Prognostic value of neutrophil to lymphocyte ratio for gastric cancer

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Background: Although the prognostic value of the neutrophil to lymphocyte ratio (NLR) in gastric cancer (GC) patients has been investigated by many studies, the results are heterogeneous. The objective of this systematic review is to ascertain the prognostic value of NLR in GC patients.

Methods: PubMed and Embase were retrieved to identify potential studies published before 8 June, 2014. Newcastle-Ottawa Scale (NOS) for cohort study was used to assess the quality of all eligible studies.

Results: Of the 20 studies included in this systematic review, 17 studies investigated the effect of NLR on overall survival (OS), 11 studies reported that NLR negatively affected OS in their multivariante analysis, and 16 studies reported that NLR negatively affected OS in univariate analysis. Three studies investigated the effect of NLR on progression-free survival (PFS), reporting that increased NLR was associated with worse PFS. Four studies investigated the effect of NLR on disease-free survival (DFS), two of which reported that increased NLR was associated with worse DFS. Two studies investigated the effect of NLR on disease special survival (DSS), but neither observed any significant association between NLR and DSS. The major design deficiencies of the studies available were retrospective data collection, inadequacy of follow-up cohorts, and unavailability of the method used for outcome assessment.

Conclusions: Based on the above findings, we conclude that NLR may be a useful prognostic index (PI) for GC. In addition, future studies with prospective design, long-term follow-up and fully adjusted confounding factors are needed to rigorously assess the prognostic value of NLR for GC.

Keywords: Neutrophil to lymphocyte ratio (NLR); gastric cancer (GC); systematic review; prognosis

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Introduction

Gastric cancer (GC) is one of the most prevalent malignant diseases worldwide, accounting for about 8% of all cancers and 10% of cancer-related deaths (1). Although the survival benefit of palliative chemotherapy and surgical treatment in GC has been well recognized, the outcome remains dismal. To improve the outcome of GC patients, prognostic assessment is a critical, for it can affect decision-making for GC treatment (2). Generally, prognostic assessment is based on various prognostic factors, among which the most well established include TNM stage (3,4), pathohistological classification (5), resection margin (6), serosal invasion (6), inflammation factors (7), and tumor markers (8-10). Although there are various prognostic factors available, some of them are invasive and/or cannot be acquired before treatment, and therefore their value in clinical practice is limited to some extent, especially during the

initial phase of GC treatment.

Inflammation is known to be involved in the occurrence and development of GC (11-13), and inflammatory markers such as C-reactive protein (CRP) (14,15) and the erythrocyte sedimentation rate (ESR) (16) have been regarded as the useful diagnostic or prognostic markers for GC. As most inflammatory markers are non-invasive and can be acquired before treatment, their prognostic value has aroused much interest.

The neutrophil to lymphocyte ratio (NLR) is a well-recognized inflammatory index and has been reported as a useful prognostic index (PI) in GC in many studies. However, the results remain inconsistent. The objective of this systematic review is to ascertain the prognostic value of NLR for GC.

Materials and methods

Literature searching strategy

Two authors independently searched the electronic databases including PubMed and Embase to identify potential studies. The last search was performed on 8 June, 2014. The search terms for PubMed were: ("neutrophil/lymphocyte" or "neutrophil to lymphocyte" or "neutrophil lymphocyte" OR "neutrophil-lymphocyte") AND ("stomach cancer" OR "gastric cancer" OR "Stomach Neoplasms [MESH]" OR "stomach malignant"). Similar strategies were used for EMBASE. Manual searches were also performed by reviewing the references listed at the end of eligible studies.

Study selection

The inclusion criteria for the present systematic review were as follows: (I) studies that evaluated the prognostic value of NLR in GC patients; (II) studies with a follow-up duration longer than 6 months; (III) studies reporting at least one of the following endpoints: overall survival (OS), progression-free survival (PFS), disease-free survival (DFS) and disease special survival (DSS). The following were excluded: (I) animal studies; (II) conference abstracts; (III) duplicated publications; and (IV) manuscripts in languages other than English. Screening of eligible studies was conducted in two steps: first, two authors independently reviewed the abstracts and titles of the retrieved studies to identify potentially eligible studies, and then reviewed their full texts. Any disagreement in study selection was resolved by discussions.

Data extraction

Two authors independently performed data extraction and quality assessment. The following data were extracted: name of the first author, publication year, participant characteristics, sample size, follow-up duration, endpoint and corresponding hazard ratio (HR) and 95% confidence interval (CI), and confounding factors adjusted. If more than one HR was provided in an individual study, the most fully adjusted HR was extracted. The corresponding authors of the eligible studies were not contacted for further information.

The Cochrane recommended Newcastle-Ottawa Scale (NOS) (17) for cohort study was used for quality assessment, with minor modifications. This tool consisted of three domains: selection domain (maximum: four score), comparability (maximum: two score), and outcome (maximum: three score).

Any disagreement in data extraction and quality assessment was resolved by discussions among all authors.

Results

Summary of eligible studies

Figure 1 indicates the flowchart describing our literature search. A total of 20 studies (18-37) were included and the summaries of eligible studies are shown in *Table 1*. Since none of the eligible studies declared that they reported the results according to the reporting recommendations for tumor marker prognostic studies (REMARK) (38), some of the design details or results were not reported and thus labeled as "not reported (NR)". Seven studies were from Japan (20,28,32-35,37), six from Korea (18,23,24,27,30,31), three from China (19,21,29), two from Turkey (22,36), and two from UK (25,26). The sample size ranged from 46 to 1,220. Eight studies were conducted in patients with advanced GC patients (stage III or IV) (18,20,21,27-29,31,36), eight in all stages of GC (22-24,26,32-35), and two in GC patients undergoing surgical resection (25,30). Two studies did not report the characteristics of GC patients (19,37). Generally, the male/female ratio in GC cohorts arranged approximately from 1.5 to 4, and the mean or median age was older than 50 years. Sixteen studies (18,20-25,27-31,33-36) were retrospective, one study (37) was post hoc analysis, and three studies (19,26,32) did not report how they collected the data.

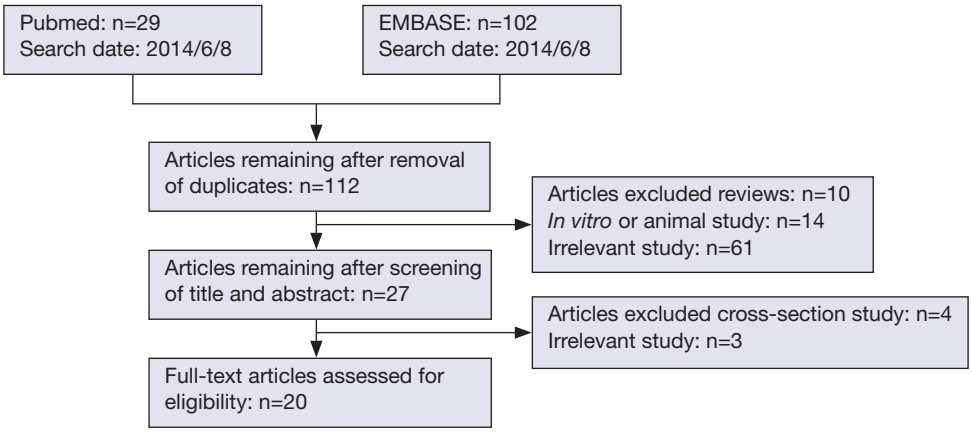

Figure 1 Flowchart describing the systematic literature search and study selection process.

Table 1 Summary of eligible studies

First author	Year	Country	No.	Patient characteristics	Age (years)	Sex (M/F)	Design	NOS
Cho (18)	2014	Korea	268	Inoperable AGC	55±12	175/93	Retrospective	3/2/1
Li (19)	2014	China	384	NR	NR	273/111	NR	4/2/1
Mohri (20)	2014	Japan	123	Gastric cancer and synchronous distant metastasis	Median:66 (range: 18-94)	85/38	Retrospective	4/2/2
Jin (21)	2013	China	46	TNM I/II/III/IV (0/0/40/6)	Median: 60 (range: 37-77)	36/10	Retrospective	3/1/2
Dirican (22)	2013	Turkey	236	TNM I/II/III/IV (6/20/105/105)	Median: 58 (IQR: 30-86)	162/74	Retrospective	3/2/1
Lee (23)	2013	Korea	220	TNM I/II/III/IV (120/35/62/3)	Median: 57 (range: 23-89)	149/71	Retrospective	3/2/1
Lee (24)	2013	Korea	174	TNM I/II/III/IV (7/22/41/104)	Median: 55 (range: 24-74)	114/60	Retrospective	4/2/2
Noble (25)	2013	UK	246	Patients undergoing oesophagogastric resection	Median: 67 (range: 37-85)	195/51	Retrospective	4/2/2
Dutta (26)	2012	UK	120	TNM I/II/III/IV (56/27/37/0)	NR	78/42	NR	3/2/1
Jeong (27)	2012	Korea	104	Stage IV unresectable AGC	Median: 53 (range: 28-82)	69/35	Retrospective	3/2/3
Kunisaki (28)	2012	Japan	83	TNM I/II/III/IV (0/0/22/61)	NR	57/26	Retrospective	4/2/2
Wang (29)	2012	China	324	TNM I/II/III/IV (0/0/324/0)	NR	225/99	Retrospective	3/2/2
Kim (30)	2012	Korea	93	Patients undergoing complete resection of gastric cancer	NR	57/36	Retrospective	3/2/2
Jung (31)	2011	Korea	293	TNM I/II/III/IV (0/0/143/150)	Median: 63 (range: 21-96)	193/100	Retrospective	4/2/1
Shimada (32)	2010	Japan	1,028	JGCA I/II/III/IV (584/132/153/159)	Median: 65 (range: 26-89)	709/319	NR	3/2/1
Ubukata (33)	2010	Japan	217	JGCA I/II/III/IV (123/14/33/47)	NR	171/46	Retrospective	3/1/2
Ubukata (34)	2010	Japan	157	TNM I/II/III/IV (45/30/39/43)	Average: 65	106/51	Retrospective	3/1/2
Mohri (35)	2010	Japan	357	TNM I/II/III/IV (232/57/68/0)	Median: 63 (range: 32-87)	245/112	Retrospective	3/2/1
Aliustaoglu (36)	2010	Turky	168	Locally-advanced gastric cancer	60±12	114/54	Retrospective	3/1/1
Yamanaka (37)	2007	Japan	1,220	NR	NR	869/251	Post hoc	3/2/2

NOS, The Newcastle-Ottawa Scale; AGC, advanced gastric cancer; NR, not reported; JGCA, Japanese Gastric Cancer Association.

Quality assessment of eligible studies

Generally, the selection domains of all eligible studies were good, including 14 studies (18,21-23,26,27,29,30,32-37) that were labeled as three because the authors did not report how they enrolled the patients (consecutively, randomly or neither). Comparability domains in four studies (21,33,34,36) were labeled as one because the confounding factors were not fully taken into consideration. Outcome domains in most of the eligible studies were label as one or two because: (I) the authors did not report how to get the information of endpoints (18,19,21-23,27,30-36); and/or (II) did not report the follow-up rate (18,30,32,37), or the follow-up rate was lower than 80% (19,20,22,23,25,28,29, 31,32,35,36). The score of each domain is listed in *Table 1*.

Major findings of eligible studies

As shown in *Table 2*, 10 (19,21-23,30,31,33,34,36,37) of the 20 eligible studies did not report the follow-up duration,

Table 2 NLR and gastric cancer prognosis

First author	Follow-up (months)	Thresholds	Confounding factors adjusted		HR (95% CI)
			Pre-treatment	Treatment or post-treatment	
Cho (18)	Median: 11.3 (range: 2.40-59.87)	3	Age, gender, ECOG, Hb, PLT	Differentiation, distant metastasis, chemotherapeutic regimen, response to first line chemotherapy	PFS: 1.48 (1.15-1.89); OS: 1.57 (1.23-2.01)
Li (19)	NR	2.75	Gender, WBC, Neu, Lym, PLT, PLR, CRP, Alb, GPS, PI, PNI, KPS	Tumor stage, differentiation, distant metastasis, first-line chemotherapy cycles, gastrectomy after chemotherapy	OS: NS
Mohri (20)	Median: 13.1	3.1	Age, gender, BMI, Hb, CRP, Alb, CEA, CA19-9, performance status	Tumor location, differentiation, adjacent organ invasion, bulky LN, distant metastasis, gastrectomy, chemotherapy	OS: 2.30 (1.44-3.67)
Jin (21)	NR	2.5	Neu	Radicality, differentiation	PFS: 2.33 (1.07-5.07); OS: NS
Dirican (22)	NR	3.8	dNLR, PLR, MPV, PLT, CA 19-9, CA 125, AFP	Tumor depth, LN metastasis, distant metastasis, histology	OS: 2.74 (1.9-3.7)
Lee (23)	NR	2.15	ESR, CEA, CA19-9	Tumor size, TNM stage	OS: 0.83 (0.40-1.67)
Lee (24)	Median: 14.9	3	Age, CEA, PLR, gender, previous operation, change of NLR and PLR	Histology, adjuvant chemotherapy, distant metastasis	PFS: 2.30 (1.43-3.69); OS: 2.25 (2.09-3.63)
Noble (25)	Median: 42	2.5	Age, gender, WBC, Neu, Lym, Alb, smoker, PLT, PLR, PNI, ASA, performance status	Neoadjuvant, tumor stage, vascular invasion, lymphatic invasion, perineural invasion, histology, resection clearance	OS: 1.19 (1.09-1.30); DFS: NS
Dutta (26)	Median: 55	2.5 and 5	Age, gender, WBC, Neu, Lym, PLT, GPS, PLR	TNM stage, differentiation, resection margin, LN metastasis, neoadjuvant therapy	DSS: NS
Jeong (27)	Median: 11.9	3	Alb, CRP, Neu, GPS	Histology, distant metastasis	OS: 1.65 (1.03-2.64)
Kunisaki (28)	14.5±7.1	5	GPS	Gastrectomy after chemotherapy	DSS: NS

Table 2 *(continued)*

Table 2 *(continued)*

First author	Follow-up (months)	Thresholds	Confounding factors adjusted		HR (95% CI)
			Pre-treatment	Treatment or post-treatment	
Wang (29)	Median: 39.9 (range: 23.77-57.43)	5	Weight loss, GPS	TNM stage, tumor differentiation, adjuvant chemotherapy	DFS: 1.76 (0.88-3.51); OS: 1.87 (0.90-3.87)
Kim (30)	NR	1.8	BMI, gender	Tumor size, TNM, categorical transfusion variable, NLR on postoperative day 3 and 7	DFS: NS
Jung (31)	NR	2.0 and 3.0	NR	TNM stage, operation type, histology, perineural invasion, postoperative chemotherapy	OS: 1.46 (1.03-2.07); DFS: 1.65 (1.09-2.52)
Shimada (32)	Median: 23 (range: 12-84)	4	Gender, age, PLT	Tumor stage, differentiation	OS: 1.85 (1.24-2.75)
Ubukata (33)	NR	5	NR	NR	OS: 2.87 (0.45-17.70)
Ubukata (34)	NR	5	NR	NR	OS: 5.78 (0.95-35.17)
Mohri (35)	Median: 68 (range: 1-70)	2.2	Hb, Alb, CRP, cholinesterase	Tumor size, and clinical T and N grouping	OS: 4.28 (2.89-6.45)
Aliustaoglu (36)	NR	2.56	NR	NR	OS: significant, but NR
Yamanaka (37)	NR	2.5	Age, gender, BMI, WBC, Neu, Lym	Disease status, metastasis	OS: 1.52 (1.32-1.75)

NLR, neutrophil to lymphocyte ratio; HR, hazard ratio; CI, confidence interval; ECOG, the Eastern Cooperative Oncology Group; Hb, hemoglobin; PLT, platelet; PFS, progression-free survival; OS, overall survival; NR, not reported; WBC, white blood cell; Neu, neutrophil; Lym, lymphocyte; PLR, platelet-to-lymphocyte ratio; CRP, C-reactive protein; Alb, albumin; GPS, Glasgow prognostic score; PI, prognostic index; PNI, prognostic nutritional index; NS, not significant; BMI, body mass index; CEA, carcinoembryonic antigen; LN, lymph node; MPV, mean platelet volume; ESR, erythrocyte sedimentation rate; ASA, American Society of Anesthesiologists physical status classification System; DSS, disease special survival.

and the median follow-up duration of the remaining studies arranged from 11 to 68 months. The threshold of NLR used to categorize GC patients ranged from 1.8 to 5.

OS is the most widely used endpoint of cohort studies. Seventeen studies (18-25,27,29,31-37) analyzed the association between NLR and OS, of which 11 studies (18,20,22,24,25,27,31,32,35-37) found that increased NLR was associated with a higher all-cause mortality, and the remaining six studies (19,21,23,29,33,34) failed to observe the association between NLR and OS. However, univariate analysis of 16 studies (18,19,21-25,27,29,31-37) showed that increased NLR was associated with worse OS. PFS was set as the endpoint in three studies (18,21,24), and the association between increased NLR and worse PFS was observed in two (18,21). DFS was set as the endpoint in four studies (25,29-31), and two (25,31) of them found that increased NLR was associated with worse DFS. DSS was set as the endpoint in two studies (26,28), and neither concluded that NLR could affect DSS.

The confounding factors, including pre-, intra- and post-treatment ones, were various in the eligible studies. The most common pretreatment factors adjusted in eligible studies were age, gender, platelet count, CA19-9, body mass index (BMI) or weight loss, CRP, albumin, ESR, carcinoembryonic antigen (CEA), PI, prognostic nutritional index (PNI) and the Eastern Cooperative Oncology Group (ECOG). The most common intra-treatment or post-treatment factors adjusted were tumor differentiation, adjuvant chemotherapy, tumor stage or location, operation type, histology or perineural invasion.

Meta-analysis was not performed to further investigate the prognostic value of NLR due to the following reasons: (I) the subjects were heterogeneous in all eligible studies, especially in tumor stage and treatment strategies; (II) the threshold to categorize GC patients was heterogeneous;

(III) the confounding factors adjusted in all eligible studies were heterogeneous; and (IV) HR was not reported in some of the eligible studies, especially the studies with negative findings.

Discussion

The present systematic review investigated the prognostic value of NLR for GC. We found that the 20 studies available were heterogeneous in subjects, statistical analysis and data presentation. Most of the eligible studies reported that NLR was a useful index to estimate the OS, PFS and DFS, but not DSS. In addition, 16 of the 17 studies that investigated the effect of NLR on OS reported that increased NLR was associated with worse OS in univariate analysis, suggesting that NLR is a useful index to estimate the prognosis of GC. In addition to the major findings of the studies available, some methodological problems should not be ignored and need to be carefully addressed in future research.

The first methodological problem is the bias of participant selection. It should be noted that all the eligible studies were retrospective and only six (19,20,24,25,28,31) out of the 20 studies reported that they included the entire potential eligible subjects admitted in the hospitals. As subject enrollment in a retrospective study largely depends on the completeness of medical records, some potentially eligible patients without complete medical records may be excluded from the study, which may introduce participant selection bias. To avoid cohort selection bias, consecutive enrollment for subjects is essential. Unfortunately, only five studies reported that they enrolled their subjects consecutively.

The second methodological problem is the process of data analysis. All but one (26) categorized the subjects into two groups with variable thresholds. Although this is a common approach used by most retrospective studies, it may cause a great information loss (39). The threshold used to transform continuous data into binary data has a great effect on the result of the Cox model (39,40). It would be better to investigate the prognostic value of NLR in three or four groups rather than just in two groups (39). In addition to the threshold to categorize continuous variables, confounding factors constitute another methodological problem in data analysis. Many of these confounding factors were adjusted in the Cox model, and categorized into three types: pre-, intra- or post-treatment as shown in *Table 2*. Some of the eligible studies found that NLR had no independent effect on the prognosis of GC, although univariate analysis showed that increased NLR was associated with the worse prognosis of GC. Statistically, all the potential confounding factors should be adjusted for analysis. But clinically, noninvasive prognostic factors should be preferred for easy acquisition, especially those obtained before treatment because they can affect the establishment of initial treatment strategies. In other words, it is valuable to see whether the prognostic value of intra- or post-treatment factors is independent of pretreatment factors, but not the opposite. Among the well-recognized pre-treatment prognostic factors, NLR may be preferable because it is non-invasive and inexpensive

High neutrophil counts have long been reported to negatively affect the prognosis of GC (41), probably because they could promote the proliferation, invasion and angiogenesis of cancer by producing various factors, and effectively suppress anti-tumor response initiated by the immune system (42). On the other hand, low lymphocyte counts are believed to be associated with worse prognosis in various types of cancer because they weaken the lymphocyte-mediated anti-tumor cellular immune response, and also reflect the status of malnutrition in GC patients. NLR, defined as the absolute number of neutrophils divided by the absolute number of lymphocytes, has incorporated the prognostic value of neutrophils and lymphocytes, and therefore may better reflect the prognosis of GC.

In summary, the present systematic review suggests that NLR is a useful, inexpensive and noninvasive pre-treatment prognostic factor for GC. Since most studies in the present systematic review are retrospective, we call for prospective studies with larger sample sizes to rigorously assess the prognostic value of NLR for GC in future.

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