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Review Article

Prognostic significance of the neutrophil to lymphocyte ratio in patients with non-small cell lung cancer: a systemic review and meta-analysis

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Abstract: Neutrophil to Lymphocyte Ratio (NLR) was recently demonstrated as a useful index in predicting the prognosis of Non-Small Cell Lung Cancer (NSCLC). Thus, a meta-analysis was performed to demonstrate the relationship between NLR and overall survival (OS), progress-free survival (PFS) or disease free survival (DFS) in patients with NSCLC. We searched for relevant literatures in PubMed, EMBASE and Cochrane library and pooled the eligible studies and synthesized hazard ratios (HRs) using Stata 12.0. Final analysis of NSCLC patients from 12 eligible studies was performed. Combined HR suggested that high NLR had an unfavorable effect on patients' OS (n=1700 in 11 studies; HR= 1.43, 95% CI: 1.25-1.64; I^2=80.2%, P<0.01) and PFS (n=664 in 5 studies, HR=1.37, 95% CI: 1.07-1.74; I^2=70.8%, P=0.004). Subgroup analysis based on cutoff shown that, compared with other subgroups, the subgroup with a cutoff of 5 had a significantly poorer survival (HR=1.87, 95% CI 1.49-2.34) with less heterogeneity (I^2=21.3%, P=0.28). However, subgroup analysis based on treatment method indicated that the "surgery" subgroup seemed to have not a significant impact on survival (HR=1.32, 95% CI 0.99-1.77; I^2=80.0%, P=0.063) compared with the chemotherapy subgroup (HR=1.61, 95% CI 1.24-2.10; I^2=82.6%, P<0.01). Additionally, combined odds ratio (OR) suggested high NLR was associated inversely with response to treatment (n = 276 in 2 studies; OR = 1.73, 95% CI: 1.04-2.88; I^2=0%, P=0.40). This study suggests high NLR (especially with a cutoff of 5) seems to be associated with a worse prognosis in patients with NSCLC as well as a worse response to treatments.

Keywords: Neutrophil to lymphocyte ratio, NLR, non-small cell lung cancer, NSCLC, overall survival, progress-free survival, treatment response

Introduction

Lung cancer is the leading cause of cancer-related death world-wide, accounting for about 1.1 million deaths per year [1]. Non-small cell lung cancer (NSCLC) is responsible for 85% of the total cases [2]. Although great progress made in the past decade, especially the emergence of molecular targeting therapy, has revolutionized the treatment of lung cancer, the prognosis of lung cancer is still unsatisfactory, with a five year overall survival rate of about 15% [2]. So it is necessary to identify potential prognostic indicators, especially the easy-to-access laboratory indexes for oncology doctors to well manage this strong fatal disease.

In recent years, an increasing number of studies have indicated that NLR is a useful biomarker to measure the inflammatory status of immune system [3]. The latest research suggested that NLR had a prognostic value in predicting the survival of patients with NSCLC [4-7]. Additionally, growing evidence showed that the neutrophils located in tumor stroma predict unfavorable outcomes, while tumor related lymphocytes have been associated with a better prognosis [8-10]. All taken into consideration, we deduce that NLR might have be a practical prognostic index for patients with NSCLC and performed a meta-analysis to verify it.

Methods

Search strategy

We searched PubMed, EMBASE and Cochrane library for relevant articles until March, 2014.

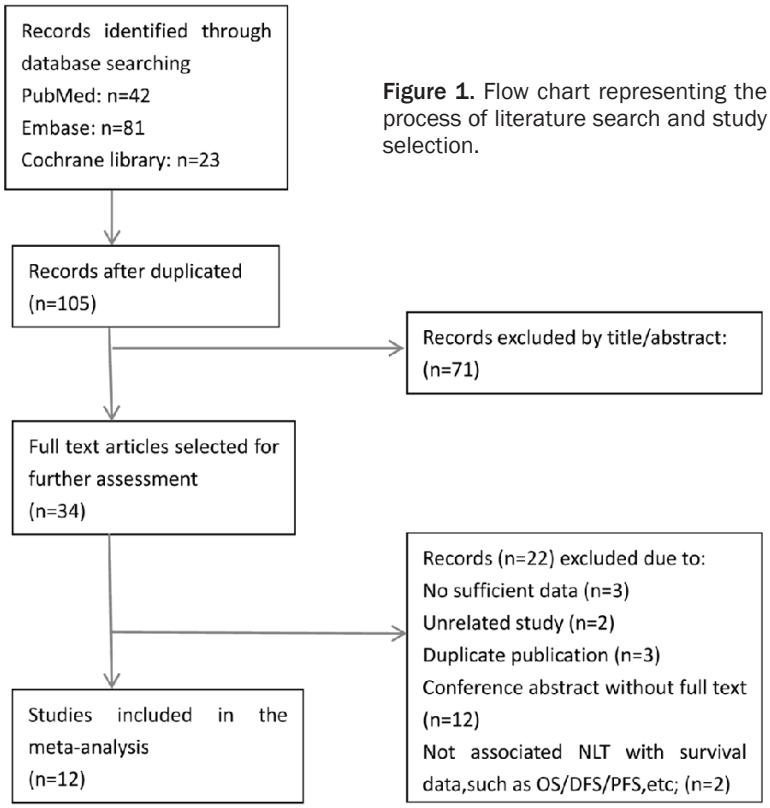

Figure 1. Flow chart representing the process of literature search and study selection.

Articles are identified using the following terms: ((lung OR pulmonary) AND (neoplasm OR cancer OR carcinoma OR tumor)) AND (neutrophil lymphocyte OR neutrophil to lymphocyte OR NLR). We restricted the above words/phrases in title/abstract and reviewed the references of included literatures for potential eligible articles.

Selection criteria

All eligible articles focusing on correlation between NLR and OS or PFS and/or clinicopathological features and treatment response in patients with NSCLC were included in this meta-analysis. All retrieved articles were carefully reviewed to identify potential relevant studies. Articles included in our meta-analysis should meet the following criteria as follows: 1) patients pathologically diagnosed as non-small cell lung cancer; 2) NLR was measured by serum based methods and should be detected before treatments; 3) information between neutrophil-lymphocyte ratio (NLR) and overall survival (OS), progress-free survival (PFS) or disease-free survival (DFS), and/or clinicopathological figures and treatment response; 4) sufficient information provided to estimate hazard ratio (HR) and 95% confidence interval (CI) of OS, PFS or DFS; 5) If multiple studies investigated the same patients or partially overlapping patients, only the most complete single study was selected. We excluded literatures, such as letters, reviews, case reports, conference abstracts editorials and articles with sample size less than 20.

Data extraction

Two reviewers (Peng and Wang) independently scanned the title and abstract of the potentially eligible articles. All candidate articles with full-text were retrieved to review, if articles could not be categorized based on title and abstract. Articles were independently read and checked according to the inclusion/exclusion criteria in this study. Any disagreement in the course of quality assessment was discussed and resolved together.

Quality assessment

In this study, we adopted the Newcastle-Ottawa Scale (NOS) which was designed for retrospective and prospective studies, to assess study quality (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). The Scale includes three parts: selection (4 points), comparability (2 points), and outcome assessment (3 points). The maximum value is 9 points.

Statistical analysis

In this meta-analysis, OR was only used to estimate the association between NLR and treatment response, since there was no sufficient studies focusing on the relationship between NLR and Clinicopathological characteristics. Therefore, the number of events (no treatment response) compared to the total number of patients in each group was subjected for the analysis of each variable.

As for OS and PFS, HR with its 95% CI was used to evaluate the significance of NLR on them.

Table 1. Clinical and methodological characteristics of included studies

Author	Years	Country	No. of patients	Gender (M/F)	Mean age (y)	UICC-stages (III/IV vs I/II)	Histology (SCC/ADC/others)	treatment methods	follow-up median (mon)	Cut-off value	survival analysis	HR estimate
KM Sarraf	2009	UK	177	NA	63	49/128	56/86/35	surgery	29	tertile	OS	MV
S Teramukai	2009	Japan	388	276/112	65	388/0	76/274/38	Chemo	19	quartile	OS/PFS	MV
M Tomita	2011	Japan	284	178/106	67	54/230	?/208/76	surgery	60.7-131.7	2.5	OS	MV
S Cedres	2012	Spain	171	143/28	63	171/0	31/69/71	Chemo	9.1	5	OS/PFS	MV/UV
Y Lee	2012	Korea	199	17/182	57	199/0	0/199/0	Chemo	36	3.25	OS/PFS	MV/MV
C Botta(1)	2013	USA	73	55/18	58	73/0	11/58/4	chemo+beva	15	4	PFS	UV
C Botta(2)	2013	USA	39	26/13	68	39/0	11446	Chemo	15	4	PFS	UV
D Unal	2013	Turkey	94	88/6	58	85/9	66/15/13	Chemo	NA	3.44	OS	UV
M Yildirim	2013	Turkey	95	77/18	59	95/0	NA	Chemo	14	5	OS	UV
V Kaya	2013	Turkey	156	80/76	60	156/0	85/44/21	Chemo	12.5	5	OS	UV
YW yao	2013	China	182	119/63	59	182/0	48/128/6	Chemo	NA	2.63	OS/PFS	MV/MV
DJ Pinato	2014	UK	220	110/110	65	29/191	53/132/35	surgery	NA	5	OS	MV
T Kacan	2014	Turkey	299	270/29	61	250/49	124/71/104	NA	NA	5	OS	MV

HR: hazard ratio, NA: not available, Mon: month, SCC: squamous cell carcinoma, ADC: adenocarcinoma, others: other types of lung cancer, MV: multivariate analysis, UV: univariate analysis, OS: overall survival, PFS: progress-free survival, Chemo: chemotherapy, beva: bevacizumab.

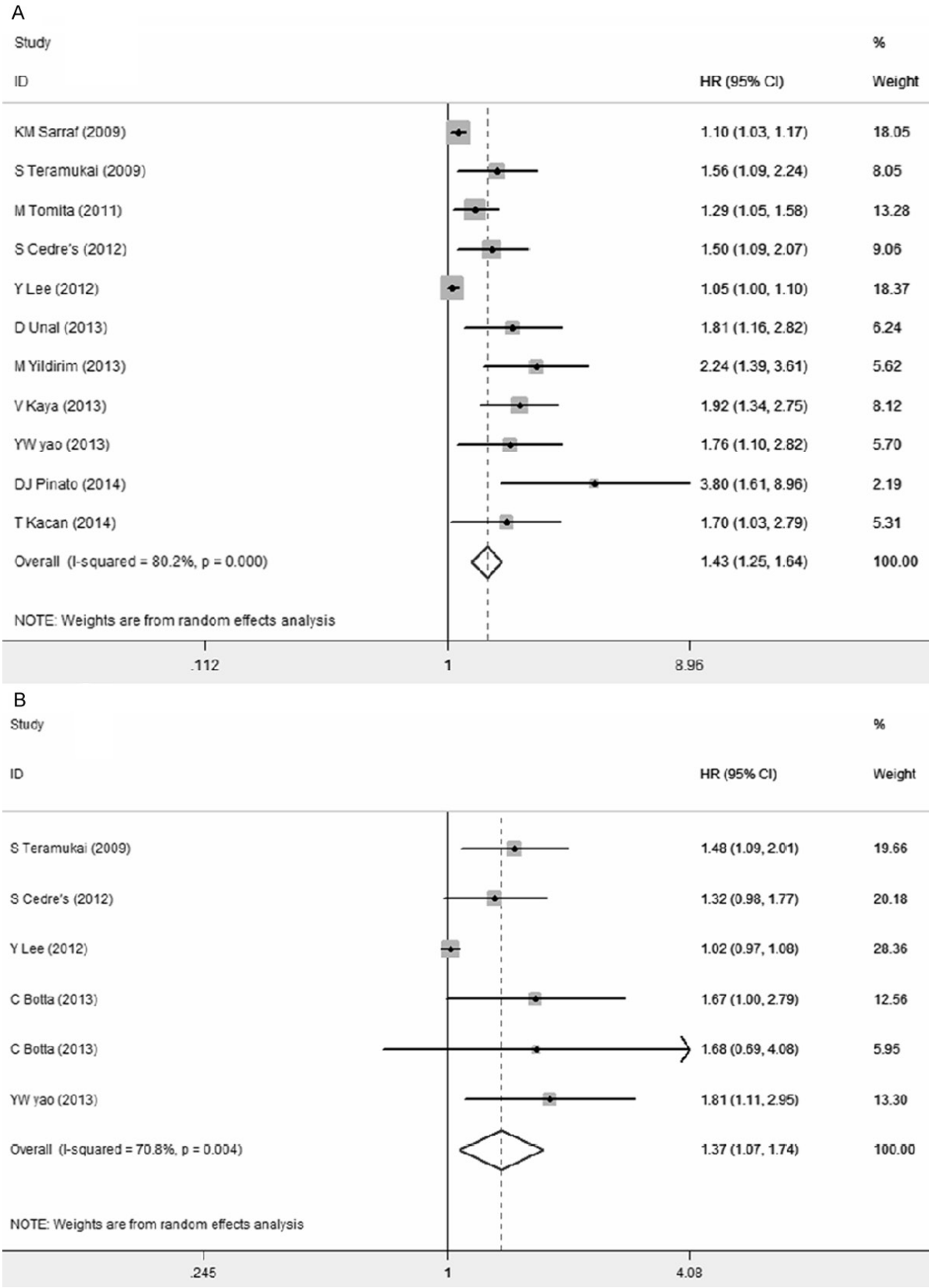

Figure 2. Meta-analysis of the association between NLR and OS (A), and PFS (B) in patients with NSCLC. Results are presented as the individual and summarized Hazard ratios (HR) with 95% confidence interval (CI).

Table 2. Subgroup analysis of summarized Hazard ratios (HRs) reflecting the association between Neutrophil to Lymphocyte Ratio (NLR) and overall survival (OS) in NSCLC

Subgroup	NO. Of studies	Cases	Pooled-data-(random)			Test-for-heterogeneity		
			HR	95 % CI	*P* value	Chi^2	*P*-value	I^2 (%)
Area								
Asia	8	1697	1.56	1.24-1.96	<0.01	39.16	<0.001	82.1
Western	3	568	1.53	0.97-2.40	0.065	11.23	0.004	82.2
Survival analysis								
Multivariate	8	1920	1.27	1.12-1.43	<0.01	27.85	<0.001	74.9
Univariate	3	345	1.96	1.54-2.50	<0.01	0.44	0.80	0
Cutting value								
=5	5	941	1.87	1.49-2.34	<0.01	5.08	0.28	21.3
3-4	2	293	1.32	0.78-2.23	0.31	5.75	0.016	82.6
2-3	2	466	1.40	1.07-1.82	0.014	1.41	0.236	28.9
Multiple cut-offs	2	565	1.25	0.90-1.74	0.185	3.51	0.061	71.5
Treatment								
Surgery	3	681	1.32	0.99-1.77	0.063	9.98	0.007	80.0
Chemotherapy	8	1584	1.61	1.24-2.10	<0.01	40.28	<0.001	82.6

For survival data presented as Kaplan-Meier curves, we extracted and calculated HR and its 95% CI according to the methods described by Parmar [11]. Kaplan-Meier curves were read by Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/). When statistical parameters were displayed as both multivariate analysis and univariate analysis, we chose the former for data combination. In very rare cases, when a study had multiple cut-offs, we use the HR of "top versus bottom group" for pooling [12]. Heterogeneity was tested by using the Cochran's test (Chi squared test) and by quantifying the inconsistency (I^2). A fixed-effect model was employed when heterogeneity was not detected(P:0.10);otherwise,arandom-effectmodel was used. Robustness of the pooled results was verified by one-way sensitivity analysis, of which, every single study was deleted and the pooled HR and 95 % CI as well as the tests for heterogeneity of the remaining studies were calculated. Funnel plots were presented to visualized publication bias. All statistical calculations including graphical presentations were performed by Stata 12.0 (STATA Corporation, College Station, TX, USA).

Results

Characteristics of studies

The initial search through PubMed, EMBASE and Cochrane library yielded 146 studies (**Figure 1**). One hundred and twelve studies were excluded by title or abstract. Upon full text review of the remaining 34 articles, another 22 studies had to be excluded as they were either articles unrelated with the topic (n=2), duplicate publication (n=3), conference abstracts without full text (n=12), reports without associating NLR with survival parameters, such as OS/DFS/PFS (n=2), or articles without sufficient data (n=3). Finally, twelve studies with a total number of 2377 patients were recruited into our meta-analysis to determine the value of NLR as prognostic and clinicopathological markers in NSCLC [4-7, 13-20]. Among the twelve articles included, one article could be split into two "sub-studies", given that it provided the survival data between NLR and PFS based on two different treatment methods.

Study demographics and quality

All articles were retrospective studies directly investigated NLR as a prognostic factor. Of the twelve eligible articles, four were performed in Turkey, two in both UK and Japan, and one in China, Korea, US and Spain, respectively. The median value of the mean age was 60.5 (range 57-68). Males accounted for 60.5% of patients from twelve reported studies. Advanced stage (stage III + IV) was observed in majority of patients with a weighted average of 74.4%. Histology was described in three categories as squamous cell carcinoma (28.6%), adenocarcinoma (56.0%) or other types (15.4%) in ten reported studies. Patients from nine studies

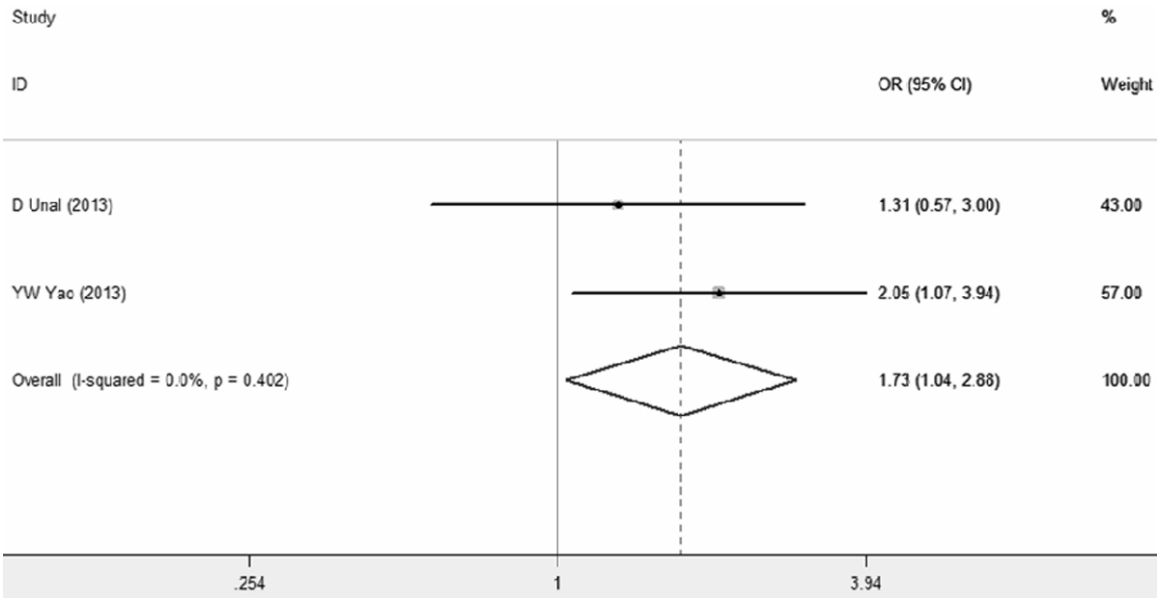

Figure 3. Meta-analysis of studies investigating the association between NLR and treatment response. Forest plot present odds ratio (OR) and 95% confidence interval (CI) calculated by a fixed effect model.

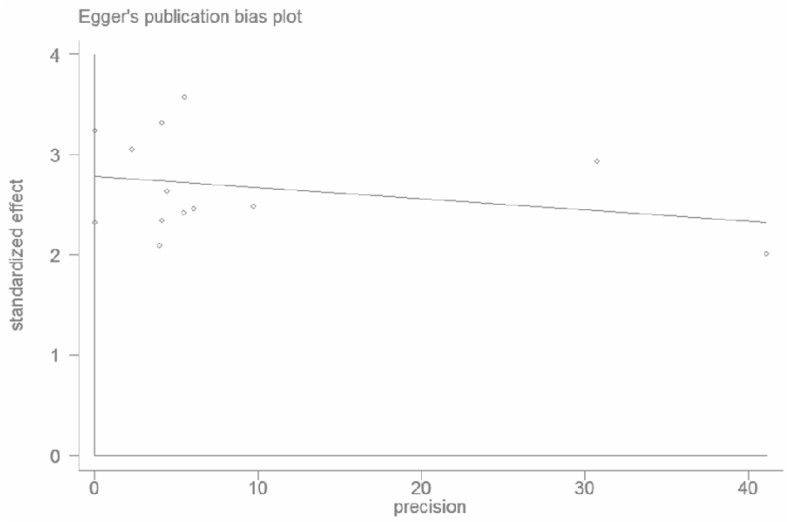

Figure 4. Egger's funnel plot for detecting publication bias of OS. There is publication bias detected (P<0.01).

underwent chemotherapy, while those from three studies underwent surgery. Eight studies were estimated by multivariate analysis, while four studies were estimated by univariate analysis. Five studies had a NLR cutoff of 5, three between 3 and 4, two between 2 and 3, one applied tertiles and one used quartiles. OS was reported or estimated in eleven studies, whereas PFS was only provided in five studies. The scores of study quality assessed by Newcastle-Ottawa quality assessment scale ranged from 5 to 7. The basic features of the twelve studies were summarized in **Table 1**.

Meta-analysis

Nine out of the twelve studies had provided the follow up time. For the overall population, high NLR was found to be significantly associated with poor OS (HR=1.43, 95% CI: 1.25-1.64; I^2= 80.2%, P<0.01) and PFS (HR=1.37, 95% CI: 1.07-1.74; I^2=70.8%, p=0.004) (**Figure 2A** and **2B**). Furthermore, the studies were stratified to evaluate HR of OS by study region, statistical method to estimate HR, cutoff value and treatment method (shown in **Table 2**). To analyze study region on evaluating HR, the studies from Asia countries showed a statistically significant HR of 1.56 (95% CI 1.24-1.96, P<0.01), however, the studies from Western countries almost had no significance (HR=1.53, 95% CI 0.97-2.40, P=0.065). In analyzing statistical method on evaluating HR, combined HR of studies by multivariate analysis was 1.27 (95% CI 1.12-1.43, P<0.01), while combined HR by univariate analysis was 1.96

(95% CI 1.54-2.50, P<0.01). A subgroup analysis was also performed for studies with respect to cutoff value in predicting OS. The results indicated that both cutoff value =5 and cutoff value between 2 and 3 showed statistically significant HR of 1.87 (95% CI 1.49-2.34, P<0.01) and 1.40 (95% CI 1.07-1.82, P=0.014), respectively. Whereas cutoff value between 3 and 4 and multiple cut-offs were not statistically significant with a pooled HR of 1.32 (95% CI 0.78-2.23, P=0.31) and 1.25 (95% CI 0.90-1.74, P=0.185), respectively. When studies were stratified by treatment method, combined HR of studies with chemotherapy showed a prognostic HR of 1.61 (95% CI 1.24-2.10, P<0.01), while surgery subgroup showed non-statistically significant HR of 1.32 (95% CI 0.99-1.77, P=0.063). Given the small number of studies for PFS, the subgroup analysis was abandoned.

In addition, we investigated the association between NLR and treatment response with a pooled OR of 1.73 (95% CI 1.04-2.88, P=0.035; I^2=0%, P=0.40), suggesting that NLR has a potential prognostic value (**Figure 3**).

Publication bias

Egger's test for publication bias suggested that there was statistically significant for OS (P< 0.01) (**Figure 4**).

Sensitivity analysis

Sensitivity analysis was conducted to test the robustness of the result of OS by removing one study each time. The combined HR and its 95% CIs were not significantly altered when any study was excluded, suggesting that any single study had not significant impact on the combined result and confirmed the robustness of the outcome of this study.

Discussion

Although great progress has been made in the treatment of NSCLC, the overall survival still has enough space for improvement. So, potential biomarkers for predicting or improving the outcomes have been explored. In recent years, the prognosis of NLR has been studied in NSCLC, so we conducted a meta-analysis to clarify the role of pretreatment NLR in the prognostic significance of patients with NSCLC. The pooled HR indicated that elevated NLR was associated with poor OS and PFS. Besides, high NLR predicted worse response to chemotherapy. Subgroup analysis suggested that a higher NLR implied a much worse OS. Subgroup by treatment method showed that elevated NLR had a prognostic significance in patients treatment by chemotherapy than surgery, however, more studies were needed to consolidate or overthrow the conclusion since only three studies were conducted based on the method of surgery. We did not make a meta-analysis on the correlation between NLR and clinicopathological characteristics due to a lack of adequate studies with sufficient data. In addition, subgroup analysis for PFS based on study region had suggested that elevated NLR had an unfavorable impact on patients with NSCLC in western countries compared with Asian countries.

Apart from NSCLC, some other solid tumors including hepatocellular carcinoma, colorectal cancer, and gastric cancer showed similar conclusion based on pooled analysis [21, 22]. The relationship between inflammation and tumor has been studied for several decades. The exact mechanism between the elevated NLR and poor prognosis in these cancer patients was still undefined. Evidence has shown that neutrophils are implicated in the promotion of metastasis in patients with pulmonary carcinoma and are prognostic indicator for patients with advanced NSCLC [23]. On the contrary, decreased lymphocyte has been demonstrated as biomarker of poor survival for patients with terminal cancer due to the key role of lymphocytes in killing cancer cells and regulating the proliferation, apoptosis, angiogenesis and metastasis of cancer by secreting cytokine [24-26]. Overall, NLR reflects the balance between tumor destruction and tumor protection.

The limitations in this meta-analysis should be addressed. Obviously, the heterogeneity was significant in both pooled HR of OS (I^2=80.2%, P<0.001) and PFS (I^2=70.8%, P=0.004). There were many possible causes to explain the heterogeneity, such as histology type, UICC stage differences, study country, treatment method, method to detect the laboratory index (such as neutrophil count and lymphocyte count), NLR cutting value, HR estimate method, quality of study and potential publication bias. To explore the possible causes of heterogeneity, subgroup was divided according to the mentioned items above. However, subgroup analysis did not eliminate the high heterogeneity based on study region and treatment method. Further analysis showed that the subgroup with

a cut-off of 5 had a decreased heterogeneity (I^2=21.3%, P=0.28), while other subgroups nearly had no obvious change. Even so, we still could not rule out the heterogeneity caused by cut-off. Additionally, from the point of clinical practice, it is necessary to unify the cut-off standard. In our meta-analysis, the included studies most set the cut-off based on the previous studies or mean of NLR, and only three studies set the cutting value by ROC. One study calculated the HR based on analysis of regression with tertiles, and another study calculated the HR based on quartiles. The method to calculate HR also contributed to the heterogeneity of pooled HR. Another disadvantage of our studies was that the publication bias was evident, and the possible causes could attribute to language restriction in the inclusion criterion or selective publication. It is worth mentioning that a total of 12 conference abstracts without full text excluded in this meta-analysis probably had a significant impact on the publication bias. By the way, because of insufficient data, we did not conduct subgroup analysis based on histology type and UICC stage differences.

In conclusion, the NLR is a useful clinical index to predict the survival and treatment response of patients with NSCLC. Subgroup analysis indicated that the patients with NSCLC treated by chemotherapy, especially those patients with a NLR more than 5 had a significant prognostic value. In future, more studies with better design are needed to confirm the conclusion.

Disclosure of conflict of interest

None.

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