

# Prognostic significance of elevated preoperative neutrophil-to-lymphocyte ratio for patients with colorectal cancer undergoing curative surgery

## A meta-analysis

Hongcai Li, MM\*, Yan Zhao, MM, Fengying Zheng, MM

### Abstract

**Background:** Preoperative neutrophil-to-lymphocyte ratio (NLR) has been suggested as a useful predictive factor for prognosis in patients with various cancers. However, the prognostic value of NLR in patients with colorectal cancer (CRC) remains controversial. Therefore, the goal of this study was to perform a meta-analysis to evaluate the prognostic value of NLR in patients with CRC undergoing curative surgery.

**Methods:** PubMed, EMBASE and Cochrane Library databases were searched to screen the relevant studies. Pooled hazard ratio (HR) with 95% confidence interval (CI) was used to assess the associations of preoperative NLR and overall survival (OS), disease-free survival (DFS), recurrence free survival (RFS) and disease specific survival (DSS) by STATA 13.0 software.

**Results:** Sixteen studies involving 5897 patients were included in our meta-analysis. Our pooled results demonstrated that high NLR was associated with poor OS (HR: 1.66, 95%CI: 1.36–2.02,  $P < .001$ ), DFS (HR = 1.54, 95%CI: 1.18–2.02,  $P = .002$ ), RFS (HR = 2.31, 95%CI: 1.68–3.17,  $P < .001$ ) and DSS (HR = 2.27; 95% CI: 1.75–2.96,  $P < .001$ ). When the patients were stratified according to country, sample size, NLR cut-off, follow up and postoperative chemotherapy, high NLR was still significantly correlated with OS. The limitation was that the majority of enrolled studies were retrospective.

**Conclusion:** Preoperative NLR may be an effective predictive biomarker for prognosis in patients with CRC. Detection of NLR may be beneficial to identify the high-risk patients who need other antitumor therapies in addition to surgery.

**Abbreviations:** CI = confidence intervals, CRC = colorectal cancer, DFS = disease-free survival, DSS = disease specific survival, HR = hazard ratio, IL = interleukin, NLR = neutrophil-lymphocyte ratio, NOS = Newcastle–Ottawa Scale, OS = overall survival, PRISMA = Preferred Reporting Items for Systematic Review and Meta-analysis, RFS = recurrence free survival, TNM = tumor-node-metastasis.

**Keywords:** colorectal cancer, meta-analysis, neutrophil-to-lymphocyte ratio, prognosis, survival

## 1. Introduction

Colorectal cancer (CRC), including colon and rectum cancer, is the most common gastrointestinal malignant tumor, with an estimated 135,430 new cases diagnosed and 50,260 death in 2017 in the

United States.<sup>[1]</sup> Surgery resection is considered as the cornerstone of curative therapy for CRC and may provide a good prognostic outcome compared with unresectable patients.<sup>[2]</sup> However, clinical studies indicate the prognosis following surgery differs substantially in different patients. Therefore, it is essential to identify preoperative biomarkers that are beneficial for assessment of treatment efficacy of patients and thus provide reference for schedules of the follow-up medical treatment program.

Conventionally, prognosis of patients with CRC can be predicted by histopathological parameters, including tumor-node-metastasis (TNM) staging, cell differentiation, tumor grade, Dukes' stage or tumor type.<sup>[3,4]</sup> Nevertheless, it is reported that heterogeneous prognostic outcomes still exist in patients with the same stage and tumor grade,<sup>[5]</sup> indicating their inaccuracy for predicting the risk of patient' mortality. Therefore, more effective, alternative biomarkers need to be identified for prognostic prediction of CRC patients.

Recently, accumulating evidence suggests that inflammation may play important roles in the development and progression of CRC.<sup>[6,7]</sup> Elevated inflammation promotes proliferation, migration, invasiveness of malignant CRC cells, while silencing of cytokines [interleukin (IL)-21, IL-8 or IL-32] reversed these effects.<sup>[8,9]</sup> Thus, systemic immune cells (such as neutrophils and lymphocytes, both of which can be used to calculate the neutrophil-lymphocyte ratio, NLR) and their released

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inflammatory cytokines may be potential predictors for prognosis of CRC patients.<sup>[9,10]</sup> This hypothesis has been demonstrated by several studies. For example, Li et al. demonstrated that CRC patients with a higher NLR had a lower overall survival (OS; HR: 1.846, 95% confidence intervals [CI]: 1.159–2.941,  $P = .01$ ) and DFS (HR: 1.855, 95% CI: 1.164–2.954,  $P = .009$ ).<sup>[11]</sup> Similarly, Ishizuka et al proved that the higher level of NLR was associated with poorer OS (HR: 1.811, 95% CI: 1.229–2.669,  $P = .003$ ).<sup>[12]</sup> However, the inconsistent results were also reported, with the study of Wei et al as an example in which Cox regression model showed NLR was not an independent prognostic factor for OS ( $P = .457$ ) and DFS ( $P = .856$ ). Therefore, the prognostic value of NLR in CRC remains controversial and it is necessary to further evaluate the prognostic significance of NLR in patients with CRC by performing a meta-analysis that can comprehensively analyze all related articles and may achieve a more convinced conclusion.

Although previous studies have investigated the prognostic value of NLR for survival in patients with CRC, all of them focused on various treatment methods,<sup>[13–15]</sup> not only on patients undergoing surgical resection, which was the goal of this study.

## 2. Materials and methods

### 2.1. Literature search strategy

A systematic literature search was performed by using PubMed, EMBASE and Cochrane Library databases to evaluate the prognostic value of NLR in patients with CRC. The key words used were the combinations of the following search terms: (“neutrophil to lymphocyte ratio” OR “neutrophil-to-lymphocyte ratio” OR “neutrophil lymphocyte ratio” or “NLR”) AND (“colon cancer” OR “CRC” OR “rectal cancer” OR “CRC”) AND (“surgery”) or (“resection”). The deadline of our primary search was April 2018. Furthermore, the reference lists of identified publications were also manually scanned to further screen potential related articles. The protocol adhered to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) Guidelines.<sup>[16]</sup> Ethics approval was not necessary as this is a meta-analytic study.

### 2.2. Inclusion and exclusion criteria

Studies were considered eligible if they met the following inclusion criteria:

1. CRC was diagnosed by pathological examination;
2. curative surgery was performed for CRC patients;
3. NLR was measured preoperatively;
4. the NLR was measured by blood-based methods;
5. the associations between NLR and prognosis related outcomes (OS, DFS, recurrence-free survival [RFS] and disease-specific survival [DSS]) were investigated;
6. HR, 95%CI could be obtained by multivariate Cox regression analysis; and
7. only English publication languages.

The exclusion criteria were:

1. abstracts, letters, reviews, case reports, comments or nonhuman studies;
2. insufficient prognosis data to estimate HR and 95%CI;
3. failed to provide the cut-off value;
4. adjuvant chemoradiotherapy was received preoperatively;
5. surgery was not performed;

6. NLR was tested after surgery;
7. combined with other cancers; and
8. literature written in other language.

### 2.3. Data extraction

Two authors (HCL and YZ) independently screened eligible studies from the databases and extracted the following data: author name, publication year, country, sampling time, sample size, patients' sex, age, pathological stage, postoperative treatment, cut-off level, follow-up, and HRs and 95% CIs for NLR in multivariable analysis and prognosis (OS, DFS, RFS and DSS). During study identification and data abstraction, discrepancy was resolved through discussion or the third researcher (FYZ).

The quality of the included studies was assessed using the Newcastle–Ottawa Scale (NOS)<sup>[17]</sup> that consists of 3 domains: patients selection (4 items: representativeness of the exposed cohort; selection of the nonexposed cohort; assessment of exposure; and outcome not present at start of study), comparability (2 items, comparability of cohorts on the basis of the design; or analysis), and outcome assessment (3 items: assessment of outcome; follow-up long enough for outcomes; and adequacy of follow-up). A positive result on any 1 of them was counted as 1 point. Studies with the scores greater than or equal to 6 were considered to be of high-quality.

### 2.4. Statistical analysis

Heterogeneity between the trials was tested by using Cochrane's  $Q$  and  $I^2$  statistic. A significant heterogeneity was defined as  $P < .10$  and  $I^2 > 50\%$ , after which a random-effects model was chosen to pool the study results;  $P \geq .10$  and  $I^2 \leq 50\%$  were considered the values that indicated homogeneity, and thus a fixed-effects model was subsequently applied. HRs with 95% CI for NLR in multivariable analysis were extracted from each study to generate a pooled HR. Egger's linear regression test and funnel plots were used to evaluate publication bias.<sup>[18]</sup> The influence of publication bias on the overall effect was assessed by the “trim and fill” method.<sup>[19]</sup> Sensitivity analysis was performed by omitting 1 study in each turn to investigate the influence of a single study on the overall HR estimates. In addition, a subgroup analysis was also performed according to stratification of country, sample size, NLR cut-off point, follow up time and postoperative chemotherapy. All statistical analyses were performed using STATA 13.0 (STATA Corporation, College Station, TX).  $P < .05$  was considered to be statistically significant.

## 3. Results

### 3.1. Description of the included studies

A flowchart of the literature search is shown in Figure 1. The initial search identified 1011 studies. After removal of duplicates, 809 studies were excluded. Of the remaining 202 studies, 105 were further excluded by reading titles and abstracts: surgery not performed ( $n = 6$ ), no prognosis information ( $n = 33$ ), not CRC ( $n = 17$ ), NLR not evaluated ( $n = 11$ ), drug therapy assessed ( $n = 1$ ), combined with other cancers ( $n = 3$ ), review ( $n = 11$ ), descriptive study ( $n = 1$ ), comments ( $n = 4$ ), non-English ( $n = 14$ ), non-preoperative NLR ( $n = 1$ ), case ( $n = 1$ ) and animal studies ( $n = 2$ ). Ninety-seven full-text articles were then downloaded to assess their eligibility, in which 81 were excluded

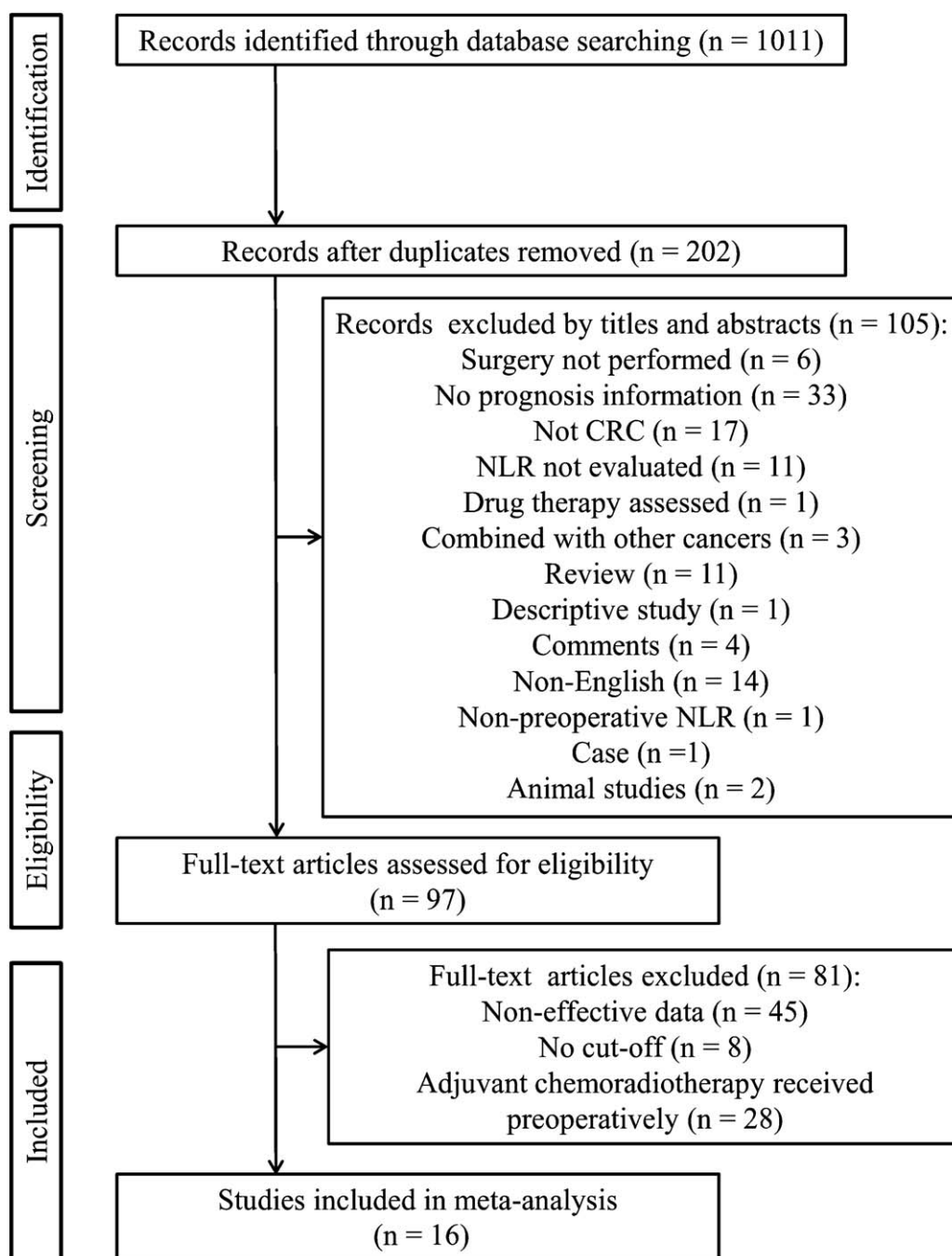


Figure 1. Flowchart of searching relevant studies used in this meta-analysis.

because non-effective data could be collected ( $n=45$ ), cut-off value was not recorded ( $n=8$ ) and adjuvant chemoradiotherapy was received preoperatively ( $n=28$ ). Ultimately, 16 studies [5897 patients/2385 (40.4%) females] published between 2010 and 2018 were included for this meta-analysis.<sup>[11,12,20–33]</sup> The characteristics of the included studies are summarized in Table 1. Five studies were performed in China, 3 in Japan, 2 in Korea, 3 in the UK, one in Australia, 1 in Turkey and 1 in USA. The NLR was calculated on the basis of preoperative laboratory data using the white blood cell (WBC) differential counts with dividing the neutrophil count by the lymphocyte count. All studies used multivariate analysis results to pool HR and 95%CI. The cut-off

value for NLR was  $<3$  in 4 studies,  $\geq 3$  in 7 studies,  $\geq 4$  in 1 study and  $\geq 5$  in 4 studies. According to the NOS score, all the studies were considered to be in high-quality, ranging from 6 to 8 (Table 2).

### 3.2. Meta-analysis results

There were 11 studies to investigate the prognostic significance of preoperative NLR for OS in CRC patients. A significant heterogeneity was present between the studies ( $I^2=56.3\%$ ,  $P=.011$ ) and thus a random-effects model was chosen to pool the study results. A pooled HR of 1.66 (95%CI: 1.36–2.02,  $P < .001$ ;

**Table 1**  
**Characteristics of all eligible studies.**

Study	Year	Country	Time	No.	F/M	Age (year)	NLR cut-off	TNM stage	Postoperative chemotherapy	Follow-up (months)	Outcome
Wei Y	2018	China	2003–2013	569	262/307	63	OS:1.975 DFS:2.585	I-III	Unclear	52	OS, DFS
Borazan E	2017	Turkey	2003–2013	95	40/55	59.79	3	I-III	No	20.77	OS
Murphy C	2017	Australia	2000–2011	488	222/266	72	5	II	Unclear	Unclear	OS, DFS
Pedrazzani C	2017	USA	2005–2013	603	81/118	Unclear	3.5	I-IV	Unclear	Unclear	OS, DFS
Ishizuka M	2016	Japan	2006–2013	627	227/400	Unclear	2.9	0-IV	Unclear	30	OS
Li H	2016	China	2008–2010	140	59/81	60	2.3	I-IV	Unclear	42	OS, DFS
Nagasaki T	2015	Japan	2004–2012	201	61/140	61	3	III-IV	Partial yes	Unclear	OS
Pine JK	2015	UK	2000–2004	358	156/202	74	5	I-IV	Unclear	>48	OS, DFS
Seong MK	2015	Korea	2007–2013	265	102/163	67	2.4	I-IV	Yes	39	DSS, DFS
Shin JS	2015	Korea	2003–2011	268	111/158	63	3	I	Unclear	70	DSS, DFS
Malietzis G	2014	UK	2006–2011	506	210/296	Unclear	3	Unclear	No	45	OS, DFS
Ying HQ	2014	China	2005–2010	205	144/61	>60	3.12	I-III	Partial yes	Unclear	OS, DSS, RFS
Maeda K	2013	Japan	2001–2009	94	43/51	60	3	IV	Partial yes	30	DFS
Mallappa S	2013	UK	2003–2004	297	140/157	70	5	I-IV	Unclear	40	RFS
Hung HY	2011	China	1995–2005	1040	479/561	Unclear	5	II	No	74.5	OS, DFS
Ding PR	2010	China	2002–2006	141	48/93	61	4	II	No	58	RFS

DFS=disease-free survival, DSS=disease-specific survival, F=female, M=male, NLR=neutrophil to lymphocyte ratio, OS=overall survival, RFS=recurrent-free survival.

Fig. 2) showed that patients with an elevated NLR were expected to have lower OS after treatment.

There were 9 studies to investigate the prognostic significance of preoperative NLR for DFS in CRC patients. A significant heterogeneity was detected between these studies ( $I^2=52.3\%$ ,  $P=.032$ ) and thus a random-effects model was applied to pool the study results. A pooled HR of 1.54 (95%CI: 1.18–2.02,  $P=.002$ ; Fig. 3) showed that patients with an elevated NLR were associated with lower DFS after treatment.

There were 3 studies to investigate the prognostic significance of preoperative NLR for RFS in CRC patients. No significant heterogeneity was present between these studies ( $I^2=0\%$ ,  $P=.424$ ) and thus a fixed-effects model was adopted to pool the study results. A pooled HR of 2.31 (95%CI: 1.68–3.17,  $P<.001$ ; Fig. 4) showed that patients

with an elevated NLR were correlated with lower RFS after treatment.

There were 4 studies to investigate the relationship between preoperative NLR and DSS in CRC patients. No evidence heterogeneity was observed between these studies ( $I^2=0\%$ ,  $P=.451$ ) and thus a fixed-effects model was adopted to pool the study results. The pooled estimates demonstrated DSS was significantly worse in the high NLR group compared with the lower NLR group after treatment (HR=2.27; 95% CI: 1.75–2.96,  $P<.001$ ; Fig. 5).

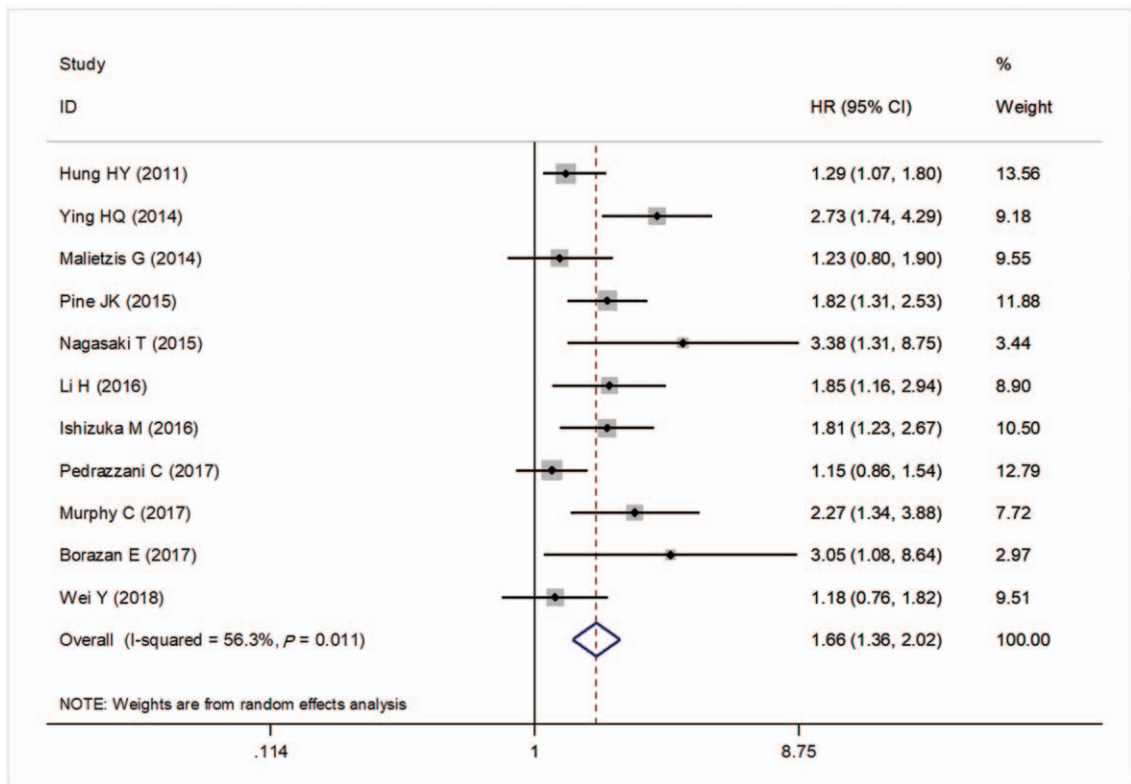
**3.3. Publication bias**

Because heterogeneity was present in studies to evaluate the prognostic significance of preoperative NLR for OS and DFS,

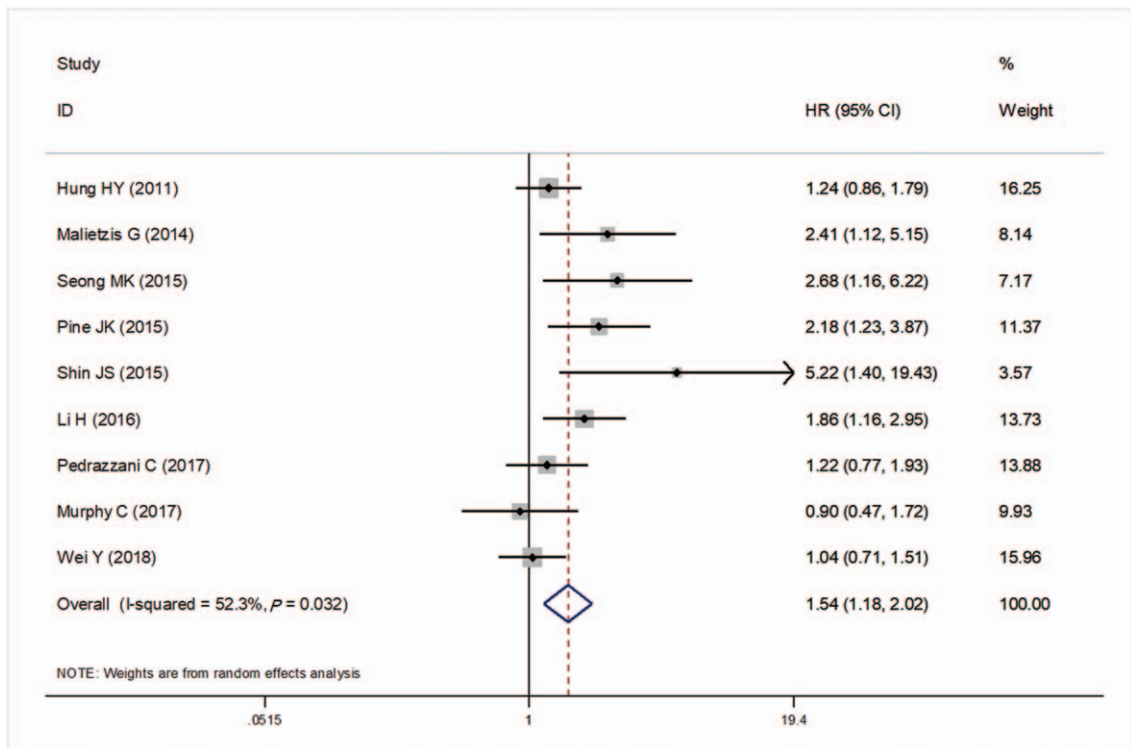
**Table 2**  
**Quality of the included studies based on the Newcastle–Ottawa scale.**

Study	Selection				Comparability		Outcome			Total scores
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Assessment of exposure	Outcome not present at start of study	Comparability of cohorts on the basis		Assessment of outcome	Follow-up long enough for outcome	Adequacy of follow-up	
					Design	Analysis				
Wei Y	+	+	+		+		+	+	+	7
Pedrazzani C	+	+	+		+		+	+		6
Li H	+	+	+		+	+	+	+	+	8
Seong MK	+	+	+		+	+	+	+	+	7
Ishizuka M	+	+	+		+		+	+		6
Pine JK	+	+	+		+		+	+	+	7
Ying HQ	+	+	+		+	+	+	+		7
Mallappa S	+	+	+		+		+	+	+	8
Murphy C	+	+	+		+		+	+		6
Ding PR	+	+	+		+	+	+	+	+	8
Nagasaki T	+	+	+		+	+	+	+		7
Shin JS	+	+	+		+	+	+	+	+	8
Malietzis G	+	+	+		+		+	+	+	8
Borazan E	+	+	+		+	+	+	+		6
Maeda K	+	+	+		+		+	+		6
Hung HY	+	+	+		+	+	+	+	+	8

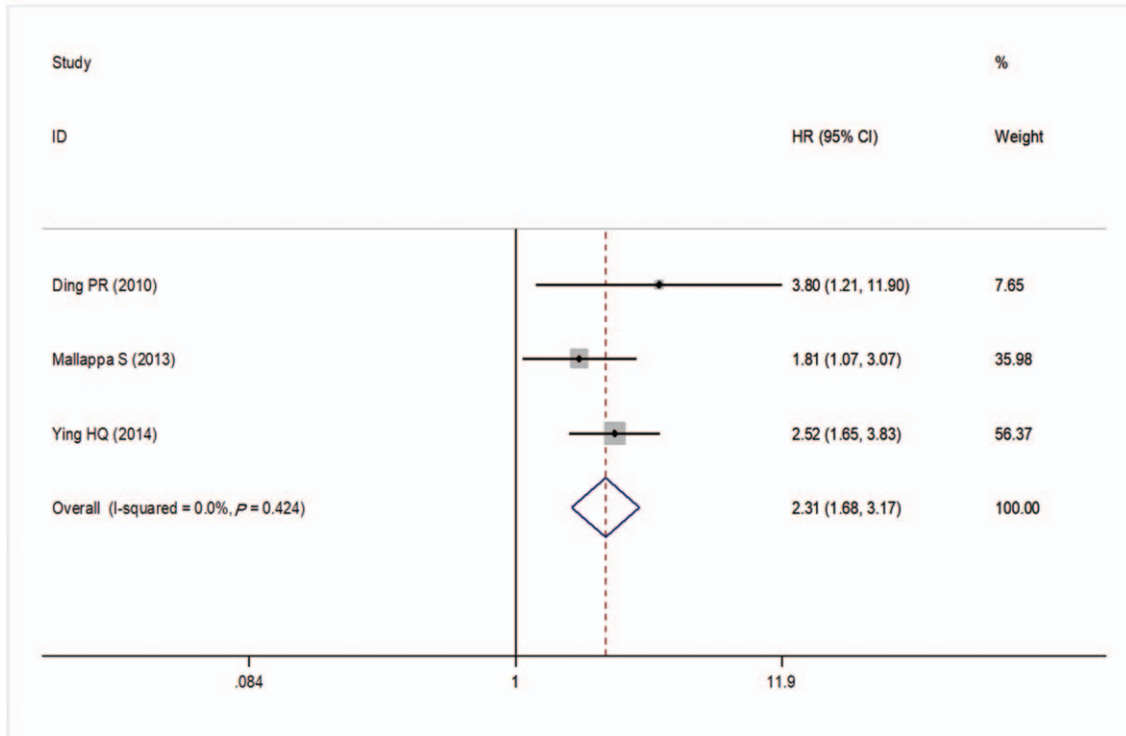
A positive result on any one of them was counted as one point.



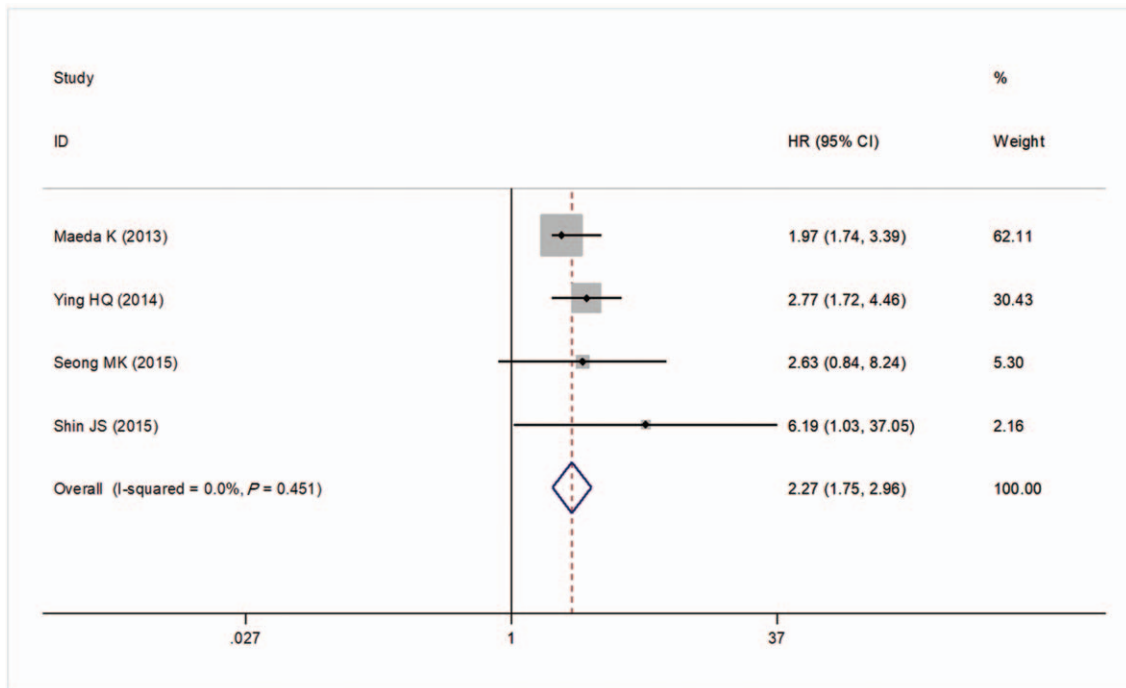
**Figure 2.** Forest plots of the correlation of NLR with overall survival. Squares indicate HR; horizontal lines indicate 95% CI; diamond indicates the summary HR estimate with its 95% CI. CI = confidence intervals, HR = hazard ratio, NLR = neutrophil to lymphocyte ratio.



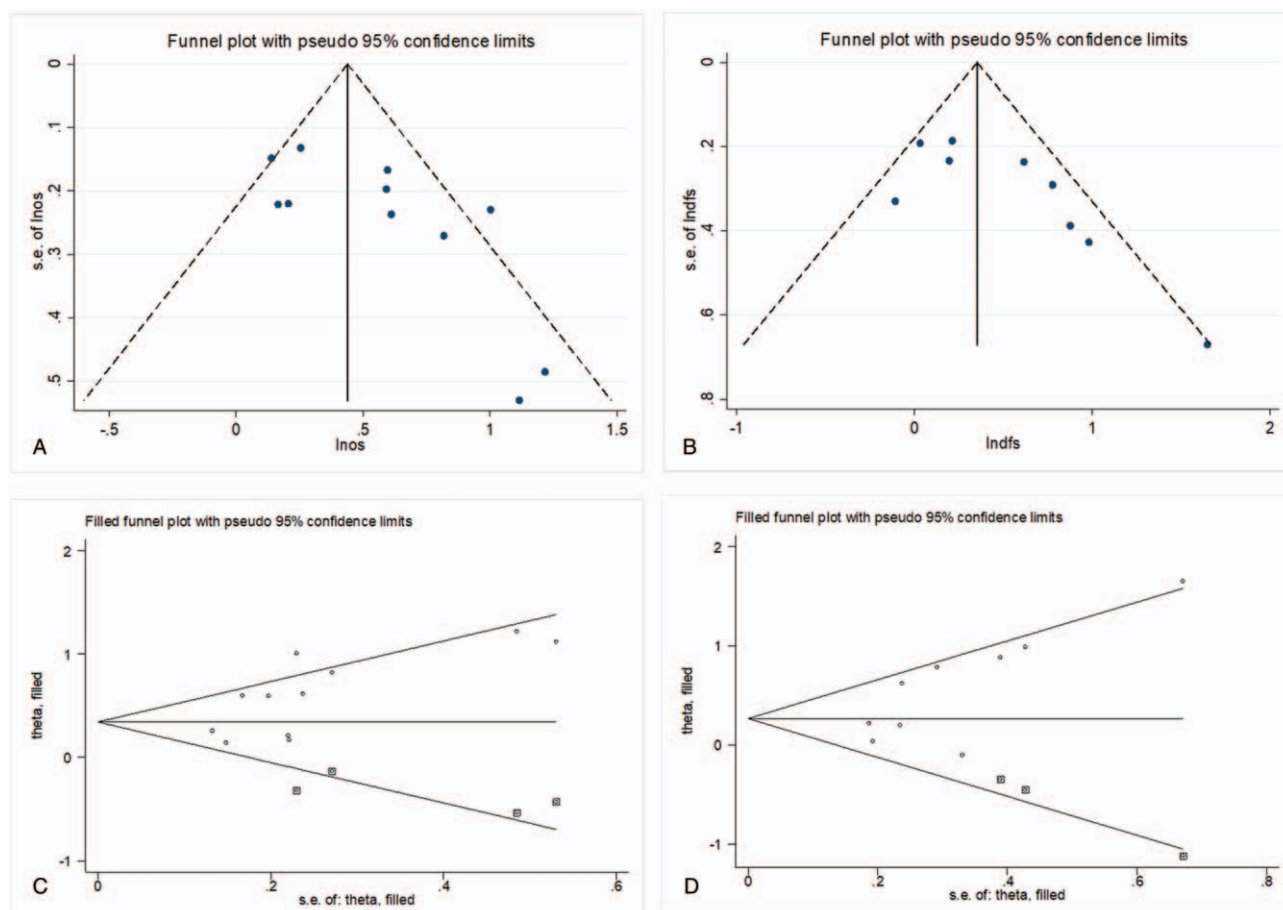
**Figure 3.** Forest plots of the correlation of neutrophil to lymphocyte ratio (NLR) with disease-free survival. Squares indicate hazard ratio (HR); horizontal lines indicate 95% confidence intervals (CI) (if it was larger, it was generated as an arrow automatically by the software); diamond indicates the summary HR estimate with its 95% CI. CI = confidence intervals, HR = hazard ratio, NLR = neutrophil to lymphocyte ratio.



**Figure 4.** Forest plots of the correlation of NLR with recurrent-free survival. Squares indicate HR; horizontal lines indicate 95% CI; diamond indicates the summary HR estimate with its 95% CI. CI = confidence intervals, HR = hazard ratio, NLR = neutrophil to lymphocyte ratio.



**Figure 5.** Forest plots of the correlation of NLR with disease-specific survival. Squares indicate HR; horizontal lines indicate 95% CI (if it was larger, it was generated as an arrow automatically by the software); diamond indicates the summary HR estimate with its 95% CI. CI = confidence intervals, HR = hazard ratio, NLR = neutrophil to lymphocyte ratio.



**Figure 6.** Funnel plot for the assessment of potential publication bias. A, Egger's funnel plot for OS; B, Egger's funnel plot for DFS; C, Trim-and-fill funnel plot for OS; D, Trim-and-fill funnel plot for DFS. The solid and dashed lines represent the estimated hazard ratio (HR) and its 95% CI. The horizontal axis was  $\ln(\text{HR})$ ; SE: standard error. CI = confidence intervals, DFS = disease-free survival, HR = hazard ratio, OS = overall survival.

thus, a publication bias estimate was used to evaluate the reliability of the meta-analysis results for these 2 indicators. Funnel plots were constructed (Fig. 6A and B), and the Egger's test showed that  $P=.028$  and  $P=.030$ , respectively, indicating the publication bias was indeed present. Subsequently, a trim-and-fill method was performed and the HR was recalculated (Fig. 6C and D). The filled meta-analysis still indicated a positive outcome for OS (HR=1.43; 95%CI: 1.15–1.76,  $P=.001$ ). However, the level of NLR could not predict the DFS after the filled meta-analysis (HR=1.32; 95%CI: 1.00–1.76,  $P=.053$ ).

### 3.4. Sensitivity analyses

A single study involved in the meta-analysis was deleted each time to unveil the influence of the individual data set to the pooled HR. The results showed that no single study could materially affect the pooled HRs in the present meta-analysis (Fig. 7).

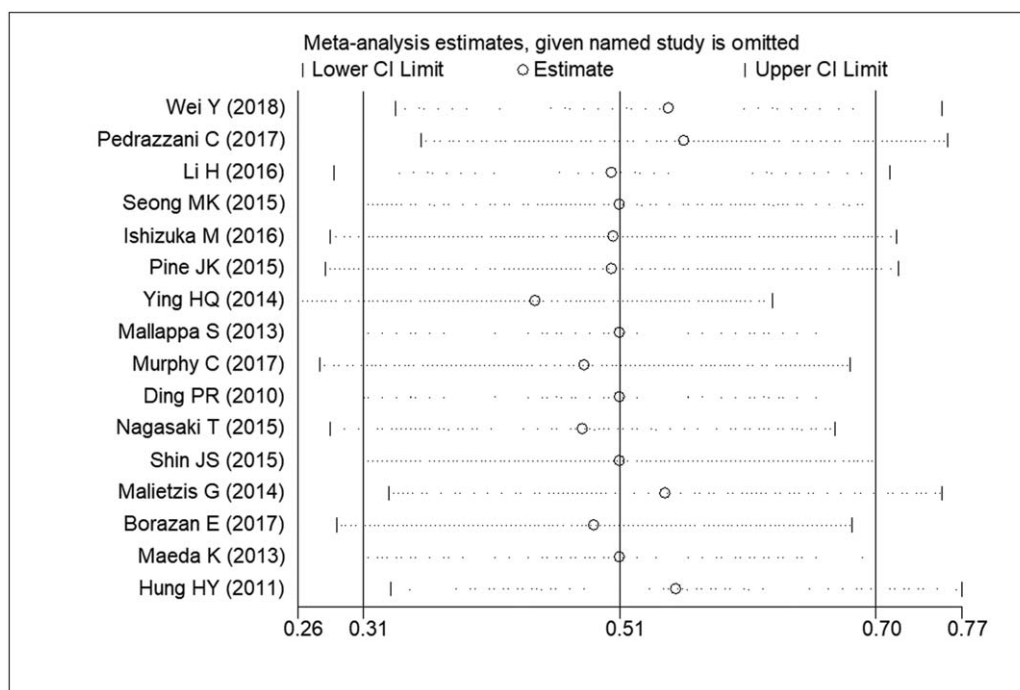
### 3.5. Subgroup analysis

Only the studies investigating the relationship between NLR and OS/DFS could be stratified by country, sample size, NLR cut-off, follow up time and postoperative chemotherapy. The results indicated that the elevated NLR predicted poor OS in all stratified categories, while high NLR only predicted poor DFS in eastern

countries (HR=1.61, 95%CI=1.082–2.38,  $P=.019$ ) and studies with NLR cut-off  $<5$  (HR=1.71, 95%CI=1.17–2.51,  $P=.006$ ), follow up time  $<36$  months (HR=1.75, 95%CI=1.26–2.43,  $P=.001$ ), postoperative chemotherapy (HR=2.68, 95%CI=1.16–6.20,  $P=.021$ ) and sample size  $<300$  (HR=2.30, 95%CI=1.45–3.66,  $P<.001$ ) or  $>300$  (HR=1.32, 95%CI=1.01–1.71,  $P=.041$ ) (Table 3).

## 4. Discussion

The present study, to our knowledge, was the first meta-analysis assessing the prognostic value of preoperative NLR and prognosis in patients with CRC undergoing curative surgery. The results indicated that, compared with low NLR, elevated NLR was associated with worse OS, DFS, RFS, and DSS in patients with CRC. Heterogeneity was present in studies investigating the relationship between NLR and OS/DFS, and thus a filled meta-analysis was performed. Consequently, the elevated NLR was still significantly related with OS, but not DFS. Subsequent subgroup analysis further demonstrated the high NLR was an OS-related factor for patients with CRC undergoing only surgery or combined with postoperative chemotherapy no matter the studies were performed in eastern or western country, with sample size  $>$  or  $<300$ , follow up  $>36$  or  $<$  months, NLR cut-off  $<$  or  $=5$ . Our study seemed to be in line with the previous meta-analyses that



**Figure 7.** Sensitivity analysis. The middle vertical axis indicates the overall HR and the 2 vertical axes indicate its 95% CI. Every hollow round indicates the pooled OR when the left study was omitted in this meta-analysis. The 2 ends of every broken line represent the 95% CI. The horizontal axis was ln(HR). CI = confidence intervals, HR = hazard ratio.

investigated the prognostic value of preoperative NLR for patients with other cancers, such as epithelial ovarian cancer,<sup>[34]</sup> upper tract urothelial carcinoma,<sup>[35]</sup> hepatocellular carcinoma<sup>[36]</sup> and all solid tumors.<sup>[37]</sup> But compared with these studies, our inclusion criteria may be more strict, including that HR and 95%CI only could be obtained by multivariate Cox regression analysis and adjuvant chemoradiotherapy could not be received preoperatively, both guaranteeing the reliability to confirm the prognostic value of preoperative NLR. Our findings suggested that the patients with an

elevated NLR may need other adjuvant treatments (such as inflammation inhibitors pre- and post-operatively) to combine with surgery to improve their prognosis.<sup>[38]</sup>

Although the exact mechanisms underlying the association of an elevated NLR with the prediction of poor survival in CRC patients remains unclear, increasing evidence suggests inflammatory and anti-inflammatory imbalance mediated by neutrophils and lymphocytes may play important roles. It had been reported that neutrophils were able to activate stromal cells in a NF-κB-

**Table 3**

**Subgroup analysis for the association between elevated preoperative NLR and prognosis of patients with colorectal cancer.**

	OS						DFS					
	No.	HR	95%CI	P	I <sup>2</sup>	P <sub>h</sub>	No.	HR	95%CI	P	I <sup>2</sup>	P <sub>h</sub>
Country												
Eastern countries	6	1.743	1.308–2.322	.000	61.7%	0.023	5	1.605	1.082–2.380	.019	61.6%	0.034
Western countries	5	1.586	1.170–2.149	.003	57.7%	0.051	4	1.511	0.980–2.329	.062	52.3%	0.098
Sample size												
<300	4	2.405	1.792–3.228	.000	0.0%	0.524	3	2.300	1.447–3.655	.000	16.1%	0.304
>300	7	1.445	1.206–1.730	.000	42.2%	0.111	6	1.317	1.012–1.714	.041	40.5%	0.135
NLR cut-off												
<5	8	1.684	1.284–2.209	.000	61.3%	0.012	6	1.713	1.170–2.509	.006	58.5%	0.034
=5	3	1.654	1.203–2.274	.002	58.4%	0.091	3	1.353	0.866–2.112	.184	54.8%	0.109
Median follow up												
<36 months	2	1.930	1.342–2.776	.000	20.6%	0.283	–	–	–	–	–	–
>36 months	5	1.438	1.197–1.727	.000	78.9%	0.003	7	1.749	1.259–2.430	.001	56.9%	0.030
Unclear	4	2.068	1.206–3.547	.008	0.0%	0.356	2	1.102	0.758–1.603	.611	0.0%	0.453
Postoperative chemotherapy												
Unclear	5	1.506	1.202–1.888	.000	45.5%	0.119	4	1.451	1.032–2.040	.032	54.0%	0.089
No	4	1.562	1.115–2.188	.010	50.2%	0.111	4	1.599	0.914–2.798	.100	62.4%	0.047
Yes	2	2.839	1.889–4.268	.000	0.0%	0.690	1	2.681	1.159–6.201	.021	–	–

CI = confidence intervals, DFS = disease-free survival, HR = hazard ratio, NLR = neutrophil to lymphocyte ratio, OS = overall survival, P<sub>h</sub> = indicate the P-value for heterogeneity.



dependent manner and then induced them transformation towards an inflammatory lymphoid stroma phenotype to trigger the survival of malignant B-cell lymphomas cells.<sup>[39]</sup> Similarly, Donati et al found neutrophil counts and its derived IL-16 were both elevated in pre-metastatic lungs in a mouse model using 4T1 tumor cells. IL-16 promoted cell adhesiveness, invasiveness, and migration, which could be reversed by using an IL-16 neutralizing antibody.<sup>[40]</sup> Furthermore, inflammatory neutrophils were speculated to enhance cancer cell growth and invasion by producing and releasing matrix metalloproteinases and angiogenesis-related gene vascular endothelial growth factor.<sup>[41–44]</sup> Conversely, infiltrating lymphocytes might exert cytotoxic roles on cancer stem cells and induce their apoptosis, ultimately preventing the progression of cancer.<sup>[45]</sup> Thus, the level of infiltrating lymphocytes may be decreased in cancer, which had been observed in the studies of Youssef et al<sup>[46]</sup> and Gulubova et al<sup>[47]</sup>. Apoptosis of T lymphocytes was also reported to be significantly correlated with Dukes' stage ( $P=.02$ ), lymphatic metastasis ( $P=.03$ ), vascular metastasis ( $P=.01$ ), lymph node metastasis ( $P=.02$ ) and age ( $P=.01$ ) of patients with CRC.<sup>[46]</sup> Accordingly, the increased neutrophils and decreased lymphocytes lead to the higher NLR, which is beneficial to the development and progression of CRC and induce poor prognosis.

The data identified in our current meta-analysis provide only limited information about the precise clinical utility of NLR for prognosis of CRC patients. The first limitation of this study was the retrospective nature present in the majority of enrolled studies that may be at high risk of patient selection bias. Secondly, detailed treatment (surgery, chemotherapy) procedures and demographic data of patients (such as age, sex, TNM staging, differentiation, tumor grade, location, etc.) could not be linked to the level of NLR. Thirdly, the cut-off value for defining high NLR was heterogeneous among studies and the prognosis outcomes were determined at different follow-up time. Fourthly, the sample size was not large, which may result in result bias. For example, only 3 or 4 studies were included to evaluate the prognostic significance of NLR for RFS and DSS, which may lead to the overestimation or underestimation of its value. Furthermore, only articles published in English language were included which also may cause a potential bias because some negative results may be published in native language. Hereby, our results should be further confirmed by more prospective and large-scale studies.

In conclusion, this meta-analysis demonstrates preoperative high blood-based NLR is associated with worse prognosis in patients who underwent surgery for CRC, especially OS. Detection of NLR may represent an inexpensive and widely available method for prognosis prediction and may be beneficial to identify the -high-risk patients who need other antitumor therapies in addition to surgery.

## Author contributions

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