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Research Paper

The value of neutrophil-to-lymphocyte ratio for response and prognostic effect of neoadjuvant chemotherapy in solid tumors: A systematic review and meta-analysis

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Abstract

Introduction: The neutrophil-to-lymphocyte ratio (NLR) has been found to be an indicator of poor prognosis in many tumour types. However, little is known about the relationship between the NLR and patients with tumours who receive neoadjuvant chemotherapy (NAC) in terms of response rate and prognostic ability. We thus performed this meta-analysis to further investigate this relationship.

Methods: An electronic systematic literature search for articles published before September 2017 was performed to explore the association between the pretreatment NLR and outcome in patients treated with NAC. Data were extracted by the reported odds ratios (ORs) and hazard ratios (HRs) with their 95% confidence intervals (CIs) for the response rate and the survival outcome, respectively. The results were pooled using the random-effect or fixed-effect model.

Results: Thirty-three studies were eventually included in our study, and all were published no earlier than 2011. An NLR that was higher than the cut-off was associated with a lower pathological complete response (pCR) rate in patients with cancer (OR = 1.72, 95% CI, 1.26-2.33). A lower NLR was associated with better overall survival (OS) (HR = 1.58, 95% CI, 1.34-1.86), cancer-specific survival (CSS) (HR = 2.22, 95% CI, 1.32-3.74), disease-free survival (DFS) (HR = 1.32, 95% CI, 1.10-1.59) and recurrence-free survival (RFS) (HR = 1.90, 95% CI, 1.50-2.40).

Conclusion: Overall, an NLR lower than the cut-off value indicated a greater chance for pCR and may predict good survival outcomes after NAC for patients with solid tumours. The use of the NLR for risk stratification before NAC should be further demonstrated by future large-scale prospective studies.

Key words: Neutrophil to lymphocyte ratio (NLR); prognosis; solid cancer; neoadjuvant therapy; meta-analysis

Introduction

Neoadjuvant chemotherapy or chemoradiation therapy plays an important role in the treatment of locally advanced cancer. In bladder cancer, platinum-based combination neoadjuvant chemotherapy has shown obvious improvements in survival, and the Canadian Association of Genitourinary Medical Oncologists (CAGMO) reached a consensus with respect to the use of neoadjuvant chemotherapy in muscle invasive bladder cancer to improve patient outcomes[1, 2]. Neoadjuvant chemotherapy regimens

used in breast cancer not only increased the rate of breast-conserving surgery but also reduced the risk of some negative outcomes[3]. It is well known that the significantly improved outcome in patients is closely associated with pathological complete response (pCR) after NAC[4, 5]. Researchers have proposed the use of many markers, such as mutated genes, that are associated with the response to neoadjuvant treatment[6, 7]. However, those markers are not easily assessable, and until now, no proven clinical biomarkers have been widely accepted to predict the tumour response after NAC. Therefore, an accurate marker is needed as it can prevent futile chemotherapy in patients so that they can receive definitive surgery in time.

Currently, increasing evidence shows that tumour-associated inflammation may be associated with systemic inflammation and may play an important role in cancer development, survival and chemo-sensitivity[8-12]. Inflammation affects blood parameters first, and abnormalities in blood cells such as neutrophilia and lymphopenia have been found in patients with tumours. The neutrophil-to-lymphocyte ratio (NLR) is an easily available and inexpensive marker of inflammation, and an elevated NLR has been used as a marker of poor prognosis in many tumours[13]. Some studies have explored the crosstalk between inflammation and chemo-sensitivity in cancer patients and found that a low NLR may be associated with a high response to NAC[14, 15]. The direct impact of the NLR on the survival of patients after NAC remains inconclusive.

One aim of our meta-analysis was to study the level of pretreatment NLR and its relationship to the pathologic complete response to NAC in patients with solid tumours. The other aim was to evaluate the prognostic value of NLR with respect to the survival outcome in cancer patients after NAC by pooling the eligible results.

Methods

Search strategy

This meta-analysis was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Relevant articles published until September 2017 were identified through searches of PubMed, Embase and the Web of Science. The related keywords used were "tumour" OR "cancer" OR "neoplasm" AND "neoadjuvant chemotherapy" OR "preoperative chemotherapy" OR "primary chemotherapy" AND "neutrophils" AND "lymphocyte" AND "ratio". Other references from previously published studies were also searched.

Study selection

Two independent authors selected the identified studies. The inclusion criteria were as follows: (1) Studies that involved patients with solid tumours who received neoadjuvant chemotherapy or neoadjuvant chemoradiation and that reported the prognostic impact of the peripheral blood NLR; in these studies, the NLR appeared as a categorical variable. (2) Studies that provided the relationship between the NLR and pCR after neoadjuvant treatment as odds ratios (ORs) with 95% confidence intervals (CIs) or studies that provided data on the number of patients who achieved pCR in the low and high NLR groups. The definition of pCR was classified as the complete absence of cancer tissue in all postoperative material. (3) Studies that provided survival data such as overall survival (OS), cancer-specific survival (CSS), disease-free survival (DFS), progression-free survival (PFS) and recurrence-free survival (RFS) in the form of hazard ratios (HRs) with 95% confidence intervals (CIs). The definitions of DFS and PFS were similar and can be combined in an analysis. (4) If duplicate or overlapping data appeared, the study report with the most samples and comprehensive information was included. (5) Abstracts from which useful information could be extracted and those with clear treatment methods were also included.

Data extraction

Two reviewers independently extracted the useful data from the eligible studies. The following information was gathered: first author's name, publication year, publication type, tumour type, research region, entire sample size, the cut-off value of the NLR, the methods by which the NLR was obtained, neoadjuvant treatment methods, neoadjuvant treatment response information, and survival outcome types. The results of multivariable analyses were given precedence, but otherwise, the results of univariate analyses were extracted.

Quality assessment

The quality of the included studies was assessed using the Newcastle–Ottawa Scale (NOS) tool. The NOS tool included three main domains: study selection (0-4 points), comparability (0-2 points) and results assessments (o-4 points). Studies were rated as high quality if the NOS scored six or higher, otherwise rated as low quality. Two independent authors performed this work, and any discrepancies were resolved by discussion.

Statistical analyses

We used RevMan 5.3 (The Cochrane Collabora-

tion, Copenhagen, Denmark) to pool the results of our meta-analysis. The pCR values and the total number of patients in the low and high NLR groups were extracted to calculate the ORs and 95% CIs; then, these results were pooled with other ORs that were provided directly to obtain the final results. A pooled OR >1 frequently indicated that a low NLR was related to a relatively better pCR rate. The HR was representative of the high blood NLR over the low blood NLR. HRs > 1 implied a poor prognosis while HRs < 1 implied a good prognosis. Heterogeneity was assessed using Cochran Q (p value for heterogeneity) and I^2 statistics. An $I^2 > 50\%$ or a $p < 0.1$ indicated significant heterogeneity then a random-effect model was used, but otherwise, a fixed-effect model was used. Subgroup analyses were performed according to our data features such as publication type, research region, tumour type, and cut-off NLR values, among others, to determine the potential source of heterogeneity.

Publication bias was assessed by Egger's test and $P>|t| < 0.05$ indicated significant publication bias. When publication bias existed, trim-and-fill methods were applied by adding the missing studies to the meta-analysis, and the new pooled results were recalculated to adjust the primary results. These analyses were performed using StataSE (StataCorp, College Station, TX, USA) software.

Results

Study characteristics

In summary, 1167 records were identified, from which 33 records met all our criteria and finally included in our meta-analysis. All the enrolled studies were published between 2011 and 2017, and 27 contained full-text data, while 6 contained supplemental abstract data (Figure 1). In all, 6243 individuals were included in the analysis with a sample size that ranged from 41 to 845. Five studies on bladder cancer[16-20], eight on breast cancer[15, 21-27], twelve on rectal cancer[28-39], six on gastroesophageal cancer[40-45], one on head and neck squamous cell carcinoma[46] and one on intrahepatic cholangio carcinoma[47]. Eighteen studies reported the relationship between the NLR and pCR, and twenty-four studies reported the association between the NLR and outcomes (OS, CSS, DFS, RFS) in patients who received NAC. The cut-off value of the NLR was reported in 32 studies but was unclear in one study (Table 1).

Relationship between the NLR and pCR

Eighteen studies reported the relationship between the NLR and pCR. A lower NLR was associated with a higher pCR rate (OR = 1.72, 95% CI, 1.26-2.33, I^2 = 66%, random effect model; Figure 2). Bladder cancer, breast cancer and rectal cancer were the three most common tumour types involved, and among them, bladder cancer (OR = 1.95, 95% CI, 1.16-3.29, I^2 = 0%) and rectal cancer (OR = 2.01, 95% CI, 1.14-3.55, I^2 = 55%) demonstrated statistical significance, while breast cancer did not demonstrate statistical significance (OR = 1.41, 95% CI, 0.91-2.19, I^2 = 68%). A stratified analysis using data from the full-texts or abstracts showed that a low NLR from the full-texts was significantly associated with the pCR rate (OR = 1.91, 95% CI, 1.28-2.84); however, a low NLR from the abstracts was not significantly associated with the pCR rate (OR = 1.35, 95% CI, 0.88-2.07). When the data were stratified according to the geographic region, for research conducted in Asia (OR = 1.82, 95% CI, 1.18-2.81) and the North America (OR = 1.64, 95% CI, 1.03-2.61), the NLR data were significantly associated with the pCR rate, while for the studies conducted in Europe, the data (OR = 1.73, 95% CI, 0.92-3.27) did not show a statistical association. For the different NLR cut-off values, NLR values higher than 3 showed an obvious association between the NLR and the pCR (OR = 3.00, 95% CI, 1.48-6.12). In contrast, values equal to 3 (OR = 1.52, 95% CI, 0.95-2.44) or lower than 3 (OR = 1.64, 95% CI, 0.97-2.77) did not show a significant association between the NLR and the pCR (Table 2).

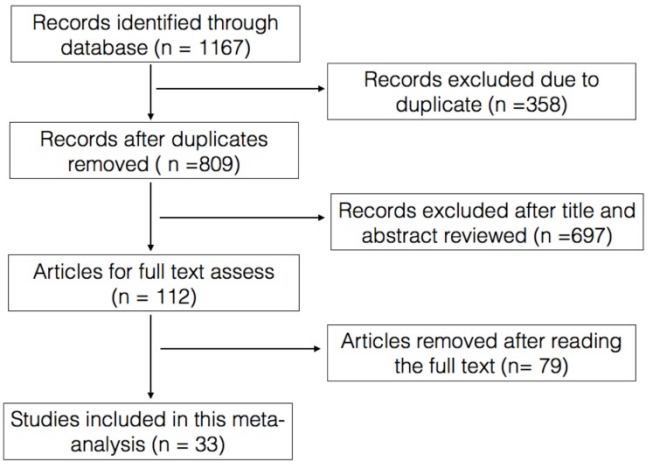

Figure 1. Flow chart of the study search.

Overall survival

Eighteen studies reported HRs for overall survival. Higher NLRs were associated with a poor OS (HR = 1.58, 95% CI, 1.34-1.86, I^2 = 77%; Figure 3 (a)). The pooled results of the NLRs for OS among the tumour subgroups showed a statistical association with OS in rectal cancer (HR = 1.93, 95% CI, 1.17-3.19) and other unselected tumours (HR = 3.04, 95% CI, 1.64-5.64), while in bladder cancer (HR = 1.52, 95% CI,

0.97-2.36), breast cancer (HR = 2.26, 95% CI, 0.82-6.28) and gastroesophageal cancer (HR = 1.36, 95% CI, 0.99-1.85), the prognostic effect of the NLR on OS was not statistically significant. A subgroup analysis by research region revealed that the prognostic effect of the NLR was lowest in Europe (HR = 1.18, 95% CI, 1.01-1.38), followed by Asia (HR = 1.65, 95% CI, 1.15-2.35) and was highest in North America (HR = 2.03, 95% CI, 1.59-2.59). A higher cut-off of the NLR showed a higher prognostic effect of the NLR, whereas an NLR lower than 3 with an HR = 1.46 (95% CI, 1.14-1.87), an NLR equal to 3 with an HR = 1.55 (95% CI, 1.16-2.07) and an NLR higher than 3 with an HR = 2.31 (1.20-4.43). Specific data regarding the subgroup analysis are shown in Table 2.

Table 1: Baseline characteristics of included studies.

Author	Publish year	Publish type	Tumor type	Country	Sample size	NLR cut-off	Method for NLR cut-off value chose	Neoadjuvant treatment type	Response rate reported (yes/no)	Types of outcome reported	NOS score
Buisan	2017	full	Muscle-invasive Bladder cancer	German	75	2.5	ROC	chemotherapy	yes	PFS, CSS, OS	7
Kessel	2016	full	Muscle-invasive Bladder cancer	Netherlands	123	2.21	ROC	chemotherapy	yes	NA	8
Leibowitz-Amit	2016	full	Muscle-invasive Bladder cancer	Israel	55	3	NA	chemotherapy	yes	NA	8
Mmeje	2016	Abstract	Bladder cancer	American	584	4.9	CART models	chemotherapy	no	CSS, OS	6
Siano	2016	Abstract	Muscle-invasive Bladder cancer	American	272	3	NA	chemotherapy	no	PFS, OS	5
Asano	2015	full	Triple-negative breast cancer	Japan	61	3	NA	chemotherapy	yes	DFS, OS	8
Chen Y	2016	full	Breast cancer	China	215	2.1	ROC	chemotherapy	yes	RFS, CSS	8
Enriquez	2017	Abstract	Triple-negative breast cancer	Peru	338	3	NA	chemotherapy	yes	DFS, OS	6
Hernandez	2017	full	Breast cancer	Spain	150	3.33	ROC	chemotherapy	yes	NA	7
Koh	2014	full	ER positive and/or PR positive and HER2-negative breast cancer	Korea	157	2.25	ROC	chemotherapy	yes	RFS, OS	9
McGuire	2017	Abstract	Breast cancer	Ireland	211	3	NA	chemotherapy	yes	NA	5
Suppan	2015	full	Breast cancer	Austria	247	NA	NA	chemotherapy	yes	DFS	8
Xu	2017	full	Breast cancer	China	128	1.67	ROC	chemotherapy	yes	NA	7
Caputo	2016	full	Rectal cancer	Italy	87	2.8/3.8	ROC	chemoradiation	yes	NA	7
Carruthers	2012	full	Locally advanced rectal cancer	UK	115	5	Pre-search data	chemoradiation	no	OS, DFS	8
Dudani	2017	Abstract	Local advanced rectal cancer	Canada	845	4	NA	chemoradiation	yes	NA	6
Hodek	2016	full	Local advanced rectal cancer	Czech	173	2.8	χ^2 text	chemoradiation	no	OS	7
Kim	2014	full	Rectal cancer	Korea	102	3	Experience	chemoradiation	yes	RFS, CSS	7
krauthamer	2013	full	Advanced rectal cancer	Israel	140	5	ROC	chemoradiation	yes	NA	7
Lee	2017	full	Local advanced rectal cancer	Korea	291	5	NA	chemoradiation	yes	NA	8
Nagasaki	2015	full	locally advanced low rectal cancer	Japan	140	3	ROC	chemotherapy	yes	OS, RFS	8
Runau	2017	full	Local advanced rectal cancer	UK	277	4.32	ROC	chemoradiation	yes	OS	7
Shen J	2017	full	Local advanced rectal cancer	China	202	3	ROC	chemoradiation	yes	OS,DFS	8
Shen L	2014	full	Local advanced rectal cancer	China	199	2.8	ROC	chemoradiation	no	OS, DFS	8
Sung	2017	full	Local advanced rectal cancer	Korea	49	1.75	The maximally selected log-rank test in R version	chemoradiation	yes	DFS	7
Aziz	2014	full	Locally advanced gastric cancer	Egypt	70	3	NA	chemotherapy	no	PFS, OS	7
Chen L	2017	full	Advanced gastric cancer	China	91	2.17	ROC	chemotherapy	yes	DFS, OS	8
Jin	2017	full	Advanced gastric cancer	China	119	2.23	ROC	chemotherapy	no	RFS, OS	7
Ji	2016	full	Local advanced esophageal cancer	China	41	5	NA	chemotherapy	no	CSS, PFS	8
Miyata	2011	full	Esophageal cancer	Japan	152	4	NA	chemotherapy	no	OS	7
Salih	2016	Abstract	Oesophageal/gastroesophageal junction (O/GOJ) adenocarcinoma	UK	368	3	NA	chemotherapy	no	OS	6
Rosculet	2017	full	Head and neck squamous cell carcinoma	American	123	2.7	Median value	chemoradiation	no	OS, RFS	7
Omichi	2017	full	Intrahepatic cholangiocarcinoma	American	43	3	NA	chemotherapy	no	RFS, OS	8

Abbreviations: NLR: neutrophil-to-lymphocyte ratio; NOS: Newcastle–Ottawa Scale; OS: overall survival; CSS: cancer special survival; DFS: disease-free survival; RFS: recurrence-free survival; NA: not available; ROC: receiver operating characteristic curve.

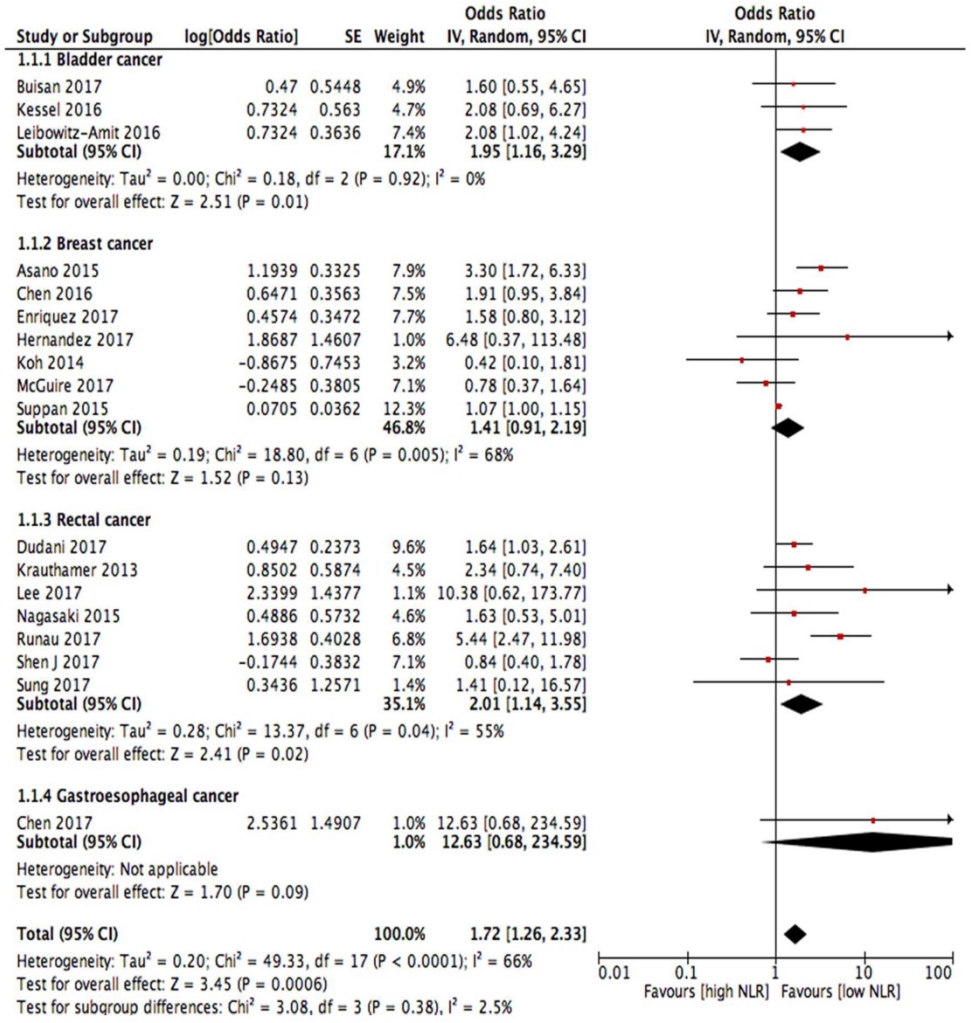

Figure 2. Forest plots for association between NLR and pCR.

Cancer-specific Survival

Only five studies reported the HRs for CSS. Two studies examined bladder cancer, one examined breast cancer, one examined oesophageal cancer and one examined rectal cancer. A higher NLR was associated with poor CSS in all five studies. The pooled HR for CSS was 2.22 (95% CI, 1.32-3.74; Figure 3 (b)) with significant heterogeneity (I^2 = 81%) using a random effect model.

Disease-Free survival

Eleven studies reported DFS data. Overall, a lower NLR was associated with higher DFS (HR = 1.32, 95% CI, 1.10-1.59, I^2 = 73%, random effect model; Figure 3(c)). When stratified by tumour type, only the results for bladder cancer (HR = 1.32, 95% CI, 1.08-1.61) reached statistical significance. Breast cancer (HR = 1.14, 95% CI, 0.87-1.49), rectal cancer (HR = 1.84, 95% CI, 0.94-3.60) and gastroesophageal cancer (HR = 1.34, 95% CI, 0.76-2.36) all showed a non-significant association between a low NLR and a high DFS. No statistically significant difference was observed among tumour types ($P_{interaction}$ = 0.58).

Recurrence-Free Survival

A total of seven records reported the hazard ratios for RFS. The pooled HR for RFS was 1.90 (95% CI, 1.50-2.40) with no heterogeneity (I^2 = 36%, fixed effect model; Figure 3 (d)).

Publication Bias

For the pCR and OS subset, the asymmetry of the funnel plot indicated potential publication bias, which was confirmed by Egger's test (all $p < 0.001$). After adjusting the results using the trim-and-fill method, the pooled OR for pCR was 1.64 (95% CI, 1.22-2.23; Figure 4 (a)), and the pooled HR for OS was 1.37 (95% CI, 1.16-1.62; Figure 4 (b)) according to a random effect model. The results were roughly consistent with the primary results.

Table 2: Subgroup analyses of the associations between NLR and OS, DFS and pCR

Variables	Overall survival (OS)				Disease-free survival (DFS)				pathological complete response (pCR)			
	No of studies	HR (95%CI)	I^2, Phet	$P_{interaction}$	No of studies	HR (95%CI)	I^2, Phet	$P_{interaction}$	No of studies	OR (95%CI)	I^2, Phet	$P_{interaction}$
Total	18	1.58 (1.34-1.86)	p < 0.0001		11	1.32 (1.10-1.59)	p < 0.0001		18	1.72 (1.26-2.33)	p < 0.0001	
Publication type				p = 0.63				p = 0.28				p = 0.24
Full text	14	1.70 (1.34-2.16)	p < 0.0001		9	1.27 (1.03-1.55)	p = 0.0004		15	1.91 (1.28-2.84)	p < 0.0001	
Abstract	4	1.53 (1.04-2.23)	p < 0.0001		2	1.51 (1.18-1.92)	p = 0.71		3	1.35 (0.88-2.07)	p = 0.23	
Research region				p = 0.002				p = 0.74				p = 0.98
Asia	8	1.65 (1.15-2.35)	p = 0.05		5	1.31 (0.88-1.96)	p = 0.09		10	1.82 (1.18-2.81)	p = 0.10	
Europe	4	1.18 (1.01-1.38)	p = 0.002		3	1.24 (0.94-1.63)	p < 0.0001		6	1.73 (0.92-3.27)	p = 0.001	
North America	4	2.03 (1.59-2.59)	p = 0.34		1	1.59 (1.10-2.29)	-		1	1.64 (1.03-2.61)	-	
Others	2	1.92 (1.09-3.39)	p = 0.22		2	1.44 (1.07-1.94)	p = 0.93		1	1.58 (0.80-3.12)	-	
Sample size				p = 0.78				p = 0.88				p = 0.08
< 100	5	1.57 (0.99-2.49)	p = 0.05		5	1.37 (1.03-1.83)	p = 0.23		5	2.50 (1.63-3.83)	p = 0.56	
>100	13	1.69 (1.35-2.11)	p < 0.0001		6	1.33 (1.00-1.77)	p = 0.0006		13	1.54 (1.10-2.14)	p = 0.001	
Tumor type				p = 0.19				p = 0.58				p = 0.38
Bladder cancer	3	1.52 (0.97-2.36)	p < 0.0001		2	1.32 (1.08-1.61)	p = 0.23		3	1.95 (1.16-3.29)	p = 0.92	
Breast cancer	3	2.26 (0.82-6.28)	p = 0.03		3	1.14 (0.87-1.49)	p = 0.09		7	1.41 (0.91-2.19)	p = 0.005	
Rectal cancer	5	1.93 (1.17-3.19)	p = 0.001		4	1.84 (0.94-3.60)	p = 0.003		7	2.01 (1.14-3.55)	p = 0.04	
Gastroesophageal cancer	5	1.36 (0.99-1.85)	p = 0.09		2	1.34 (0.76-2.36)	p = 0.88		1	12.63 (0.68-234.59)	-	
Others	2	3.04 (1.64-5.64)	p = 0.98		-	-	-		-	-	-	
Cut-off value of NLR				P = 0.43				p = 0.05				p = 0.27
<3	7	1.46 (1.14-1.87)	p = 0.005		4	1.44 (1.05-1.97)	p = 0.14		6	1.64 (0.97-2.77)	p = 0.35	
3	8	1.55 (1.16-2.07)	p = 0.002		5	1.31 (1.04-1.63)	p = 0.32		6	1.52 (0.95-2.44)	p = 0.04	
>3	3	2.31 (1.20-4.43)	P = 0.01		1	4.10 (1.70-9.89)	-		5	3.00 (1.48-6.12)	p = 0.08	

Abbreviations: NLR: Neutrophil to lymphocyte ratio; NAC: neoadjuvant chemotherapy; OR: odds ratio; HR: hazard ratios; CI: confidence interval; pCR: pathological complete response; OS: overall survival; CSS: cancer special survival; DFS: disease-free survival; RFS: recurrence-free survival; Phet: pvalue for heterogeneity

Discussion

The NLR has been used as a systematic marker of inflammation and has garnered the interest of physicians in recent years. The prognostic significance of the NLR has been demonstrated by many meta-analyses in almost all tumour types[48] as well as in select tumour stages[49]. Some studies have explored the effect of the pretreatment NLR in cancer patients who received neoadjuvant chemotherapy, but the exact results are still undefined. In this meta-analysis, we included 33 studies and found that all studies were published within the past 6 years. Neoadjuvant chemotherapy was not given to patients with certain tumour types, and thus only 6 cancer types were eligible for our study, and among them, more than 2 studies were available for result pooling this only for bladder cancer, breast cancer, rectal cancer and gastroesophageal cancer. After all the relevant results were pooled, we found that a lower NLR was associated with a higher pCR rate and that a lower NLR served as a prognostic indicator, as it was associated with good OS, CSS, DFS and RFS.

The reason why an elevated NLR is associated with a lower pCR rate and worse outcomes is not completely understood. The most reasonable explanation is that the NLR is related to systematic inflammation in patients with tumours[50]. Host immune system and tumours interaction significantly associated with cancer patients' prognosis and measure some simple systemic immune reaction markers such as neutrophil, lymphocyte and NLR can generally represent the host-tumor interaction conditions[51, 52]. Neutrophils can produce some types of cytokines, such as transforming growth factor-beta and vascular endothelial growth factor especially after they integrated with cancer cells; this in turn leads to cancer cell proliferation, infiltration

and metastasis[53-56]. In addition, blood neutrophils were found to inhibit the function of lymphocytes when co-incubated these two kind of cells, which may influence patients' immune system[57]. Lymphocytes, however, are known to play an important role in the suppression of cancer via the induction of cytotoxic cell death, and a higher pretreatment lymphocyte count was found to be associated with good neoadjuvant treatment response in patients with locally advanced rectal cancers[58]. The interaction between the immune system and cancer cells mostly occurs near the tumour tissue, and thus there may be some connection between the peripheral NLR and tumour-infiltrating lymphocytes. An increase in tumour-infiltrating lymphocytes has been shown to play a significant role in prognosis in many types of cancer such as breast cancer, lung cancer and gastric cancer[59-61].

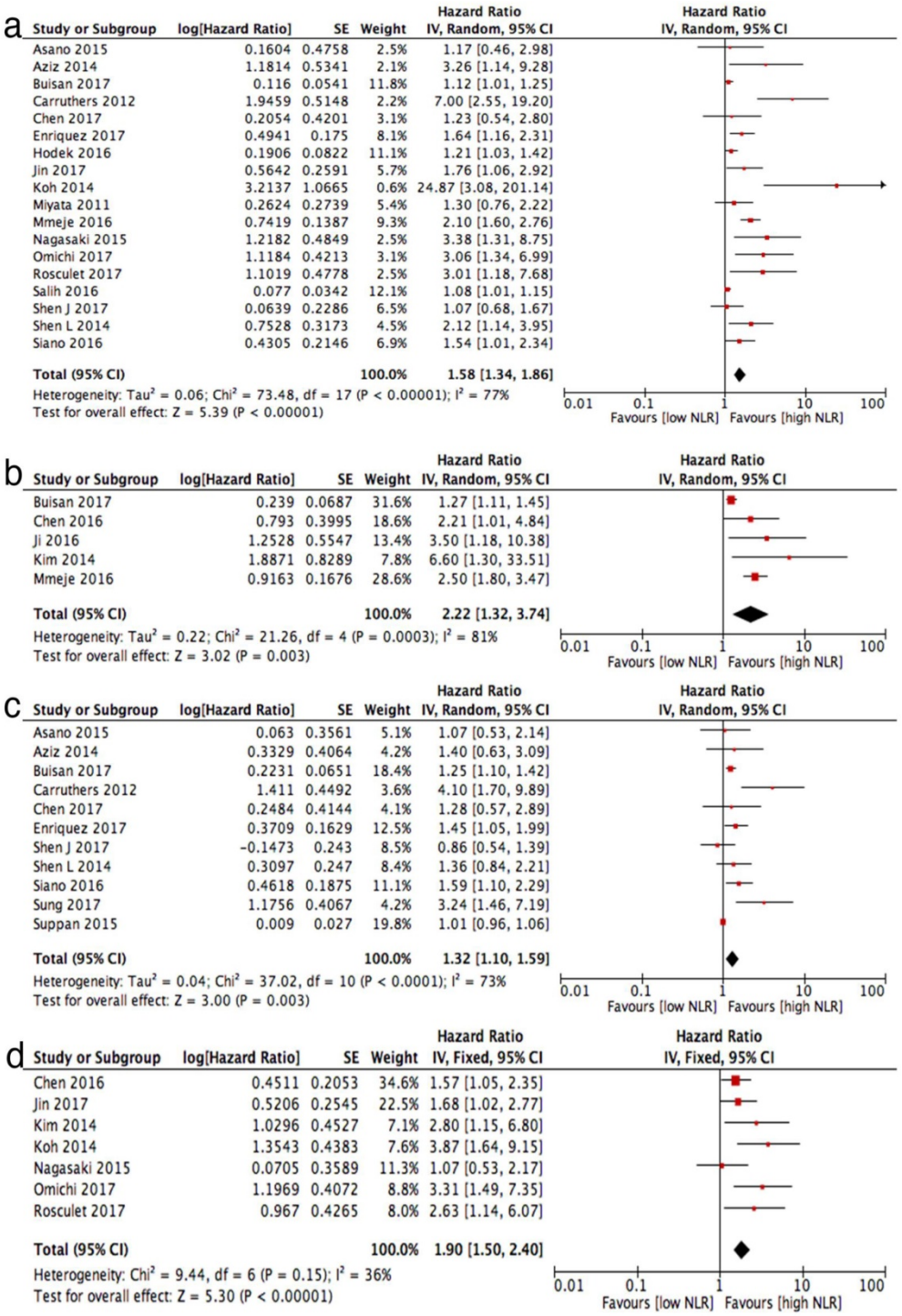

Figure 3. Forest plots for associations between NLR and (a) overall survival, (b) cancer special survival, (c) disease-free survival, (d) recurrence-free survival.

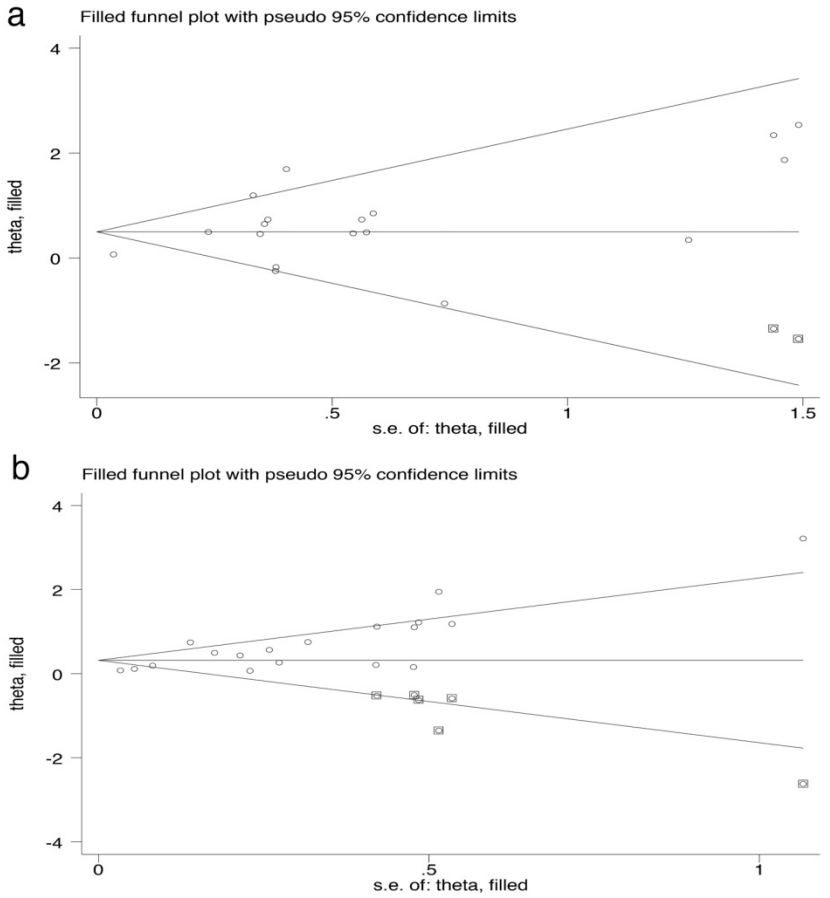

Figure 4. Funnel plot used trim-and-fill methods for (a) pathological complete response and (b) overall survival.

The effect of tumour-infiltrating lymphocytes was also found to be closely associated with neoadjuvant treatment response especially in breast cancer[62, 63]. Other studies have investigated the association between the NLR and circulating cytokines. Motomura and Kantola found that tumours with an elevated NLR also had higher levels of some interleukins and MCP-1, among other cytokines. This suggested that the NLR may partly influence the immune response[64, 65].

In this analysis, all bladder cancer patients were treated with neoadjuvant chemotherapy followed by radical cystectomy. A low pretreatment NLR was associated with a significant increase in the pCR rate and a longer DFS, but for OS, its protective effect was not statistically significant. Bladder cancer is thought to be an immune-related disease as it responds well to immunotherapy[66]. Many other immune-related markers such as lymphocyte-to-monocyte ratio (LMR), hemoglobin, platelet-to-lymphocyte ratio (PLR) were found to significantly associated with outcomes in bladder cancer patients but their research in neoadjuvant chemotherapy patients were few[67-70]. In a small sample retrospective study conducted by Seah, NLR were found to sustained decreased in NAC response patients, this decrease of inflammatory burden may associated with patients' pathological response[14]. Viers explored 899 bladder cancer patients and found that the NLR may be used as a prognostic marker for risk stratification including for the selection of patients who might benefit from neoadjuvant therapy[71]. The finding that the NLR did not show a statistically significant relationship with OS may be partly due to indelible heterogeneities such as tumor burden and invasive ranges.

The NLR seems not to be a good marker for patients with breast cancer who received neoadjuvant chemotherapy, as the pooled data for OS, DFS and pCR all did not appear to show significant differences. Although breast cancer is not generally regarded as an immune-related disease, a low NLR in unstratified breast cancer patients in previous studies was still found to be associated with good OS and DFS[72-74]. Marin retrospective 150 breast cancer patients and found some immune-related markers such as high lymphocyte-to-monocyte ratio (LMR) and low NLR were associated with favorable prognoses in patients treated with NAC[23]. The inconsistent results of the NLR in breast cancer may partly due to the different molecular subtypes of tumours. Yao and Asano reported that the NLR was a good prognostic marker in triple-negative breast cancer[15, 75], but Noh found that an elevated NLR was associated with a poorer disease-specific survival, which was evident mostly in the luminal A subtype[76]. The dominant molecular subtype in a cohort of breast cancer patients may obviously influence the prognostic effect of the NLR.

A low NLR was associated with a significantly higher pCR rate and a protective effect with respect to OS in rectal cancer patients who received pre-operative treatment. This may be attributed to a variety of reasons. On the one hand, colorectal cancer is found closely associated with systemic inflammation, as Guthrie found that several systemic inflammation-related markers exhibited prognostic value in colorectal cancer patients[77] and Burn discovered that long-term use of aspirin, a non-steroidal anti-inflammatory drug, can decrease the risk of colorectal cancer[78]. On the other hand, all the studies except one treated patients with neoadjuvant chemoradiation and compared them

with patients who were treated only with neoadjuvant chemotherapy, which increased the chance of a pCR and a survival benefit would be achieved. However, the definitive effect of neoadjuvant radiation on patients with rectal cancer is still controversial. But other factors may challenge the use of NLR in rectal cancer just like Krauthamer found that NLR was an independent factor for CPR after neoadjuvant treatments in clinical stage (CS) III while not in clinical stage (CS) II locally advanced rectal cancers[39]. Except for tumour burden the low or high location may also influence the effect of NLR in rectal cancer but until now few articles definitely analyzed this field.

In gastroesophageal cancer, the association of the NLR and OS showed no statistical significance. In other types of tumours, the number of studies was limited to come to an exactly conclusion, which is a limitation of our meta-analysis. Our study has other limitations, which are discussed below. First, the studies enrolled in our analysis were mostly retrospective, and therefore, some individual data such as specific regimens and doses of neoadjuvant treatment were not considered. Second, publication bias still exists in our study, and although we chose to include all the data from full-text studies and abstracts and even used the trim-and-fill method to confirm our results, some negative data that were omitted by us may still have influenced the results. Third, the heterogeneity could not be fully eliminated in this analysis, examples include tumour stage, age distribution, and the cut-off value of the NLR, among others. Finally, the presence of other diseases in addition to cancer, such as coronary artery disease, hepatic disease, metabolic syndrome and any inflammation-related diseases, can alter the level of the NLR, which may have affected our results[79-81].

Conclusions

Our meta-analysis pooled 33 studies to assess the response rate and prognostic effect of the NLR in patients who received NAC. In summary, patients in many types of solid tumours who had an NLR lower than the cut-off values were more likely to achieve pCR after NAC. The NLR may serve as a convenient marker in patients who receive NAC with respect to survival outcome and prognosis, as a higher NLR indicates a worse survival outcome, including OS, CSS, DFS and RFS. NLR is a simply accessible and cost-effective prognostic marker that may identify high-risk patients with certain types of tumours. Further prospective studies with large sample sizes and suitable patients are needed to validate our results and to determine the consensus cut-off value of NLR for each cancer type.

Abbreviations

NLR: Neutrophil to lymphocyte ratio; NAC: neoadjuvant chemotherapy; OR: odds ratio; HR: hazard ratios; CI: confidence interval; pCR: pathological complete response; OS: overall survival; CSS: cancer special survival; DFS: disease-free survival; RFS: recurrence-free survival; NOS: Newcastle–Ottawa Scale

Conflicts of interest

The authors declare that they have no conflict of interest.

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