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Original Article

Neutrophil-lymphocyte ratio predicts the prognosis of patients with colorectal cancer: a meta-analysis

Ding-Cheng Zheng[1], Cheng Zheng[1], Jian Wu[2], Hua Ye[1], Jing-Jie Chen[1], Bin Zhou[1], Qi Zheng[1], Feng Wu[1], Wen-Yu Dai[1], Ping Chen[1], Qiao-Ming Zhi[3]

[1]Department of General Surgery, Ningbo No. 2 Hospital, Ningbo, China; [2]Department of Liver Surgery, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China; [3]Department of General Surgery, The First Affiliated Hospital of Soochow University, Suzhou 215006, China

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Abstract: Emerging evidences show that host inflammatory responses are associated with tumor progression. NLR, which is calculated as the ratio of neutrophils to lymphocyte count, is regarded as a useful marker of reflecting the general immune response to various stress stimuli. Our aim of this meta-analysis is to evaluate the prognostic role and clinicopathological differences of NLR in CRC patients. A total of 21 studies with 9363 CRC patients up to February 2015 were included in our study. Our data indicated that elevated NLR was a negative predictor for OS (HR=1.918, 95% CI=1.585-2.323, P<0.001) and PFS (HR=1.918, 95% CI: 1.508-2.438, P=0.007) in CRC. Subgroup analyses were performed based on the location, treatment and cut-off value, and none of the subgroup estimations altered the prognostic role of NLR for OS and PFS in CRC. Meanwhile, elevated NLR was significantly associated with the presence of tumor differentiation (OR=1.558, 95% CI: 1.220-1.990, P<0.001), advanced TNM stage (OR=1.248, 95% CI: 1.055-1.477, P=0.01) and a higher incidence of CEA≥5 ng/ml (OR: 1.502, 95% CI: 1.320-1.710, P<0.001). Our findings suggested that NLR, which could be examined in a simple and invasive way as a common hematologic marker, might serve as a novel and effective prognostic biomarker in CRC. NLR can be a potential direction for developing diagnostic and therapeutic approaches in CRC.

Keywords: Colorectal cancer, NLR, prognosis, meta-analysis

Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors and ranks as the third leading cause of cancer-related deaths worldwide [1]. Despite a significant improvement in CRC management and new developments for cancer surveillance, the long-term outcome remains dismal due to its high disease recurrence and fatality [2, 3]. To date, the Tumor Node Metastasis (TNM) system and Duke's system remain the most common prognostic factors for predicting the clinical outcomes of patients with CRC. However, the accuracy of TNM/DUKES' stage is still unsatisfactory, and it is fairly common that patients belonging to the same stage have different outcomes [4, 5]. Therefore, there is an urgent need for us to perform researches to identify some novel and effective prognostic biomarkers with high specificity and sensitivity, which can help clinicians to adopt more effective measures for at-risk CRC patients.

Recently, emerging evidences showed that host inflammatory responses were associated with tumor progression, including promotions of tumor invasion and metastasis, and inhibiting apoptosis by regulations of some cytokines, such as TNF alpha, CRP, neutrophilia, IL-17 and chemokines [6, 7]. Some other studies also demonstrated that increased systemic inflammations closely correlated with the overall survival (OS) of patients with cancers [8, 9]. Systemic inflammations can be evaluated by several available indexes including albumin, C-reactive protein (CRP) level and platelet/lymphocyte ratio (PLR).

NLR, which is calculated as the ratio of neutrophils to lymphocyte count, is regarded as another useful marker of reflecting the general

immune response to various stress stimuli [10]. Interestingly, recent evidence showed that elevated NLR participated in the tumor progression [11-13], and NLR can be considered as an effective prognostic predictor in many malignant tumors, including non-small-cell lung cancer, ovarian cancer, gastric cancer and hepatocellular carcinoma [14-17]. Several other clinical studies investigated the prognostic role of NLR in CRC which focused on the overall survival (OS), progression-free survival (PFS) and clinicopathological factors [18, 19], but their conclusions were still controversial. Therefore, we performed a meta-analysis of all eligible studies to acquire a more precise evaluation of the prognostic significance of NLR for the OS and DFS of patients with CRC. In addition, the relationships between the NLR level and some other clinicopathological variables such as lymph node metastasis, tumor differentiation, TNM stage and CEA levels were also examined.

Materials and methods

Search strategy

Up to February 2015, we performed a comprehensive literature search from the electronic databases: Pubmed, Ovid, Embase, the Cochrane Library and Web of Science databases. The search strategy was based on combinations of the following keywords: "CRC" ("colorectal cancer", "colon cancer" or "rectal cancer"), "NLR" ("neutrophil to lymphocyte ratio", "neutrophil lymphocyte ratio", "neutrophil/lymphocyte ratio" or "neutrophil-to-lymphocyte ratio") and "prognosis" ("outcome", "survival", "prognosis", "mortality" or "recurrence"). Articles were included in this meta-analysis if they met the following criteria: (i) studies had to investigate the correlations between the serum NLR levels and OS/PFS in CRC patients, (ii) the NLR levels were measured preoperatively, (iii) studies directly extracted the hazard ratio (HR) and 95% confidence intervals (CI) or provided sufficient information to estimate them, and (iv) the sample size of the study was equal to or greater than 20. The excluded criteria were as follows: (i) conference abstracts, editorials, letters, review articles, or case reports, (ii) studies with insufficient data for estimating the HR (OR) and 95% CI, and (iii) studies did not provide the cut-off value to define "elevated NLR". When there were multiple publications from the same institutions or overlapping patient cohorts, only the most recent or most complete study was included in our analysis to avoid duplicate information.

Qualitative assessment

Quality assessment of the cohort studies was evaluated in each of the acceptable studies in duplicate by independent reviewers (Cheng Zheng and Wu jian) using the Newcastle-Ottawa Scale (NOS). This scale consists of 8 factors and 3 categories: the patient selection, comparability of study groups and assessment of outcomes. A score between 0 and 9 was used to designate the lowest and highest quality studies. Studies labeled with a score of 6 or higher were considered to be of high quality.

Data extraction and management

3 investigators independently evaluated all searched articles, and the relevant information was extracted according to the guidelines of the meta-analysis of Observational Studies in Epidemiology. Any discrepancies were resolved by discussions. Data extracted from eligible studies included first author's name, year of publication, country of origin, number of patients, stage, detection method, cut-off value, tumor characteristics, follow-up period, study outcomes, HRs, and 95% CIs for OS/PFS. If a study reported the results of multivariate and univariate proportional hazard regression analysis, the former was preferred. When the HRs and 95% CIs were not directly reported, we calculated them from the available numerical data according to the methods developed by Parmar et al [20]. Data were extracted from Kaplan-Meier survival curves, and an HR estimate and its variance were reconstructed according to the described method. The Newcastle-Ottawa Scale (NOS) was used to evaluate the study quality. Each study was given a point rating (range: 0-9 points) after discussion of any discrepancies, and a study with a score of 6 or higher was considered a high-quality study.

Statistical analysis

The included studies were divided into two groups for our analyses: those with OS data and those with DFS data. Combined HRs and their 95% CIs were used to estimate the

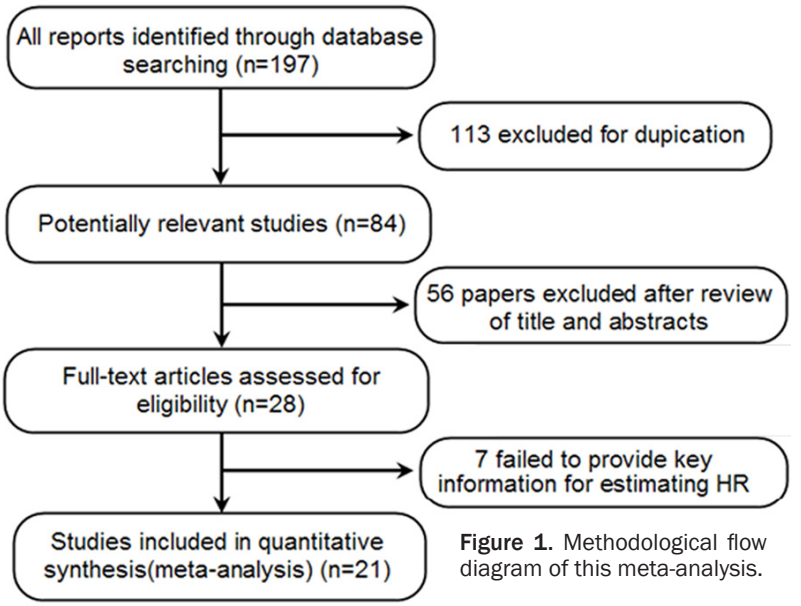

Figure 1. Methodological flow diagram of this meta-analysis.

strength of associations between the NLR level and OS or PFS, while pooled odds ratios (ORs) and their 95% CIs were used to assess the relationships between NLR and clinicopathologic characteristics, including lymph node metastasis, tumor differentiation, TNM stage and CEA levels.

The heterogeneity of combined HRs was determined using Cochran's Q test and Higgins' I-squared statistic. A P<0.05 for the Q-test was considered as significant heterogeneity among the studies. The random-effects model (DerSimonian-Laird method) was used if heterogeneity was observed (P<0.05). Otherwise, the fixed-effects model (Mantel-Haenszel method) was performed to generate pooled HRs/ORs. An observed HR>1 indicated poor prognosis for patients with increased NLR levels, and it was considered to be statistically significant if the 95% CI for the overall HR did not overlap 1. To investigate the potential source of heterogeneity among studies, meta-regression and subgroup analysis was conducted using variables such as study location, ethnicity, analytic method and cut-off value. Publication bias was evaluated by the Begg's funnel plot and Egger's test. To validate the reliability of outcomes, sensitivity analysis was performed by sequentially deleting each individual study to examine the influence of individual dataset on the combine HR. The influence of publication bias on overall effect was estimated using the "trimandfill" method. All statistical calculations were performed by using STATA Version 12.0 software (StataCorp, College Station, TX, USA).

Results

Included eligible studies

Using our search strategy, a total of 84 relevant articles were identified after removing the duplicate records. After our careful evaluation by applying our exclusion criteria mentioned above, 28 studies evaluating the prognostic value of NLR in CRC patients were eligible for this meta-analysis. By full-text reviewing, 2 studies were excluded because of non-English published literatures, and 5 studies were excluded due to a lack of data integrity, including cut-off, HR and 95% CI. The searching results were shown in **Figure 1**. Therefore, 21 studies with 9363 CRC patients who met our inclusion criteria were ultimately included in this meta-analysis. The mean number of patients per study was 446 (range: 50-3731) and the mean or median age ranged from 56 to 70 year old. Most of the studies were performed within the past 5 years, and 6 trials were reported in 2013. 17 articles provided OS data, whereas PFS was only reported in 14 studies. Each individual study reported a "high" NLR level with survival data, and the NLR cut-off values applied in the studies were inconsistent. The main features of the included studies were listed in **Table 1**.

Impact of NLR on OS in CRC patients

18 eligible studies containing a total of 8795 patients provided the information of OS in CRC patients. As shown in **Figure 2A**, an elevated level of pre-treatment NLR was significant associated with the enhanced mortality risk of CRC patients with a random-effects model (combined HR=1.918, 95% CI=1.585-2.323, P<0.001) despite exhibiting heterogeneity among studies (I^2=69.4%, $p_{heterogeneity}$<0.001). Subgroup analyses by type of treatment

Table 1. Main features of included studies in our meta-analysis

Study	Year	Country	Racial	Number	Treatment	Study period	Mean/median Ages (years)	TNM	Follow-up Mean/median (months)	Outcome measured	Multivariate analysis	NLR cut-off	NOS score
Leitch	2007	UK	Western	149	resection	1998-2006	<65 ys: N=48; 65-74 ys: N=52; >75 ys: N=49	I-III	48 (36-73)	OS	Yes	5	6
				84	chemotherapy			IV					
Halazun	2007	UK	Western	440	resection	1996-2006	64 (32–88)	NR	24 (11-97)	OS	Yes	5	6
										PFS			
Kishi	2009	USA	Western	200	chemotherapy-resection	1997-2007	56 (26–81)	NR	28 (2-102)	OS	Yes	5	7
				90	chemotherapy				16 (3-99)				
Ding	2010	China Mainland	Asian	141	resection	2002-2006	61 (24–80)	II	58 (43-74)	PFS	Yes	4	7
Liu	2010	China Mainland	Asian	123	resection	1999-2006	mean: 61.2 range: (28-81)	I-IV	NR	OS	Yes	2	5
Chua	2011	Australia	Western	171	chemotherapy	1999-2007	61 (33–84)	NR	NR	OS	Yes	5	5
										PFS			
Hung	2011	Taiwan	Asian	1039	resection	1995-2005	>65 ys: N=610; <65 ys: N=429	II	74.5 (45.9-136.8)	OS	Yes	5	6
										PFS			
Zhang	2011	China Mainland	Asian	92	radiofrquency ablation	2000-2008	59 (43–78)	I-IV	27.1 (5-62)	OS	Yes	5	6
										PFS			
Carruthers	2012	UK	Western	115	chemoradia-tion	2000-2005	63.8 (32.3-81.1)	NR	31.7	OS	Yes	5	4
										PFS			
Chiang	2012	Taiwan	Asian	1943	resection (colon)	1998-2003	NLR<3: meadian=62.3; NLR>3: median=63.9	I-III	96.2 (11.6-139.1)	OS	Yes	3	7
				1788	resection (rectal)	1998-2003							
Kaneko	2012	Japan	Asian	50	chemotherapy	2005-2010	60 (30–81)	NR	17 (0.77-61.6)	OS	Yes	4	4
										PFS			
Kwon	2012	Korea	Asian	200	resection	2005-2008	64 (26–83)	I-IV	33.6	OS	Yes	5	6
Guthrie	2013	UK	Western	206	resection	2006-2010	<65 ys: N=74; 65-74 ys: N=79; >75 ys: N=53	I-IV	36 (12-71)	OS	No	5	6
He	2013	China Mainland	Asian	243	chemotherapy	2005-2010	56 (18–83)	IV	21.87	OS	Yes	3	6
								I-IV		PFS			
Mallappa	2012	UK	Western	297	resection	2003-2004	70 (23–93)	I-IV	3.35 (0.1-8)	PFS	Yes	5	5
Zeman	2013	Poland	Western	130	resection	2001-2009	60 (33-82)	IV	39.3 (2-156)	PFS	Yes	5	4
Son	2013	Korea	Asian	624	resection	2005-2007	60	I-III	42 (1-66)	OS	Yes	5	6
										PFS			
East	2013	Ireland	Western	50	resection	2000-2010	NR	I-IV	42	OS	Yes	3.4	5

Abseger	2013	Austria	Western	504	resection	2002-2011	65 (27-95)	II-III	45 (1-108)	OS	Yes	4	6
										PFS	No		
Toiyam	2013	Japan	Asian	84	chemotherapy-resection	2001-2012	64.5 (33-80)	I-III	56 (2-147)	OS	Yes	5	6
										PFS	No		
Paik	2013	Korea	Asian	600	resection	2006-2009	62.3	I-IV	27.4 (1-72)	OS	No	5	6
										PFS	No		

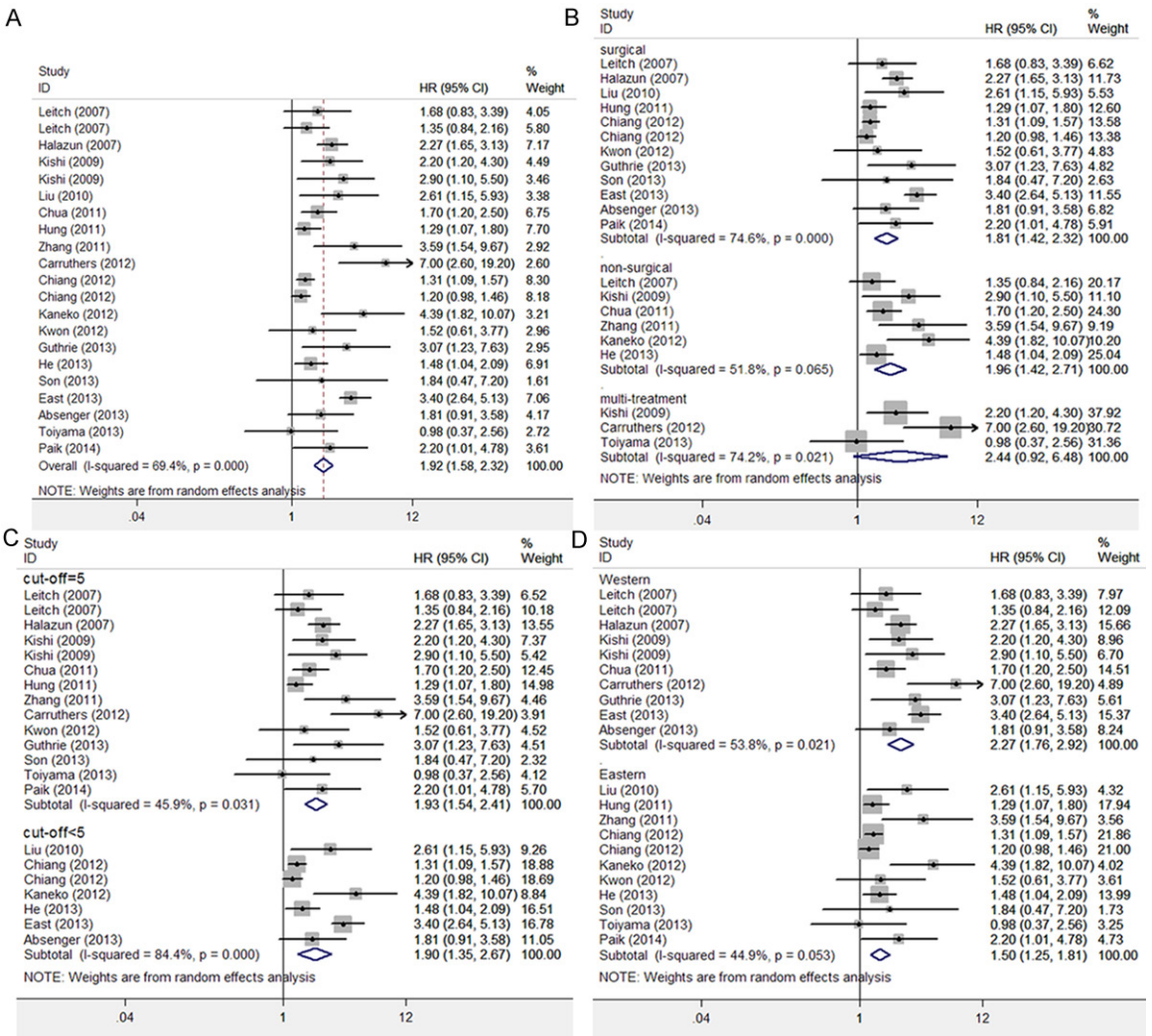

Figure 2. Forest plots of the associations between NLR and the OS of patients with CRC. A. Stratified forest plots of the relationships between NLR and OS; B. Subgroup analysis of patients who received different treatments; C. Subgroup analysis of studies with NLR cut-off values of 5 or less than 5; D. Subgroup analysis of the location including 9 Eastern and 8 Western studies.

revealed that the prognostic role of NLR for OS was favored in most studies, and the pooled estimate of NLR was significant for all subgroups including resection group (HR=1.814, 95% CI: 1.421-2.316, I^2=74.6%, $P_{heterogeneity}$< 0.001), non-surgical group (HR=1.962, 95% CI: 1.420-2.713 I^2=51.8%, $P_{heterogeneity}$=0.065) and multi-treatment group (HR=2.436, 95% CI: 1.248-5.111, I^2=0.0%, $P_{heterogeneity}$=0.326) (**Figure 2B**). Although the NLR cut-off was different for each study, we divided all of the studies into two groups by defining the cut-off of elevated NLR (5 vs less than 5). Our results indicated that the pooled estimation of NLR was significant for both groups (5 group, HR=1.928, 95% CI: 1.544-2.407, I^2=45.9%, $P_{heterogeneity}$=0.031; less than 5 group, HR=1.897, 95% CI: 1.349-2.667, I^2=84.4%, $P_{heterogeneity}$<0.001) (**Figure 2C**). In a subgroup analysis based on location, a negative predictor of NLR for OS was found in the Eastern (HR=1.502, 95% CI: 1.247-1.808, I^2=44.9%, $P_{heterogeneity}$=0.053) and Western group (HR=2.271, 95% CI: 1.764-2.923, I^2=53.8%, $P_{heterogeneity}$=0.021) (**Figure 2D**).

To further explore the source of heterogeneity, meta-regression was conducted by treatment, cut-off value and location. Our results indicated that the location had significant heterogeneity (P=0.001), which could potentially explain 42.45%. We also found the type of treatment partially explained the source of the heteroge-

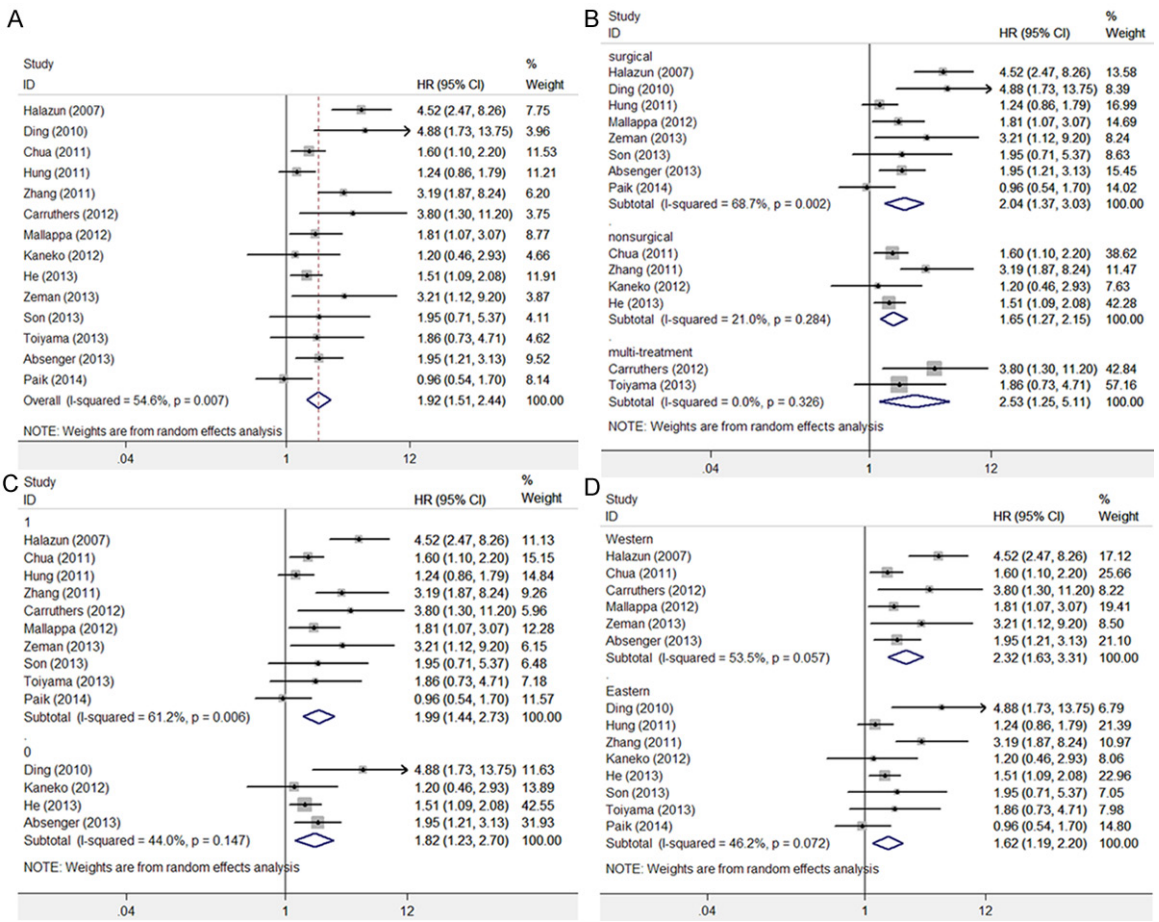

Figure 3. Forest plots of the associations between NLR and the PFS of patients with CRC. A. Stratified forest plots of the relationships between NLR and PFS; B. Subgroup analysis of patients who received different treatments; C. Subgroup analysis of studies with NLR cut-off values of 5 or less than 5; D. Subgroup analysis of the location including 9 Eastern and 8 Western studies.

neity (P=0.02). Other factors had no obvious role in heterogeneity because they had adjusted R-squared values less than 5%.

Impact of NLR on PFS in CRC patients

14 eligible articles including a total of 4530 patients presented the information of pre-treatment NLR and PFS in CRC. The prognostic role of high NLR for PFS was shown in **Figure 3**. Our data showed that elevated NLR predicted a worse outcome for PFS with the combined HR of 1.918 (95% CI: 1.508-2.438, I^2=54.6%, $P_{heterogeneity}$=0.007) (**Figure 3A**). The subgroup analyses were also performed based on treatment, NLR cut-off value and location (**Figure 3B-D**). All subgroup analyses implied that an elevated NLR level was associated with the poor PFS, which were similar to those subgroup analyses for OS. Due to the high heterogeneity, meta-regression analyses demonstrated that "location" could explain 49.48% heterogeneity (P=0.001), and different types of treatment could also partially account for the source of the heterogeneity (P=0.046). These results indicated that location and type of treatment were the main sources of heterogeneity.

Sensitivity analysis

To test the robustness of HR estimates, sensitivity analyses were done by the sequential removal of individual studies. Our results indicated that the pooled effects of NLR were not affected by omitting each individual study in the OS and PFS groups, which verified the stability of our meta-analyses (**Figure 4A**, **4B**).

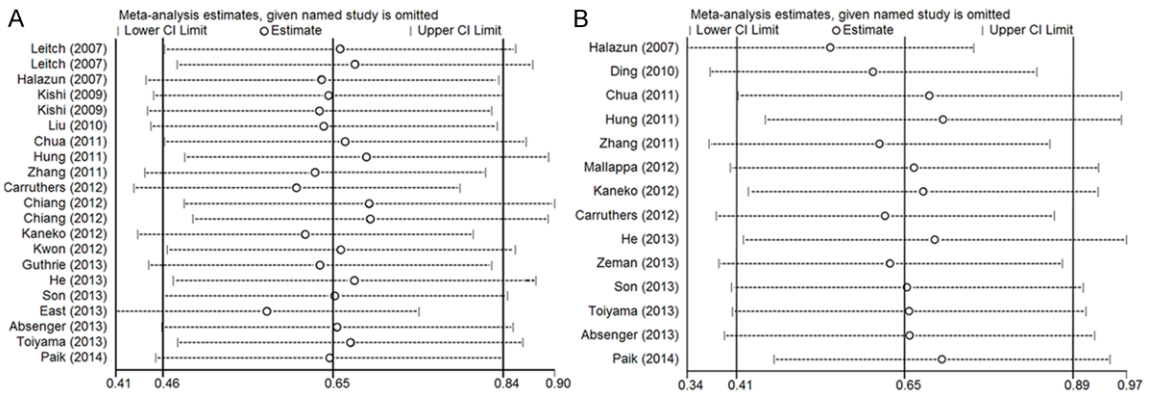

Figure 4. Sensitivity analyses in our meta-analysis. A. OS; B. PFS in CRC patients.

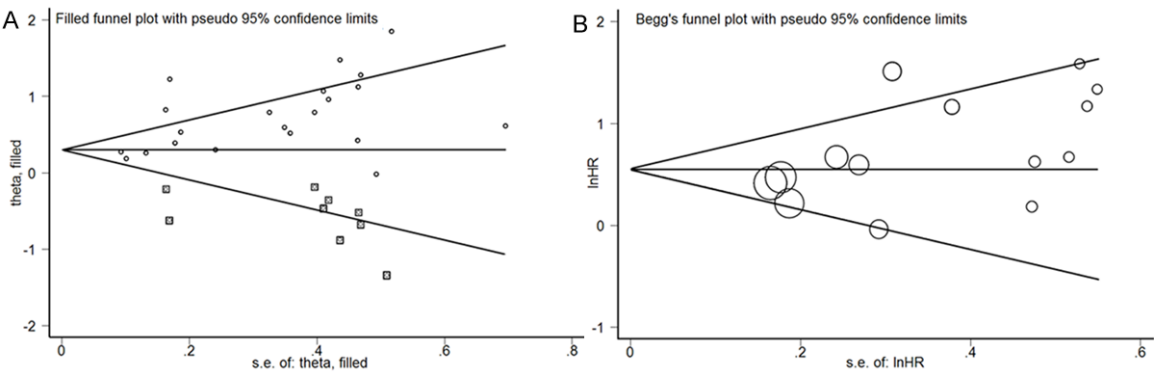

Figure 5. Funnel plots for publication bias in our meta-analysis. A. OS; B. PFS in CRC patients.

Publication bias

We used Begg's funnel plot and Egger's test to assess the publication bias in our literatures. The shape of the funnel plots indicated that there was evidence of publication bias for OS (P=0.008) and without bias for PFS (P=0.051). After using the trim and fill method, our results showed that the adjusted combined HR concerning the relationships between elevated NLR and OS (HR=1.405, 95% CI: 1.139-1.732) was attenuated but remained significant, indicating the stability of our pooled results (**Figure 5A**, **5B**).

Relationships between NLR and clinicopathological parameters in CRC patients

As shown in **Figure 6A**, 5 eligible studies showed that the elevated pre-treatment NLR level was not associated with lymph node metastases (OR=0.99, 95% CI: 0.908-1.069, P=0.723) with no obvious heterogeneity (I^2<0.01%, P=0.697). However, our analysis indicated that high NLR in patients with CRC was associated with the following clinicopathological parameters: tumor differentiation (95% CI: 1.220-1.99, **Figure 6B**), advanced TNM stage (OR=1.248, 95% CI: 1.055-1.477, P=0.01, **Figure 6C**) and CEA levels (OR: 1.502; 95% CI: 1.320-1.710, P<0.001, **Figure 6D**) with no heterogeneities.

Discussion

Experimental and clinical data indicate that chronic inflammation has been shown to play critical roles in cancer development [21, 22]. Inflammation participates in tumor development via multiple mechanisms, including initiation, malignant conversion, the promotion of angiogenesis, invasion, and metastasis [23-25]. Though it has been confirmed that the presence of systemic inflammatory response may lead to poorer outcomes by many studies, the mechanisms of NLR effects the tumor pro-

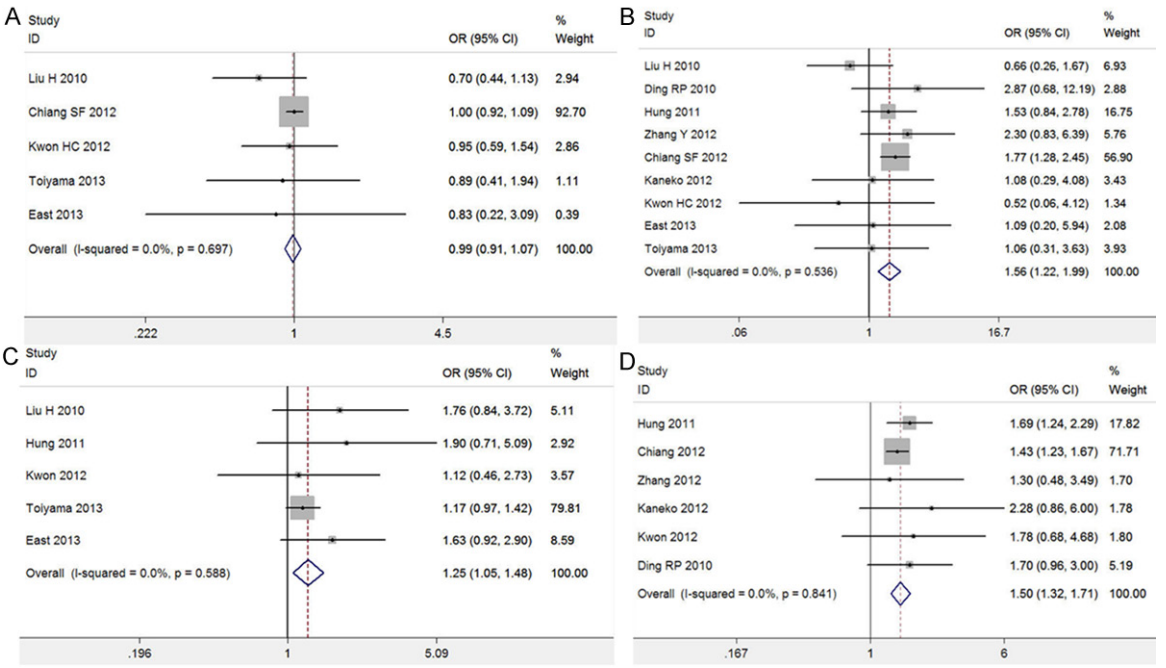

Figure 6. Forest plots of the associations between NLR and clinicopathological parameters. A. Lymph node metastasis; B. Tumor differentiation; C. TNM stage; D. An elevated CEA level in CRC patients.

gression remains undefined. Some close attentions have recently been focused on the associations between NLR and OS of patients with cancer. According to the recent studies, there are several potential explanations. One possible explanation is that patients with a high NLR level usually have an enhanced neutrophil response [26]. Increased numbers of circulating neutrophils have been shown to produce and secrete a vast majority of pro-angiogenetic factors and cytokines, such as interleukin-6, tumor necrosis factor, matrix metalloproteinase (MMP) and vascular endothelial growth factor (VEGF), which may contribute to the progression of malignancy and lead to a poor prognosis [27-29]. Others studies also reported that elevated NLR related to the increased interleukin-17 and the peritumoral infiltration of macrophages, which may induce elevated circulating concentrations of several cytokines (IL-1ra, IL-6, IL-7, IL-12, interferon γ, interferon γ-induced protein, macrophage inflammatory protein 1β, and platelet-derived growth factor) [30-32]. Another explanation is that patients with elevated NLR usually have relative lymphocytopenia, which always associates with a poorer lymphocyte-mediated immune response to tumors [33]. Because the host immune response to tumors mainly depends on lymphocytes, increased NLR attenuates lymphocyte-mediated anti-tumor immune reactions and promotes the recurrence and metastases of tumors [34]. Such a vicious cycle may lead to a poorer prognosis for affected patients. Furthermore, elevated neutrophils, which contribute to suppressing the cytolytic activity of lymphocytes, cytotoxic T8 cells and natural killer cells, can suppress immune surveillance and affect tumor growth in a negative way [35, 36].

Recently, there has been increasing evidence that inflammation plays an important role at the earliest stages of neoplastic progression and associates with a poor outcome in patients with cancer [37]. Emerging studies have also examined the prognostic value of various inflammation-based factors including CRP, Glasgow Prognostic Score (GPS), PLR and NLR in cancer populations [38-40]. Changes in blood NLR may be a useful index of predicting outcomes in patients with cancer, though reliable biomarkers are still unclarified. Because NLR assessment may be obtained easily from routine blood tests, it has the advantage of more cost-effectiveness in clinical practice. Therefore, elevated NLR, which has local and systemic effects in the microenvironment, may

reflect a novel inflammatory response and is associated with poor prognosis in cancer.

The prognostic value of NLR in CRC remains controversy. Inconsistent data have emerged regarding the prognostic value of NLR for predicting the OS and PFS in CRC patients [18, 19]. In addition, the relationships between NLR and tumor clinicopathological variables also remain contradictory and not convincing. We thus conducted this meta-analysis to obtain a precise evaluation of elevated NLR in CRC.

Previously, a meta-analyses published by Li et al. had investigated the associations between elevated NLR and higher risks for OS and RFS poorer outcome in patients with CRC [41]. Compared with the preceding of meta-analysis, our study contained 21 studies with 9,363 patients, more than 16 studies of 6,859 patients in Li's study. In the current meta-analysis, preliminary combined HRs showed that high NLR was significantly associated with a poor OS (HR=1.918, 95% CI=1.585-2.323, P<0.001) and PFS (HR=1.918, 95% CI: 1.508-2.438, P=0.007) in CRC patients, which was similar to the results of Li et al. But differently, we performed the main subgroup analyses based on the location, treatment and cut-off value. Despite heterogeneity, our data indicated that none of the subgroup estimations altered the prognostic role of NLR on OS and PFS in CRC. All of the subgroup estimations indicated that increased NLR could lead to a poorer OS. Furthermore, meta-regression was performed to explore potential sources of heterogeneity. Our results showed that the main heterogeneity was primarily due to treatment and NLR cut-off value for OS. Some studies used NLR cut-offs according to the previous evidence, while others set the cut-off by using receiver operating characteristic (ROC) curve analyses. However, subgroup analyses demonstrated that the results were also consistent whether using 5 (HR 1.98, 95% CI: 1.58-2.49, I^2=46.8%) or less than 5 (HR 1.90, 95% CI: 1.35-2.67, I^2=84.4%) as the cut-off value. Moreover, studies concerning nonsurgical treatment suggested that patients were in a higher clinical tumor stage, which had an impact on heterogeneity.

We also conducted the pooled analyses of the relationships between elevated NLR and clinicopathologic characteristics in CRC patients. Similar to the previous study [41], our results suggested that increased NLR was closely related to tumor differentiation, higher incidence of CEA≥5 ng/ml. But interestingly, our data implied that increased NLR level was also significantly associated with the advanced TNM stage of CRC. These indicators such as tumor differentiation, CEA level and TNM stage were all the most powerful variables, which were associated with CRC metastases and recurrences. In other words, increased NLR was significantly associated with the highly aggressive phenotype of CRC, which could be seen as a potential prognostic factor.

When interpreting the results of our present meta-analysis, certain limitations cannot be ignored. Firstly, the majority of enrolled studies were retrospective, which may lead to some biases. Secondly, the cut-off value for defining high NLR was set differently among studies, which led to between-study heterogeneity and might affect our results. Thirdly, in this analysis, only articles published in English language were included which may cause a potential bias. Because positive studies were more likely to be published in English, while negative results tended to be published in native language. Meanwhile, negative or small-sample studies were less likely to be published. Thus, the pooled results might be somehow overestimated. Finally, in the absence of directly reported HRs and corresponding 95% CIs, these data were calculated from an available numerical index from survival curves. The reliability of the pooled analyses may thus be impaired. Due to these limitations, our results should be interpreted with caution. Likewise, high-quality and large multi-center prospective studies are needed to obtain more convincing evidence in the future.

Though larger well-designed studies with more ethnic groups and larger population studies are required, to the best of our knowledge, this is the first comprehensive meta-analysis to evaluate the prognosis role of NLR in CRC. Our results demonstrated that elevated NLR was a negative predictor for OS and PFS in CRC. Meanwhile, elevated NLR was significantly associated with the presence of tumor differentiation, TNM stage and a higher incidence of CEA≥5 ng/ml. These results suggested that NLR, which can be examined in a simple and invasive way as a common hematologic marker,

may serve as a novel and effective prognostic biomarker in CRC. NLR can be a potential direction for developing diagnostic and therapeutic approaches in CRC.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Ping Chen, Department of General Surgery, Ningbo No. 2 Hospital, Ningbo, China. E-mail: chenpingmaster@yeah.net; Dr. Qiao-Ming Zhi, Department of General Surgery, The First Affiliated Hospital of Soochow University, Suzhou 215006, China. E-mail: strexboy@163.com

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