HR = 1.73, 95% CI = [1.53, 1.95]; >3 HR = 1.96, 95% CI = [1.67, 2.29]). Subgroup analysis by treatment types suggested the same conclusions in chemotherapy (HR = 1.68, 95% CI = [1.55, 1.82]), chemo/targeted therapy (HR = 1.85, 95% CI = [1.47, 2.34]), and immunotherapy (HR = 2.30, 95% CI = [1.47, 3.61]). The results of subgroup analyses were summarized in Figure 3, highlighting that elevated pretreatment NLR was correlated with poor OS.

For OS subset, the asymmetry of funnel plot indicated that there existed publication bias (Supplementary Figure 1B). Egger’s test was used for further validation (Supplementary Figure 1C). The Duval and Tweedie trim-and-fill method was then conducted and twelve studies were filled, without changing the conclusion in both fixed effect model (HR = 1.32, 95% CI = [1.27, 1.36]) and random effect model (HR = 1.58, 95% CI = [1.43, 1.74]).

Correlation between pretreatment NLR and PFS

Seventeen studies including 3318 patients were included to analyze the relationship between pretreatment NLR and PFS. Due to significant heterogeneity, we applied a random effect model and the results suggested that higher pretreatment NLR was related to inferior PFS (HR = 1.63, 95% CI = [1.39, 1.91]) (Figure 4). The fixed effect model (Figure 4) and sensitivity analysis (Supplementary Figure 2A) did not change the conclusion.

To investigate the origin of heterogeneity, univariate meta-regression was performed. We did not find the possible significant moderator (Table 4). To validate the

![Figure 2. Forest plot for the hazard ratios (HRs) of overall survival (OS) in gastric cancer patients with systemic therapy between low and high pretreatment NLR. “D+L” means DerSimonian and Laird method. “I-V” means generic inverse variance method.](image)
Table 3. Univariate meta regression of hazard ratios (HRs) of overall survival (OS) in inoperable gastric cancer patients with systemic therapy.

| Variables                      | β     | 95% LCI | 95% UCI | P     |
|-------------------------------|-------|---------|---------|-------|
| Country                       |       |         |         |       |
| Japan                         | 1.00  | 0.82    | 1.23    | 0.991 |
| China                         | 0.94  | 0.76    | 1.17    | 0.589 |
| Korea                         | 0.98  | 0.80    | 1.20    | 0.817 |
| Europe                        | 1.13  | 0.88    | 1.44    | 0.341 |
| Study type                    | 0.92  | 0.71    | 1.20    | 0.545 |
| Cases                         |       |         |         |       |
| <100                          | 0.99  | 0.78    | 1.26    | 0.952 |
| 100–200                       | 1.17  | 0.99    | 1.39    | 0.072 |
| >200                          | 0.87  | 0.72    | 1.05    | 0.141 |
| Analysis of HR                | 0.86  | 0.70    | 1.06    | 0.153 |
| Cut-off                       |       |         |         |       |
| <3                            | 0.90  | 0.75    | 1.08    | 0.235 |
| =3                            | 0.99  | 0.81    | 1.22    | 0.98  |
| >3                            | 1.20  | 0.98    | 1.47    | 0.08  |
| Treatment                     |       |         |         |       |
| Chemotherapy                  | 0.96  | 0.79    | 1.16    | 0.665 |
| Chemo/targeted therapy        | 1.00  | 0.82    | 1.22    | 0.994 |
| Immunotherapy                 | 1.39  | 0.80    | 2.40    | 0.234 |

Abbreviations: LCI, Lower confidence interval; UCI, Upper confidence interval.

For PFS subset, the funnel plot was not symmetrical and five studies were over the pseudo 95% CI (pseudo 95% CI was defined as 95% CI assuming these included studies did not have heterogeneity [53]) (Supplementary Figure 2B). We then performed the Egger’s test, which detected the existence of publication bias (P < 0.001) (Supplementary Figure 2C). Twelve studies were filled after the Duval and Tweedie trim-and-fill method. The conclusion remained consistent in both fixed effect model (HR = 1.27, 95% CI = [1.20, 1.34]) and random effect model (HR = 1.55, 95% CI = [1.34, 1.80]).

DISCUSSION

Gastric cancer has become a threat worldwide with over one million estimated new cases and about 784000 deaths globally annually [1]. Even worse, many cases were diagnosed at advanced stages and lost the chance of gastrectomy. Systemic therapy has been recommended to treat those patients with inoperable gastric cancer, but the prognostic biomarkers have not been well clarified.

Increasing studies demonstrated the association of systemic inflammation and the prognosis of gastric cancer with systemic therapy [54–57]. As the representative of systemic inflammation, NLR is easily calculated from regular blood tests. There were accumulating studies on the topic of the prognostic effect of pretreatment NLR on the gastric cancer patients with systemic therapy [16–51]. Therefore, an extensive analysis on the topic is essential to clarify the association.
In this study, a total of 36 studies including 8,614 patients were finally enrolled through searching all the relevant articles. We found that higher pretreatment NLR was associated with an inferior OS and PFS. Considering the huge heterogeneity in these comparisons, univariate meta-regression analyses were conducted to investigate the origin of heterogeneity. Case load and cutoff of pretreatment NLR could be the possible significant moderators for OS. Moreover, six studies used the Engauge Digitizer software to estimate the univariate HRs, which were grouped into subgroup with univariate analysis. However, the conclusions were not changed by fixed effect model, sensitivity analyses and subgroup analyses, which highlights the prognostic value of pretreatment NLR in inoperable gastric cancer patients with systemic therapy.

Currently, quite a few meta-analyses with regard to the prognostic effect of NLR on gastric cancer were published. In 2015, Chen et al. performed a meta-analysis based on nine studies including 3709 gastric cancer patients, and suggested that higher pretreatment NLR was associated with poorer OS and PFS in gastric cancer patients undergoing resection and palliative chemotherapy [15]. However, this study did not describe the prognostic effect of pretreatment NLR on targeted therapy or immunotherapy. Moreover, Sun and his colleagues included 19 studies in the meta-analysis and validated Chen et al.’s conclusion [14]. Furthermore, Kim et al. comprehensively assessed the association between the OS of gastric cancer patients and NLR. They included 24 studies to analyze the pooled HRs of OS but did not report the prognostic effect of NLR on the prognosis of inoperable gastric cancer patients with systemic therapy [13]. Overall, these studies mainly focused on the gastric cancer patients with gastrectomy, while we concentrated on inoperable gastric cancer patients with systemic therapy. We highlighted the prognostic effect of pretreatment NLR not only on

| Subgroup             | Studies | HR (95% CI)          |
|----------------------|---------|----------------------|
| **Country**          |         |                      |
| Japan                | 13      | 1.89 (1.50, 2.40)    |
| China                | 9       | 1.20 (1.15, 1.26)    |
| Korea                | 8       | 1.64 (1.45, 1.85)    |
| Europe               | 6       | 1.70 (1.52, 1.89)    |
| **Study type**       |         |                      |
| Single-center        | 31      | 1.60 (1.32, 1.94)    |
| Multi-center         | 5       | 1.56 (1.38, 1.73)    |
| **Cases**            |         |                      |
| <100                 | 10      | 2.05 (1.45, 2.91)    |
| 100-200              | 15      | 1.15 (1.10, 1.21)    |
| ≥200                 | 11      | 1.90 (1.69, 2.13)    |
| **Analysis of HR**   |         |                      |
| Univariate           | 11      | 1.90 (1.72, 2.10)    |
| Multivariate         | 25      | 1.59 (1.48, 1.70)    |
| **Cut-off**          |         |                      |
| <3                   | 12      | 1.93 (1.65, 2.25)    |
| 3                    | 10      | 1.92 (1.69, 2.19)    |
| >3                   | 13      | 1.72 (1.51, 1.95)    |
| **Treatment**        |         |                      |
| Chemotherapy         | 20      | 1.67 (1.39, 2.01)    |
| Chemo/targeted therapy | 13  | 1.23 (1.18, 1.28)    |
| Immunotherapy        | 3       | 1.73 (1.53, 1.95)    |

Figure 3. Subgroup analysis of OS. “D+L” means DerSimonian and Laird method. “I-V” means generic inverse variance method.
Table 4. Univariate meta regression of hazard ratios (HRs) of progression-free survival (PFS) in inoperable gastric cancer patients with systemic therapy.

| Variables            | β   | 95% LCI | 95% UCI | P     |
|----------------------|-----|---------|---------|-------|
| Country              |     |         |         |       |
| Japan                | 1.13| 0.65    | 1.96    | 0.647 |
| China                | 0.83| 0.62    | 1.10    | 0.176 |
| Korea                | 1.06| 0.79    | 1.43    | 0.668 |
| Europe               | 1.11| 0.80    | 1.54    | 0.497 |
| Study type           | 1.10| 0.73    | 1.67    | 0.618 |
| Cases                |     |         |         |       |
| <100                 | 1.20| 0.76    | 1.91    | 0.411 |
| 100-200              | 1.05| 0.79    | 1.40    | 0.719 |
| >200                 | 0.88| 0.66    | 1.19    | 0.381 |
| Analysis of HR       | 0.85| 0.65    | 1.11    | 0.204 |
| Cut-off              |     |         |         |       |
| <3                   | 1.01| 0.76    | 1.35    | 0.919 |
| =3                   | 1.09| 0.79    | 1.51    | 0.561 |
| >3                   | 0.91| 0.67    | 1.22    | 0.498 |
| Treatment            |     |         |         |       |
| Chemotherapy         | 0.96| 0.66    | 1.39    | 0.819 |
| Chemo/targeted therapy | 0.98| 0.61    | 1.56    | 0.919 |
| Immunotherapy        | 1.13| 0.65    | 1.96    | 0.647 |

Abbreviations: LCI, Lower confidence interval; UCI, Upper confidence interval.

Figure 4. Forest plot for the HRs of progression-free survival (PFS) in gastric cancer patients with systemic therapy between low and high pretreatment NLR. “D+L” means DerSimonian and Laird method. “I-V” means generic inverse variance method.
the gastric cancer patients with chemotherapy, but also on gastric cancer patients with chemo/targeted therapy and immunotherapy.

The mechanisms underlying the relationship between pretreatment NLR and the prognosis of inoperable gastric cancer patients with systemic therapy were poorly known, but many studies provided the potential mechanisms [13–15, 58]. In summary, most neutrophils promote the progression of tumors through inhibiting immune activity, while lymphocytes are regarded as the primary effector cells in the immunotherapy. NLR is calculated by circulating neutrophil to lymphocyte counts, which reflects a balance between the detrimental roles of neutrophilia and the beneficial roles of lymphocyte-mediated immunity [59]. Even so, more studies are still needed to investigate the underlying mechanism in the association. There are other predictive biomarkers with prognostic value in gastric cancer patients with systemic therapy. For example, a recent study showed that an immune checkpoint score system could be used for the evaluation of prognosis and the selection for adjuvant chemotherapy in gastric cancer [60]. Moreover, a deep learning computed tomography (CT) signature was developed to predict the prognosis and benefit from adjuvant chemotherapy in gastric cancer [61]. Many single biomarkers such as MTA1 [62], TFF3 [63], and CA72-4 [64] were also reported to be related to the prognosis of gastric cancer with systemic therapy. As a simple and feasible biomarker, NLR is easily obtained from the regular blood tests, which highlights its practicability in clinical practice.

Admittedly, some limitations existed within our meta-analysis. First, two eligible studies were meeting abstracts providing limited data and this could be

| Subgroup          | Studies | HR (95% CI) |
|-------------------|---------|-------------|
| **Country**       |         |             |
| Japan             | 3       | 1.83 (1.08, 3.10) |
| China             | 4       | 1.67 (1.13, 2.47) |
| Korea             | 6       | 1.43 (1.05, 1.96) |
| Europe            | 4       | 1.13 (1.06, 1.21) |
| **Study type**    |         |             |
| Single-center     | 15      | 1.57 (1.38, 1.79) |
| Multi-center      | 2       | 1.56 (1.38, 1.76) |
| **Cases**         |         |             |
| <100              | 4       | 1.73 (1.33, 2.26) |
| 100-200           | 8       | 1.69 (1.42, 1.99) |
| ≥200              | 5       | 1.69 (1.34, 2.17) |
| **Analysis of HR**|         |             |
| Univariate        | 10      | 1.62 (1.37, 1.92) |
| Multivariate      | 7       | 1.58 (1.19, 2.11) |
| **Cut-off**       |         |             |
| <3                | 7       | 1.48 (1.33, 1.64) |
| 3                 | 5       | 1.48 (1.33, 1.64) |
| >3                | 5       | 1.48 (1.33, 1.64) |
| **Treatment**     |         |             |
| Chemotherapy      | 12      | 1.70 (1.47, 1.97) |
| Cicho/targeted therapy | 2   | 1.67 (1.49, 1.87) |
| Immunotherapy     | 3       | 1.50 (1.20, 1.88) |

Figure 5. Subgroup analysis of PFS. “D+L” means DerSimonian and Laird method. “I-V” means generic inverse variance method.
improved by updating with the latest data. Second, considerable heterogeneity existed in the meta-analysis, though sensitivity analyses and subgroup analyses did not change the conclusion. Third, publication bias existed in both OS and PFS, though the Duval and Tweedie trim-and-fill method indicated the same trend of the results. Finally, NLR is a non-specific biomarker and could be affected by the concurrent disease, such as infections and drug therapy. Most of the studies did not include these descriptions.

In conclusion, as a simple, inexpensive and readily available biomarker, NLR could be used to predict the benefit of inoperable gastric cancer patients with systemic therapy. Measurement of this biomarker before treatment will assist clinicians with patient counseling and clinical treatment guiding accordingly.

MATERIALS AND METHODS

Search strategy

We implemented the meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [65, 66]. The databases of the PubMed, Embase and Cochrane libraries were retrieved from inception to September 16th, 2020. The search terms were indicated as below: “Stomach neoplasms” OR “gastric and (cancer or carcinoma? or adenocarcinoma? or neoplasm? or neoplasia)” OR “stomach adj3 (cancer or carcinoma? or adenocarcinoma? or neoplasm? or neoplasia)” AND (“Neutrophil-Lymphocyte ratio” OR “Neutrophil to Lymphocyte ratio” OR "Neutrophil-to-Lymphocyte ratio" OR "Neutrophil to Lymphocyte ratio" OR "Neutrophil/Lymphocyte ratio" OR NLR). There was no limitation of language and study type. References lists of eligible articles and main reviews were explored manually to guarantee a thorough literature search. We have registered our systematic review in PROSPERO website (https://www.crd.york.ac.uk/PROSPERO/). The identifier of systematic review registration was PROSPERO CRD42021224114.

Selection criteria

NLR was defined as absolute neutrophil counts divided by absolute lymphocyte counts. Studies eligible for inclusion should satisfy the following inclusion criteria: (1) the patients with metastatic or inoperable gastric cancer; (2) receiving systemic therapy, including chemotherapy, targeted therapy and immunotherapy; (3) accessible HR and their corresponding 95% CI for OS and PFS between high and low pretreatment NLR group; (4) nonrandomized studies with or without the use of randomized samples. Exclusion criteria were as follows: (1) studies receiving gastrectomy or not specifying therapy types; (2) studies including patients with other types of tumors without performing of subgroup analysis about gastric cancer; (3) duplicated studies with small sample size in the same institutes or hospitals; (4) studies with insufficient usable data; (5) review, case reports or meta-analyses.

Data extraction and quality assessment

Two authors (FZ, ZF) autonomously selected eligible studies, and discordance was resolved by a third author (GD). The following information were collected from eligible studies: first authors, published year, country, type of study, case load, age, gender, cutoff of pretreatment NLR, treatment types, HR and their corresponding 95% CI for OS and PFS. HRs were extracted from multivariable analyses preferentially where available; otherwise, HRs were retrieved from univariate analyses. If studies did not report specified HRs, Engauge Digitizer software was adopted to digitize and estimate HRs from Kaplan-Meier curves between high and low NLR groups [67, 68]. Six studies in the meta-analysis used the Engauge Digitizer software to estimate the univariate HRs [20–23, 25, 48]. Newcastle-Ottawa Scale (NOS) was used for quality evaluation in three aspects: selection, comparability and outcome [52]. Studies with stars above six were regarded as high-quality.

Statistical analysis

STATA software (Version 12.0; STATA Corporation) was applied for all the statistical analyses. HRs with their corresponding 95% CI were pooled to evaluate the survival values. Statistical heterogeneity was assessed with I^2 and P-value. Considering the existence of heterogeneity in the comparisons, random effect model was preferentially performed for all the analyses. To ensure the robustness of the results, fixed effect model was also performed in all the analyses. Univariate meta-regression analysis was conducted to investigate the origin of heterogeneity. Moreover, sensitivity analysis was executed by omitting one study each time as previously described [69]. Subgroup analyses were used to test the consistency of the results based on country, study type, case load, analysis of HR, cutoff of pretreatment NLR, or treatment types. Funnel plots and Egger’s tests were performed to assess publication bias. Duval and Tweedie trim-and-fill method was used for the adjustment of the publication bias. P value less than 0.05 was regarded statistically significant.
Abbreviations

NLR: neutrophil-to-lymphocyte ratio; OS: overall survival; PFS: progression-free survival; HR: hazard ratio; CI: confidence interval; NOS: Newcastle-Ottawa Scale.

AUTHOR CONTRIBUTIONS

Songtao Du: Data curation; Resources; Roles/Writing – original draft. Zhenhao Fang: Data curation; Resources; Writing - review & editing; Lin Ye: Writing – review & editing; Huiyan Sun: Writing – review & editing; Guangtong Deng: Conceptualization; Funding acquisition; Supervision; Roles/Writing – original draft. Wei Wu: Supervision; Funding acquisition. Furong Zeng: Conceptualization; Data curation; Formal analysis; Funding acquisition; Methodology; Software; Writing – review & editing.

CONFLICTS OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary Figure 1. Sensitivity analysis (A), Funnel plot (B) and Egger test (C) for the pooled HRs of OS in gastric cancer patients with systemic therapy between low and high pretreatment NLR.
Supplementary Figure 2. Sensitivity analysis (A), Funnel plot (B) and Egger test (C) for the pooled HRs of PFS in gastric cancer patients with systemic therapy between low and high pretreatment NLR.