Original Article
Prognostic significance of preoperative neutrophil/lymphocyte ratio (NLR) in patients with resectable non-small-cell lung cancer: a meta-analysis

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Abstract: Background: Neutrophil/lymphocyte ratio (NLR) has been demonstrated to have negative correlation with prognosis in a variety of carcinomas. However, it has not yet been confirmed whether preoperative NLR is associated with the prognosis of resectable non-small-cell lung cancer (NSCLC) patients. Therefore, we conducted this study to explore the correlation between preoperative NLR and survival in NSCLC patients treated with surgery. Method: We have completed an extensive literature retrieval which was conducted in Pubmed, Embase, Web of Science database and Cochrane library by using keywords and MeSH terms from inception up to July 1, 2019. The Newcastle-Ottawa Scale (NOS) was adopted to evaluate the quality of articles involved by two researchers who had no interference with each other. Hazard ratio (HR) and 95% confidence intervals (95% CIs) were directly extracted or estimated from literature. Results: Twenty-seven cohort studies including 13692 patients were incorporated in our meta-analysis. This study revealed that the level of NLR was negatively correlated with OS (HR: 1.478; 95% CI: 1.319-1.657) and DFS (HR: 1.770; 95% CI: 1.525-2.053) from all included individuals. Further classification analysis performed by histologic type and critical value showed that the subgroup with cut-off value of 5 (HR: 1.789, 95% CI: 1.420-2.254, I^2: 0, p=0.745) and adenocarcinoma squamous carcinoma (HR: 2.021, 95% CI: 1.555-2.626, I^2: 0, P=0.533) had a shorter OS with less heterogeneity. In addition, critical value <2.5 and NOS score ≥7 had a shorter DFS with less heterogeneity. Conclusion: The result of this meta-analysis confirmed that NLR of high level resulted in poor OS and DFS in resectable NSCLC patients. NLR was an indicator to estimate the prognosis and provide guidance in classification of patients and development of the adjuvant therapeutic strategies.

Keywords: NLR, non-small-cell lung cancer, meta-analysis

Introduction

As one of the main reasons of cancer-related-death, lung cancer is the most common form of carcinoma [1, 2]. Non-small-cell lung cancer (NSCLC) is the main pattern of lung carcinoma, which comprises about 85% of overall lung carcinoma. With increasingly more research on the diagnosis and the use of new techniques such as minimally invasive techniques for diagnosis and treatment, the mortality has been decreased, but high postoperative recurrence and poor prognosis are still prevailing [3].

A simple and instructive indicator is required to predict postoperative clinical therapeutic effect, recurrent ratio and survival condition before surgery. In recent years, increasingly more evidence has shown that many hematological parameters as well as systemic inflammation factors, such as platelet counts, platelet lymphocyte ratio (PLR), monocyte counts, C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR) and Glasgow Prognostic Score (GPS), might be indicators to predict prognosis and guide clinical treatment strategies in various solid tumors [4-10].

Neutroohil-lymphocyte ratio (NLR) is based on clinical hematological indexes, and a calculation using neutrophil and lymphocyte counts. The evidence accumulated gradually has shown that the pretreatment neutrophil-lymphocyte ratio (NLR) was significantly related to out-
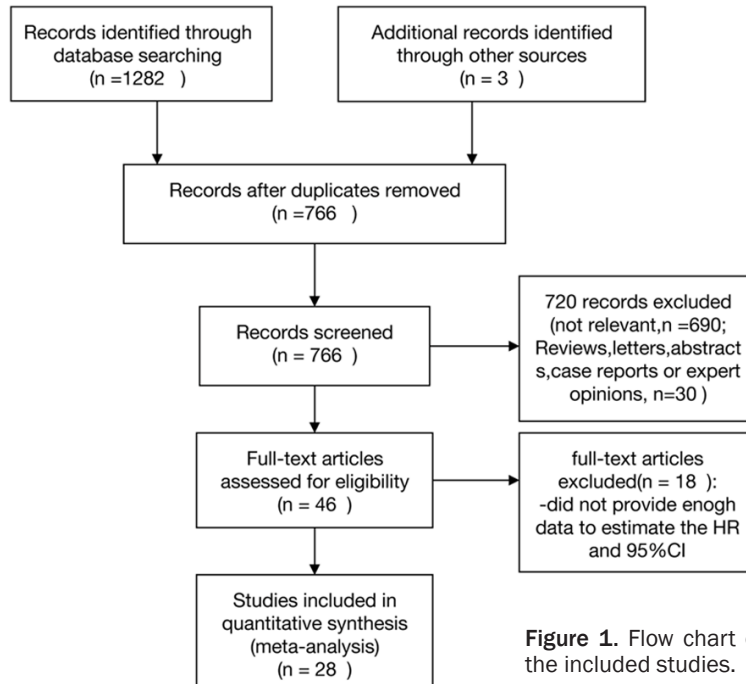
Figure 1. Flow chart of the included studies.

citations of the literatures and possibly relevant papers were also performed.

Study selection

Two independent researchers (Yu Zhang and Lan LYu) reviewed the titles and abstracts to select studies for inclusion. The literatures, which could not been identified by the title and abstract review, were identified in full text review to determine whether they would be included in our study. Discrepancies were resolved through discussion and forge agreements with another researcher (Wei Wang).

Inclusion criteria

The literature inclusion criteria we developed are as follows: (1) Patients with resectable NSCLC were confirmed by pathological examination. (2) Investigated the correlation of preoperative NLR with overall survival (OS), disease free survival (DFS) or recurrence-free survival (RFS). (3) Hazard ratio (HR) and 95% confidence intervals (95% CIs) were directly extracted or estimated from the data in the paper. (4) If multiple studies investigated the same patients or partially overlapping patients, only the most complete single study was selected. (5) The articles in English must be in full text form.

Exclusion criteria

The literature exclusion criteria are as follows: (1) Abstracts, letters, reviews, expert opinion, case reports. (2) Articles with number of cases less than 20.

Data extraction

We extracted the following information: title of paper, journal name, name of the primary author, duration, year of publication, country or region, research method (prospective or retrospective), essential information of study, preoperative neutrophil-lymphocyte ratio (NLR), pathological type and malignant stage, treatment

come of NSCLC [10, 11], however there are inadequate sample sizes and conflicting research conclusions on the prognostic significance of NLR in resectable NSCLC in the recent related studies [12-14]. Thus, it is indispensable to conduct this study to assess the impact of level of NLR on survival in resectable NSCLC patients. This meta-analysis has been registered on the prospero website with a registration ID of CRD42019143309.

Methods

Search strategy

A review of articles were conducted by searching the Pubmed, Embase, Web of Science and Cochrane library databases using keywords and MeSH terms from inception up to July 1, 2019. The key words of search included: [(neutrophil to lymphocyte ratio) OR (neutrophil-to-lymphocyte ratio) OR (neutrophil lymphocyte ratio) OR (neutrophil-lymphocyte ratio) OR (NLR)] AND [(Lung Neoplasms) OR (Pulmonary Neoplasms) OR (Lung Neoplasm) OR (Pulmonary Neoplasm) OR (Lung Cancer) OR (Lung Cancers) OR (Pulmonary Cancer) OR (Pulmonary Cancers) OR (Cancer of Lung) OR (NSCLC) OR (non-small-cell lung cancer) OR (non small cell lung cancer) OR (small cell lung cancer) OR (lung carcinoma)]. The searches of

Table 1. Main characteristics and result of the eligible studies

Study	Year	Country	Sample size	Gender (M/F)	Age (year) (median/mean)	Stage (I/II/III/IV)	Histology (ADC/SCC/others)	Treatment	Follow-up (month)	Cut-off value	NOS
Cata [15]	2016	USA	861	394/467	65.29	861/0/0	501/0/0	S, C, R	108.28	5	6
Chen [16]	2018	CHN	577	410/167	60	577/0/0	331/193/53	S, C	93.77	3.13	7
Yuan [17]	2017	CHN	1466	1058/408	NA	715/248/503	819/515/132	S, C	69.9	2.06	6
Choi [18]	2015	USA	1139	602/537	64.73	606/253/280	630/509*	S, C, R	NA	5	6
Gao [19]	2016	CHN	358	247/111	61	173/87/98	125/162/71	S, C, R	36	2.14	7
Gao (2) [20]	2018	CHN	410	267/143	60	172/98/140	168/191/51	S	54	1.9	7
Guo [21]	2019	CHN	569	425/144	60	147/177/245	295/225/49	S	60.3	1.74	6
Huang [22]	2018	CHN	589	390/199	60	131/18/58	241/273/75	S	NA	2.3	5
Ichinose [23]	2016	JPN	717	NA	NA	NA	NA	S	47	3	5
Jin [24]	2016	CHN	123	94/29	62	123 (I)	60/49/14	S	69	2.5	7
Kobayashi [25]	2018	JPN	166	74/92	NA	166 (Ia)	166/0/0	S	55.1	3.43	6
Kumagai [26]	2017	JPN	604	376/228	70	470/98/36	440/123/41	S, C	NA	2.1	5
Lan [27]	2013	CHN	174	122/52	59.02	11/125/38	64/96/14	S, C, R	11	2.9	5
Liang [28]	2017	CHN	456	318/138	61	170/101/185	157/238/61	S	42	2.28	7
Liao [29]	2013	CHN	59	47/12	63.5	25/21/13	27/29/3	S	30	NA	5
Mizuguchi [30]	2018	JPN	382	232/150	NA	382 (I)	264/92/26	S, C	67.2	1.5	6
Okui [31]	2017	JPN	26	23/3	68.8	15/8/3	0/0/26	S, C	54.4	1.7	7
Osugi [32]	2016	JPN	327	199/128	69	232/49/46	232/78/17	S, C	65	5	6
Sarraf [33]	2009	UK	177	104/73	63	83/45/45/4	85/56/35	S	29	3.81	6
Shimizu [34]	2015	JPN	334	213/121	69.3 (mean)	239/55/40	231/69/34	S	32	2.5	6
Takahashi [35]	2015	JPN	342	167/175	68	342 (I)	257/66/19	S	73.5	2.5	7
Tomita [36]	2011	JPN	284	178/106	67	189/41/54	208/76#	S	NA	2.5	7
Jun Wang [37]	2016	USA	1245	622/623	66	253/525/467	722/317/206	S, C, R	50.6	2.48	7
Yan Wang [38]	2019	CHN	261	144/117	NA	134/80/47	190/46/25	S	38	2.12	5
Ying Wang [39]	2018	CHN	952	674/278	59	NA	536/416/0	S, C	40	3.1	7
H Zhang [40]	2015	CHN	678	449/229	61	304/135/239	277/317/84	S, C, R	43.5	2.3	7
H Zhang (2) [41]	2015	CHN	1238	812/426	60	536/264/438	502/582/154	S, C, R	45	2.3	7
T Zhang [42]	2014	CHN	400	272/128	62	310/90/0	239/161/0	S	46	3.3	7

ADC: Adenocarcinoma; SCC: squamous carcinoma; others: Pathological types other than adenocarcinoma and squamous carcinoma; NA: Not available; CHN: China; JPN: Japan; S: Surgery; C: Chemotherapy; R: Radiotherapy; Re: Retrospective study; OS: Overall survival; DFS: Disease free survival; RFS: Recurrence free survival; MV: Multivariate analysis; UV: Univariate analysis; *: Adenocarcinoma/other pathological type; #: adenocarcinoma: no adenocarcinoma.
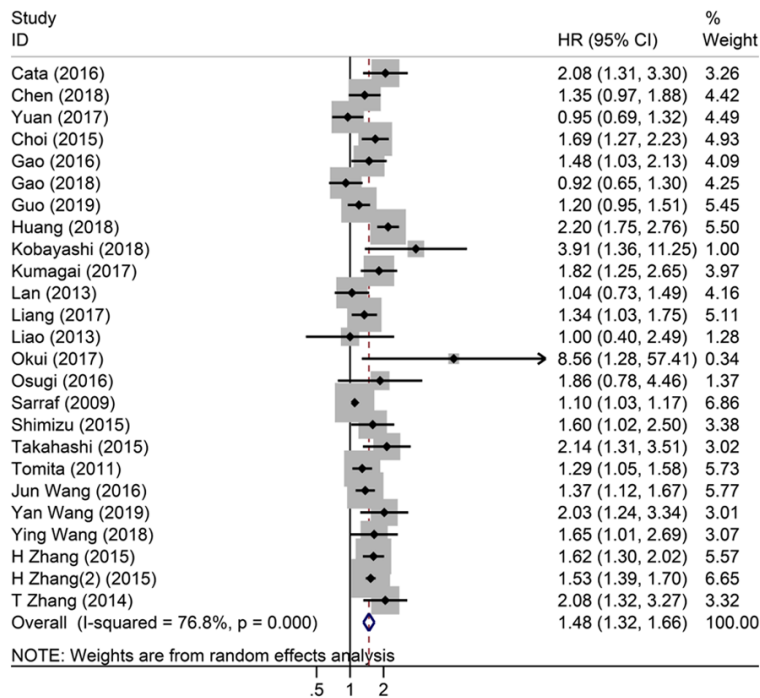
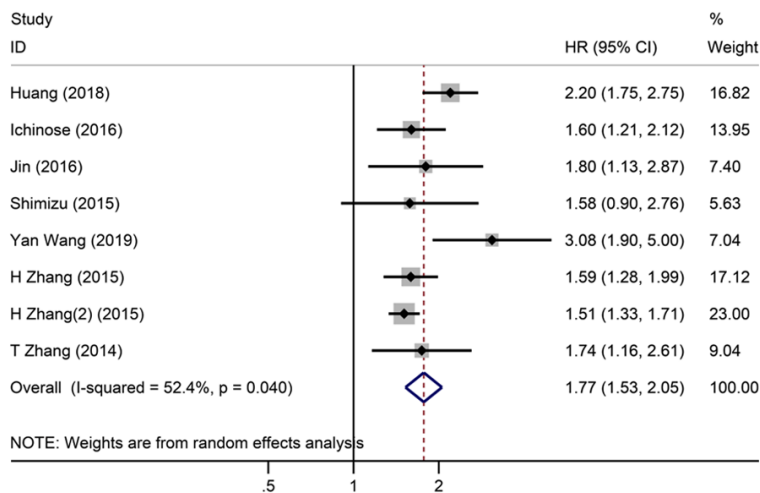**Figure 2.** Forest plot of the association between NLR and OS of all patients.

Figure 3. Forest plot of the association between NLR and DFS of all patients.

(surgery, chemotherapy, radiation therapy or neoadjuvant therapy), survival indexes (OS, DFS, and RFS; HRs and 95% CIs and/or *P* values), analytical method (multivariable analysis and/or univariable analysis), and follow-up time.

Quality assessment

The NOS which was designed for retrospective and prospective studies was adopted to evaluate the quality of the inclusive studies by two

investigators who had no interference with each other (Yu Zhang and Lian-Fu Zhang). The articles with NOS scores ≥7 were assigned to the group with more credible evidence.

Statistical analysis

HR and 95% CI were obtained from articles or indirectly calculated from the extracted data. A HR >1 was considered to be a shorter survival in patients with NSCLC with higher NLR level. We used the Cochrane's Q statistic to judge the heterogeneity of each study. I^2 less than 50% was considered to have no obvious heterogeneity, and the fixed-effects model was used. If not, the random-effects model was applied. To examine the reason of heterogeneity, subgroup analysis and meta-regression analyses were implemented. Sensitivity analyses, which observed how the pooled outcome of study changed after each study was excluded, were implemented to appraise the stability of the results through the metainf command of STATA. We applied Begg's rank correlation test and Egger's regression asymmetry test to determine whether there was a significant publication bias that might have influenced the results. In addition, trim and fill method, which verifies the sensitivity and potential publication bias, was implemented through the metatrim command of STATA. The software version used for statistical analysis was STATA 12.0.

Result

Study characteristics

The literatures selection process was illustrated in **Figure 1**. Twenty-eight studies published between 2009 and 2019 with 14971 patients
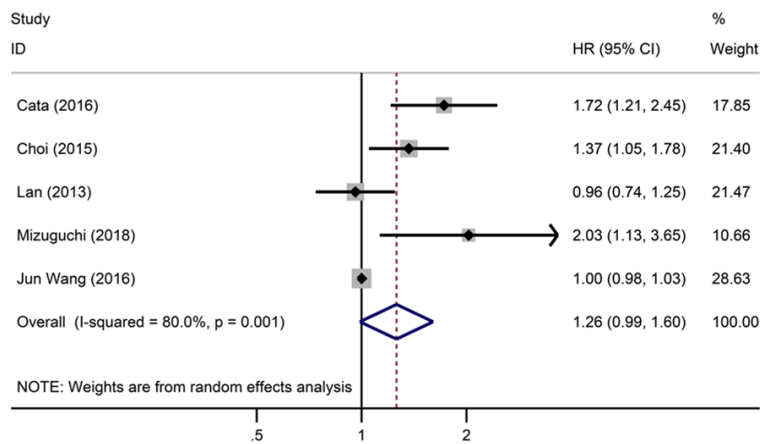
Figure 4. Forest plot of the association between NLR and RFS of all patients.

76.8%, P<0.001; H=2.1, 95% CI=1.7-2.5) was detected.

NLR and DFS in NSCLC

Eight cohort studies including 4340 patients examined the effect of preoperative NLR to DFS. Meta-analysis of these eight studies suggested that high NLR was particularly related to shorter DFS. The pooled HR was 1.770 (95% CI: 1.525-2.053) with the use of random-effects model (**Figure 3**), although there was significant heterogeneity (I^2=52.4%, P<0.001; H=1.4, 95% CI=1.0-2.2) between studies.

NLR and RFS in NSCLC

Five cohort studies including 3801 patients reported the correlation of preoperative NLR and RFS in NSCLC patients. The pooled HR was 1.260 (95% CI: 0.99-1.60), which illustrates that the effect of high preoperative NLR on RFS was not statistically significant (**Figure 4**) with the use of random-effects model, and significant heterogeneity was detected.

Heterogeneity and subgroup analyses

Meta-regression was implemented to investigate the underlying causes of inter-study heterogeneity among the trials. The results indicated that heterogeneity of studies on OS was not caused by study region (P=0.815), sample size (P=0.779), histologic type (P=0.923), treatment method (P=0.728), cut-off value (P=0.841), analysis method (P=0.942) or NOS score (P=0.825). Moreover, the data revealed that sample size (P=0.184), follow-up time (P=0.501), cut-off value (P=0.428), analysis method (P=0.272) and NOS (P=0.540) were not the cause of inter-study heterogeneity for DFS. Meta-regression was not conducted for the studies on RFS because of insufficiency of the data.

Further research was performed to explore possible reasons for the significant inter-studies heterogeneity (**Table 2**). Regarding OS, subgroup analysis was performed by treatment, region, neoadjuvant treatment, stage, histologi-

were incorporated in our research according to our inclusion criteria [15-42]. The two researcher named Gao and Hua Zhang conducted two separate studies and reported survival indexes, so we numbered them as Gao1, Gao2, H Zhang1 and H Zhang2 [40, 41]. Of 28 studies, 25 studies with 13692 patients focused on revealing the influence of preoperative NLR on OS [15-22, 25-29, 31-42], 8 studies with 4340 patients on DFS [22-24, 34, 38, 40-42] and 5 studies with 3801 patients on RFS [15, 18, 27, 30, 37]. Four studies were conducted in western countries [15, 18, 33, 37], and other twenty-four studies were carried out in Eastern countries [16, 17, 19-32, 34-36, 38-42]. All the study corhorts were retrospectively analyzed. One study included all pathological stages, while twenty-seven studies involved only early stages (I/I-II/ I-III) [15-31, 33-42]. Five studies involved patients who received neoadjuvant therapy (neoadjuvant chemotherapy or neo-adjuvant radiotherapy) before surgery [15, 17, 18, 27, 31]. NOS score of the included articles ranged from 5 to 7. The essential features of these studies are shown in **Table 1**.

NLR and OS in NSCLC

Twenty-five cohort studies including 13692 patients examined the effect of preoperative NLR to OS. Meta-analysis of these twenty-five studies presented that NLR of high level was particularly related to shorter OS. The pooled HR was 1.478 (95% CI: 1.319-1.657, P<0.001) with the use of random-effects model (**Figure 2**), although significant heterogeneity (I^2=

Table 2. Table of subgroup analysis results

Outcome	Grouping strategy	No of studies	Random-effect		Fixed-effect		Heterogeneity	
			HR (95% CI)	P	HR (95% CI)	P	I² (%)	Ph
OS	Cut-off value							
	=5	3	1.789 (1.420-2.254)	0	1.789 (1.420-2.254)	0	0	0.745
	<5	21	1.453 (1.287-1.639)	0	1.290 (1.235-1.346)	0	79.0	0
	Histology							
	A, S	4	2.021 (1.555-2.626)	0	2.021 (1.555-2.626)	0	0	0.533
	O	21	1.420 (1.262-1.597)	0	1.288 (1.234-1.344)	0	77.8	0
DFS	Cut-off value							
	≥2.5	4	1.884 (1.467-2.418)	0	1.680 (1.525-1.851)	0	79.2	0.002
	<2.5	4	1.662 (1.369-2.017)	0	1.662 (1.369-2.017)	0	0	0.967
	NOS score							
	≥7	4	1.554 (1.402-1.724)	0	1.554 (1.402-1.724)	0	0	0.818
	<7	4	2.015 (1.543-2.632)	0	2.004 (1.710-2.348)	0	56.3	0.077
RFS	Cut-off value							
	=5	2	1.489 (1.196-1.854)	0	1.486 (1.203-1.835)	0	6.3	0.302
	<5	3	1.080 (0.849-1.373)	0.530	1.001 (0.976-1.026)	0.944	64.7	0.059
	Stage							
	Early	2	1.800 (1.331-2.435)	0	1.800 (1.331-2.435)	0	0	0.640
	Advanced	3	1.068 (0.894-1.275)	0.468	1.002 (0.978-1.027)	0.851	63.3	0.066

Random-effect: random-effect models; Fixed-effect: fixed-effect models; HR: hazard ratio; 95% CI: 95% confidence interval; Ph: P value of Q test for heterogeneity test; OS: Overall survival; DFS: Disease free survival; RFS: Recurrence free survival; A, S: only Adenocarcinoma or squamous carcinoma or both; O: Contain types other than adenocarcinoma and squamous carcinoma; Early: TNM stage I or II; Advanced: Including TNM stage III or IV.
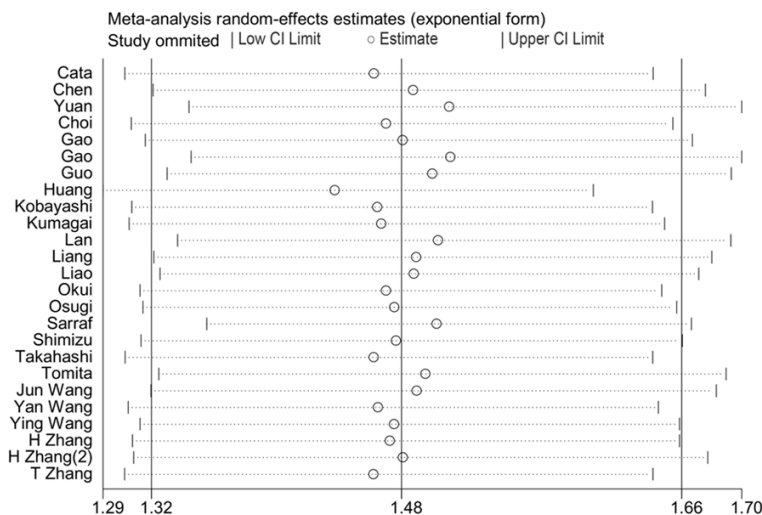

Figure 5. Sensitivity analysis of the publication in the overall survival group.

cal type, neoadjuvant treatment, sample size, NOS score follow-up time, analysis method (multivariate analysis or univariate analysis) and cut-off value. Significantly, with cut-off value of 5 (HR: 1.789, 95% CI: 1.420-2.254, I²: 0, P=0.745), adenocarcinoma or squamous carcinoma or both (HR: 2.021, 95% CI: 1.555-2.626, I²: 0, P=0.533) had a shorter OS with less heterogeneity.

Regarding DFS, subgroup analysis was performed by follow-up time, analysis method, sample size, NOS and cut-off value. In addition, cut-off value of <2.5 (HR: 1.662, 95% CI: 1.369-2.017, I²: 0, P= 0.967) and NOS ≥7 (HR: 1.554, 95% CI: 1.402-1.724, I²: 0, P=0.818) had a shorter DFS with less heterogeneity.

Regarding RFS, subgroup analysis was performed by neoadjuvant treatment, cut-off value, region, stage and sample size. Cut-off value of 5 (HR: 1.489, 95% CI: 1.196-1.854, I²: 6.3, P=0.302) and early stage (stage I, II) (HR: 1.800, 95% CI: 1.331-2.435, I²: 0, P=0.640) had a shorter DFS with less heterogeneity.
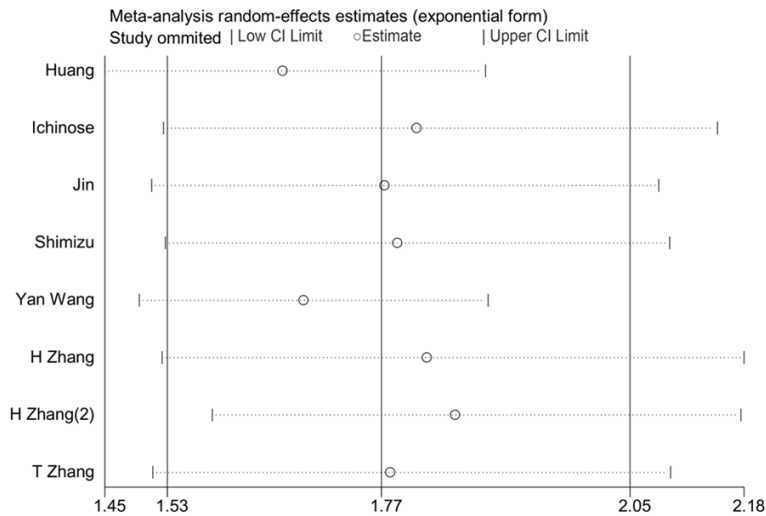
Meta-analysis random-effects estimates (exponential form)
Study ommited | Low CI Limit   ∘Estimate | Upper CI Limit

Figure 6. Sensitivity analysis of the publication in the disease free survival group.

Meta-analysis random-effects estimates (exponential form)
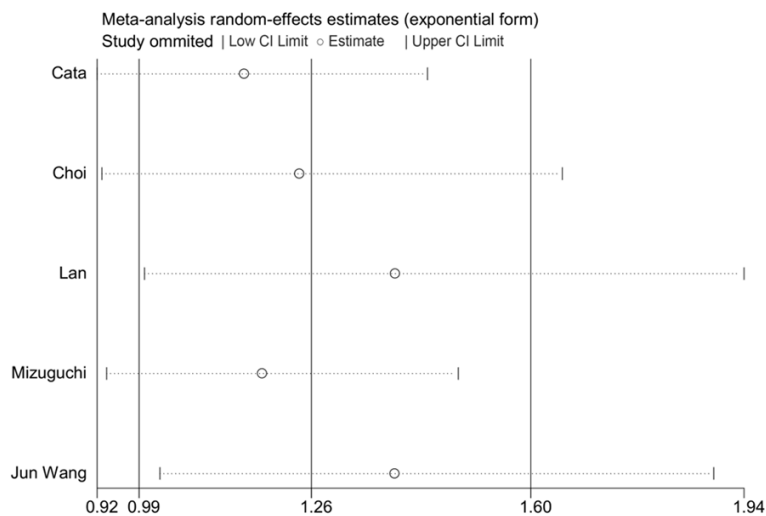Study ommited | Low CI Limit ∘ Estimate | Upper CI Limit

Figure 7. Sensitivity analysis of the publication in the recurrence free survival group.

Sensitivity analysis

Sensitivity analysis was performed with the use of metainf command of STATA to examine the stability of the results. The results indicated that removing any one of studies did not markedly change the combined result of HRs for OS (**Figure 5**), DFS (**Figure 6**) and RFS (**Figure 7**).

Publication bias

Begg's test revealed no statistically significant publication bias for OS (P=0.234) (**Figure 8**), DFS (P=0.174) (**Figure 9**) and RFS (P=0.086) (**Figure 10**). The pooled HRs (OS: HR: 1.282, 95% CI: 1.142-1.438; DFS: HR: 1.537, 95% CI: 1.324-1.784; RFS: HR: 1.047, 95% CI: 0.822-1.333) are not much different from multivariate studies with the use of trim and fill method. The above data demonstrate that the research results are stable and reliable.

Discussion

Our research was conducted to explore the impact preoperative NLR of high level on OS, DFS and RFS of NSCLC patients. The meta-analysis included 14971 NSCLC patients from 28 studies. The result showed that higher preoperative NLR pretended shorter OS and DFS, but the result of RFS did not reach significance. Despite the heterogeneity, the decrease of prognostic value was not insignificant in the subgroup analyses based on treatment, region, neoadjuvant treatment, stage, histologic type, neoadjuvant treatment, sample size, NOS score follow-up time, analysis method and cut-off value. Furthermore, in the subgroup analyses stratified by cut-off value NLR equal to 5 and pathological type as adenocarcinoma squamous carcinoma, there was an association for shorter OS with less heterogeneity. In addition, cut-off value of <2.5 and NOS ≥7 had an association with shorter DFS with less heterogeneity (**Table 2**). Our study validated that the cut-off value of 5 is more stable for predicting prognosis because of lower heterogeneity. Additionally, preoperative NLR did not have reliable prognostic value for NSCLC patients of OS who underwent neoadjuvant therapy (HR=1.439, 95% CI: 0.986-2.1), because the confidence interval contained 1. The result showed that preoperative NLR is probably a highly signifi-
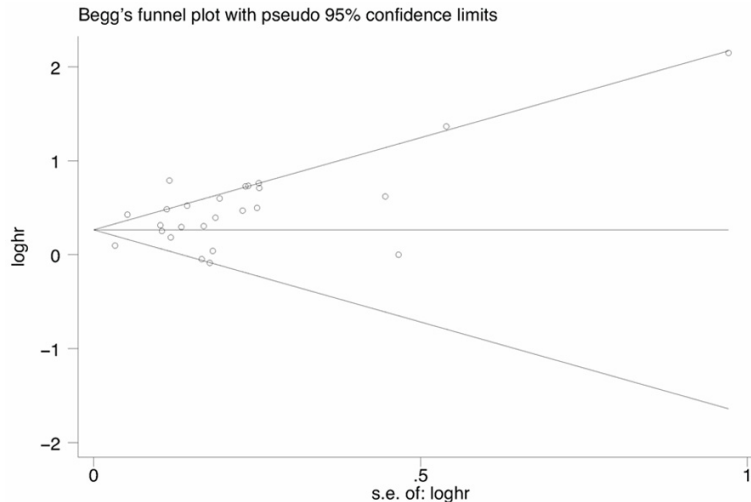
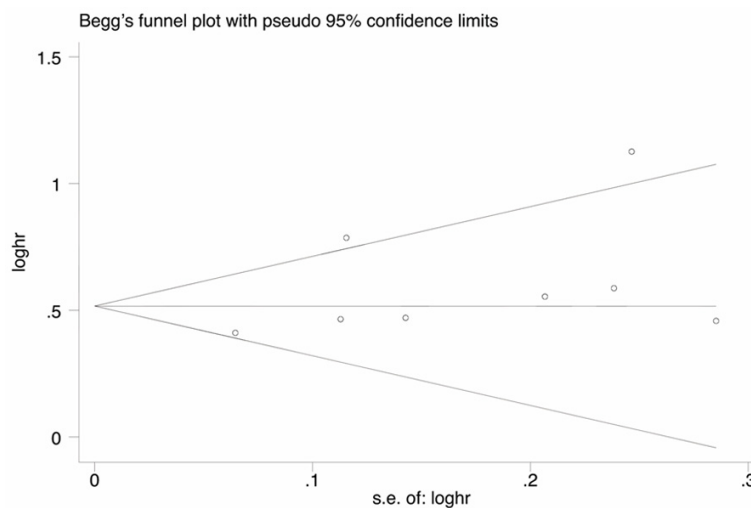**Figure 8.** Begg's funnel plot estimating the publication bias of the included studies in the overall survival group.

Figure 9. Begg's funnel plot estimating the publication bias of the included studies in the disease free survival group.

Inflammation undertakes a pivotal role in many solid tumors, however, the exact mechanism was still unconfirmed [43, 44]. A high NLR was caused by smaller denominator and/or larger numerator based on the calculation formula. An elevated neutrophil count has been proven to have an impact on the progress of metastasis and is closely related to cytolytic activity of lymphocytes and natural kill cells [45-47]. Moreover, accumulating studies have shown that lymphocytes play an important role in killing cancer cells and regulating proliferation and metastasis [48, 49]. Thus, NLR, which concerns neutrophil and lymphocyte counts into account, can partly reflect the interactions between cancer cells and internal environment.

The pretreatment NLR has been used to predict the survivals in numerous cancers, such as colon [50], pancreatic [51], renal [52], gastric [53], ovarian [54] and oral cavity squamous cell cancers [55]. Increasing amounts of retrospective studies indicated that similar relationship was found in lung cancer patients. This is consistent with the result of our meta-analysis.
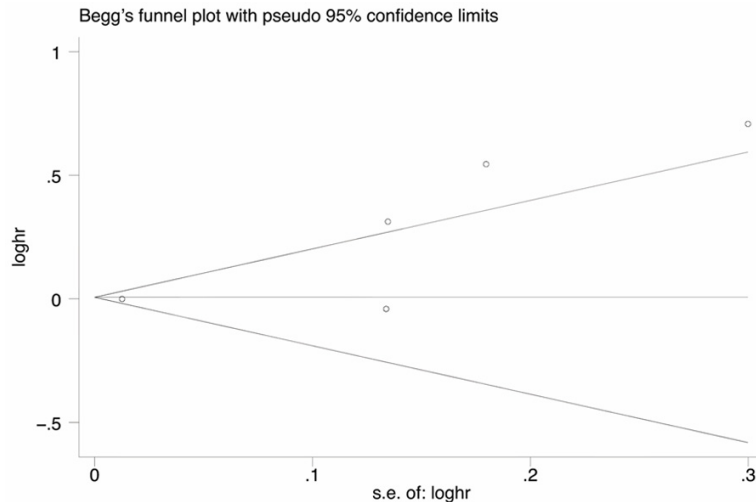
cant prognostic factor for OS of early stage NSCLC patients (HR: 1.897, 95% CI: 1.450-2.483, I^2: 35%, Pheterogeneity =0.188). Further study on DFS by analysis method also showed the same result. Meta-regression analysis based on several variables such as region, stage, cut-off value and sample size, was conducted. None of these variables contributes to inter-study heterogeneity. As far as we know, our research is the first meta-analysis to explore whether preoperative NLR is correlated with the survivals of resectable NSCLC patients.

In the last few years, accumulating meta-analyses have reported the association between NLR and survivals of NSCLC patients [56-59]. Our meta-analysis limited the investigated objects to resectable NSCLC patients, and focused on the preoperative result of NLR.

The inadequacy points of our research should be considered. First, obvious inter-study heterogeneity, including OS (I^2=76.8%, P<0.01; H=2.1, 95% CI: 1.7-2.5), DFS (I^2=52.4%, P<0.01; H=1.4, 95% CI: 1.0-2.2) and RFS (I^2=80%, P=0.001; H=2.2, 95% CI: 1.5-3.4). In

Figure 10. Begg's funnel plot estimating the publication bias of the included studies in the recurrence free survival group.

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order to examine the root reason of heterogeneity, meta-regression analysis, subroup analysis and sensitivity analysis were conducted; however, the inter-study heterogeneity could not be explained by any of these confounders. The heterogeneity may be caused by complicated multiple factors. Second, although the publication bias did not have an influence on the result, it still cannot be excluded. The publication bias was supposed to have association with the language restriction and study regions. Third, all of our inclusive primary studies are retrospectively analyzed, which raise the possibility of bias. Fourth, the influence of some factors was not analyzed, such as grade of differentiation, lymph node metastasis and the time of blood test, because of the insufficiency of data.

Conclusion

In conclusion, our study demonstrated that high preoperative NLR might be an adverse prognostic factor for resectable NSCLC patients. Thus, NLR, which can be worked out during blood routine test, may be a simple and convenient prognostic biomarker, and provides guidance in stratifying patients and developing the adjuvant treatment plan. Therefore, rigorous and large-scale clinical trials are necessary to determine the prognostic role of preoperative NLR in NSCLC patients.

Disclosure of conflict of interest

None.

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