Neutrophil-to-lymphocyte ratio as a prognostic predictor for patients with cancer treated with stereotactic body radiation therapy: A meta-analysis

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Received October 22, 2021; Accepted February 21, 2022

DOI: 10.3892/mco.2022.2531

Abstract. Stereotactic body radiation therapy (SBRT) is effective for the treatment of cancer. Neutrophil-to-lymphocyte ratio (NLR) is a common prognostic factor in predicting survival of patients with cancer. Previous studies have reported that NLR may be able to predict survival of patients with cancer treated with SBRT; however, the results are inconsistent. Therefore, the present study performed a meta-analysis to pool the data of prognostic prediction using NLR for patients with cancer who underwent SBRT. PubMed, Google Scholar, Embase and The Cochrane Library were used to search for articles published before October 2020. Pooled hazard radios (HRs) with 95% confidence intervals (CIs) were used to evaluate the association of NLR levels with patient outcome following SBRT. The primary endpoint was overall survival (OS). Subgroup analyses were used to detect sources of heterogeneity. Publication bias was assessed by Egger's test and Begg's test. A total of nine studies involving 1,010 participants were included in the present meta-analysis. Univariate and multivariate analyses revealed that elevated NLR predicted a worse outcome for OS (HR, 1.35; 95% CI, 1.22-1.49; P<0.001 and HR, 1.29; 95% CI, 1.16-1.44; P<0.001, respectively), regardless of pre- and post-treatment groups. Subgroup analysis demonstrated that the prospective group showed more significant heterogeneity (I^2=57.7%; P=0.124) than the retrospective group (I^2=0%) and overall (I^2=47.5%). In conclusion, both pre- and post-SBRT elevated NLRs were revealed to be independently associated with poor survival in patients with cancer who received SBRT.

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Abbreviations: CI, confidence interval; OS, overall survival; LR, local recurrence; PFS, progression-free survival; DMFS, distant metastasis-free survival; DSS, disease-specific survival; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; SBRT, stereotactic body radiation therapy

Key words: NLR, SBRT, prognosis, cancer, meta-analysis

Introduction

At present, cancer is a major cause of death worldwide; in 2021, there were 19.3 million new cases of cancer and 10 million cancer-associated deaths. Approximately one in five men and one in six women will develop cancer during their lifetime (1). Stereotactic body radiation therapy (SBRT), also known as stereotactic ablative radiotherapy (SABR), is an option for patients with cancer beyond chemotherapy or surgery (2). SBRT refers to the administration of high doses of radiation using several beams of various intensities aimed at different angles to precisely target the tumor. SBRT is a noninvasive technique that can deliver high precision and dose-escalated treatment throughout the body with excellent rates in local control. In addition, it has been widely used to treat various types of cancer, including gastrointestinal malignancies, prostate cancer and recurrent gastric cancer (3-6).

Although SBRT has been widely used to treat cancer for a number of years, the prognosis of the treatment is clinically heterogeneous, characterized by increased local recurrence and distant metastasis (7,8). Therefore, more effective and accurate indicators to assist clinicians with patient risk stratification and clinical therapy are required (9,10). In recent years, numerous studies have reported that tumor-associated inflammation and the tumor environment influence cancer development, progression and metastasis, which has led to much interest in the association between patient prognosis and inflammatory hematological markers (11,12). Among the inflammatory indexes, neutrophil-to-lymphocyte ratio (NLR) is an emerging biomarker of interest for several types of malignancy and is readily assessed from a serum complete blood count (CBC) with differential; notably, increased NLR has been reported to be associated with poor prognostic indicators, particularly poor overall survival (OS) in patients with advanced cancer (13).

Previous studies have shown that the number of participants included in individual studies is not large and the results are inconsistent (7,8). In addition, the association between inflammation-based biomarkers and oncological outcomes in patients with cancer who undergo SBRT is unclear. It is well known that patients receiving radiation therapy may experience a marked decline or a depletion of circulating lymphocytes (14,15), and a decreased lymphocyte count has been reported to be associated with a weaker anti-tumor immune response and a poor prognosis (16,17). It is therefore of great clinical importance to investigate the predictive roles of NLR before and after SBRT in patients with cancer.

The present study aimed to perform a meta-analysis to quantify the prognostic value of NLR on the outcome of tumors treated with SBRT. Furthermore, according to existing studies, the present study determined whether a statistical difference existed in the prognosis of cancer between pre-SBRT NLR and post-SBRT NLR.

Materials and methods

Registration number. The present study performed a systematic review and meta-analysis of the existing literature according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (18). The present study was registered in PROSPERO (registration no. CRD42020186132). All analyses were based on previously published studies; therefore, no ethics approval or patient consent were required.

Search strategy. A comprehensive retrieval of articles published between January 1, 1990 and October 5, 2020 was performed using the following databases: Embase (https://www.embase.com), PubMed (https://pubmed.ncbi.nlm.nih.gov), The Cochrane Library (https://www.cochranelibrary.com) and Google Scholar (https://scholar.google.com). Medical subject headings and abstract fields were searched combined with the related key words including 'NLR' (e.g., 'neutrophil to lymphocyte ratio' OR 'NLR' OR 'neutrophil-to-lymphocyte ratio') AND 'SBRT' (e.g., 'stereotactic body radiotherapy' OR 'SBRT' OR 'stereotactic ablative radiotherapy' OR 'SABR') AND 'cancer' (e.g., 'cancer' 'carcinoma' and 'tumor'). No language restriction was applied.

Study selection. Original assessment was based on the title and abstract of each reference. Full articles of relevant references were then reviewed for qualification using the following criteria: i) Studies involving individuals with solid tumors who underwent SBRT; ii) the association between NLR and OS was discussed; iii) baseline levels of NLR were assessed before or after SBRT treatment; iv) studies providing the hazard ratio (HR) with 95% confidence interval (CI) for OS (19), or relevant information could be estimated by Engauge Digitizer (https://markummitchell.github.io/engauge-digitizer/) to obtain the aforementioned statistics; v) a Newcastle-Ottawa Scale (NOS) score >5 (20,21). Case reports, reviews, animal studies, conference proceedings, letters to editors, abstract only and duplicated studies were excluded.

Data extraction. All candidate literature was evaluated and extracted by two independent authors. The two authors assessed all full articles for eligibility and extracted data using a preset spreadsheet. Any disagreement was resolved by a third researcher (LH) or through discussion. The primary endpoint was OS. Information summarized included: First author, publication year, research country, age, ethnicity, sample size, follow-up duration, primary location of the tumor, stage of cancer, method of treatment and NLR cut-off value. Outcome indicators, and HRs from multivariate and univariate analyses were preferred.

Data analysis. The present study evaluated the prognostic role of NLR by pooling the HRs and corresponding 95% CIs for survival analysis. I^2, calculated as follows: I^2 (%)=100 x (Q - df)/Q, where Q is Cochran's heterogeneity statistic and df is the degrees of freedom, and P-values were used to identify and quantify the degree of heterogeneity (22). When I^2 was ≥50% or P≤0.05 (significant heterogeneity) (23), random-effects model was used to combine HRs, otherwise a fixed-effects model was adopted. Subgroup analysis was used to detect sources of heterogeneity. Publication bias was assessed by Egger's test and Begg's test (24,25). Two-sided P<0.05 was considered statistically significant. Forest plot, Egger's test and Begg's test were conducted using STATA statistical software (version 12.0; StatCorp LLC). The flow diagram was generated using GraphPad Prism (version 8.0; GraphPad Software, Inc.). In addition, quality assessment was performed using RevMan (version 5.3; Cochrane Collaboration).

Results

Search and selection of studies. A total of 119 relevant articles were screened following the initial search. The process of the selection is shown in Fig. 1. Three of the studies were duplicated articles and 62 were revealed to be not relevant after scanning the abstract. A total of 31 studies were removed for other reasons (four studies were abstracts only; 21 studies were letters or reviews; and six studies were animal experiments). Subsequently, 23 full-text articles were assessed for eligibility; however, 14 articles failed to meet the inclusion criteria. Finally, nine studies (26-34) involving 1,010 participants were included for further assessment.

Study characteristics. Two studies were from China (26,30), six studies were from USA (27-29,32-34), and one study was performed in Canada (31). Four of these cohorts enrolled <100 participants (26,29,30,33) and five studies recruited >100 patients (27,28,31,32,34). Four studies investigated non-small cell lung cancer (NSCLC) (27,28,31,33), two studies investigated hepatocellular carcinoma (HCC) (26,30), and the remaining studies investigated pancreatic adenocarcinoma (34), brain metastases (32) and malignant adrenal lesions (29). Furthermore, two studies did not limit the stage of cancer (involved all disease stages) (26,28), four studies included only early-stage disease (I/I-II/I-III/II-IIIb) (27,30,31,33) and three studies included only late-stage disease (III-IV/IIIb-IV) (29,32,34). Two studies were prospective design (28,31) and seven studies were retrospective (26,27,29,30,32-34). Notably, six studies conducted both multivariate analysis and univariate analysis (26,28,29,31,32,34). In these six studies, some variables

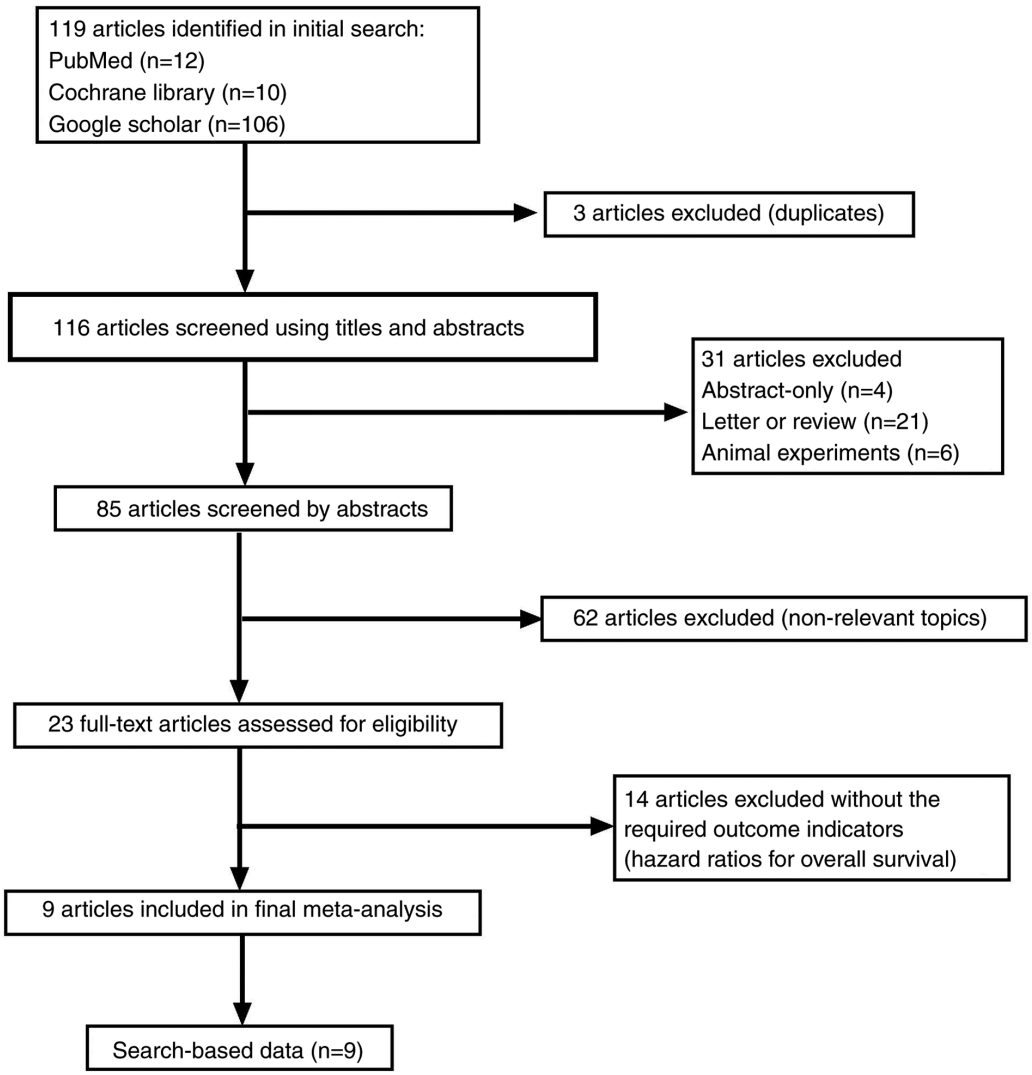

Figure 1. Flow diagram of the literature search and study selection.

were used as covariates for Cox regression multivariate analysis; therefore, their covariates are listed separately. The characteristics of the included studies are shown in Table I.

Quality assessment. The NOS was used to assess the quality of each of the included studies by two independent authors. The NOS consists of three parts: Selection, comparability and outcome assessment. For the selection of cohort item, representative exposed groups were selected for inclusion, and the non-exposed and exposed groups were from the same population in all studies. Therefore, they were considered as being at low risk of bias. Only two of the studies were prospective and seven were retrospective, thus they were regarded as high risk of bias. As for intergroup comparability, seven studies applied multivariate analysis, whereas the remaining were considered as high risk of bias because they only used univariate analysis. With regard to outcome, all studies had record linkage. Nevertheless, the follow-ups in only three studies were long enough for outcomes to occur (median >2 years). Eight studies had complete follow-ups, only one was vague in details, which was labelled as unclear risk of bias. When items conform to NOS, the circle in the figure is green; non-conforming items are red; and unclear items are yellow (Fig. 2). Studies with ≥5 green circles were assigned as mid-quality studies and those with ≥6 green circles were assigned as high-quality studies. All of the studies assessed in the present study were mid-quality or high-quality.

Univariate analysis of NLR and OS. A total of eight studies were included in the univariate analysis of NLR and OS. Among them, one study evaluated both pre-treatment and post-treatment NLR (26), one study assessed only post-treatment NLR (32), and six studies included only pre-treatment NLR (27-29,31,33,34). The univariate analysis revealed that elevated NLR predicted a worse outcome for OS with a combined HR of 1.35 (95% CI, 1.22-1.49, P<0.001), without significant heterogeneity (I^2=47.5%; P=0.055) (Fig. 3). The subgroup analysis by pre- or post-SBRT NLR showed that the pooled HRs were 1.32 (95% CI, 1.19-1.46; P<0.001; Fig. 3A) and 1.74 (95% CI, 1.23-2.47; P<0.005; Fig. 3B), respectively.

Multivariate analysis of NLR and OS. In the multivariate analysis, five studies assessed pre-treatment NLR (28-31,34) and two studies included post-treatment NLR (26,32). The

Table I. Main characteristics of all of the studies included in the meta-analysis.

First author	Year	Study region	Ethnicity	Number of participants (M/F)	Median follow-up, months(range)	Disease type	Stage	Treatment	Median age, years (range)	NLR cut-off	Outcome	HR	Covariates	(Refs.)
Alagappan	2018	USA	Caucasian	208 (109/99)	7.5 (4.6-12.0)	Pancreatic adenocarcinoma	Advanced	Combined	75.2 (65.9-86.1)	5	OS/LR	R (M/U)	Albumin; RBC; prior chemotherapy (yes)	(34)
Cannon	2015	USA	Caucasian	59 (31/28)	17	NSCLC	Early	SBRT	70 (48-89)	2.98	OS	R (U)	-	(33)
Chowdhary	2018	USA	Caucasian	188 (91/97)	13.2	Brain metastases	Advanced	Combined	NR	6	OS	R (M/U)	Active systemic disease; extracranial metastases; graded prognostic assessment; targeted therapy post-SRS; immunotherapy post-SRS	(32)
Giuliani	2016	Canada	Caucasian	122 (60/62)	26.9 (1.3-99.3)	NSCLC	Early	SBRT	76 (48-90)	3	OS	R (M/U)	Female sex; tumor stage T2; hemoglobin	(31)
Lai	2020	China	Asian	72 (61/11)	67.2 (7.7-127.4)	HCC	Early	SBRT	57 (30-84)	1.88	OS	R (M)	-	(30)
Mills	2019	USA	Caucasian	27 (12-15)	8 (1-66)	Malignant adrenal lesions	Advanced	Combined	63 (51-78)	4.1	OS	R (M/U)	Pretreatment ALC >1x10^6/ml	(29)
Sebastian	2019	USA	Caucasian	156 (89-67)	13.4	NSCLC	All stages	SBRT	72 (51-92)	3.6	OS	R (M/U)	Age; sex; T stage; histology; ECOG performance status; Charlson's Comorbidity Index; smoking; BED Gy10	(28)
Shaverdian	2016	USA	Caucasian	118	28.9	NSCLC	Early	SBRT	76	2.18	DMFS/DSS/OS	R (U)	-	(27)
Zhuang	2019	China	Asian	60 (49/11)	36.9 (4.1-73.5)	HCC	ALL stages	Combined	61.0±12.8	2.7	PFS/OS	R (M/U)	Presence of hepatitis; tumor size (≥1.5cm); pre-treatment pre-treatment AFP (≥20.0 ng/ml); pre-treatment RBC (≥4.5x10^{12}/l); post-treatment PLR (≥263.0)	(26)

M, male; F, female; USA, United States of America; NSCLC, non-small cell lung cancer; HCC, hepatocellular carcinoma; SBRT, stereotactic body radiation therapy; NR, not reported; OS, overall survival; LR, local recurrence; PFS, progression-free survival; DMFS, distant metastasis-free survival; DSS, disease-specific survival; NLR, neutrophil-to-lymphocyte ratio; HR, hazard ratio; R, obtained by reporting in text; M, multivariate analysis; U, univariate analysis; RBC, red blood cell; SRS, stereotactic radiosurgery; ALC, absolute lymphocyte count; ECOG, Eastern Cooperative Group; BED, biologically effective dose; AFP, α-fetoprotein; PLR, platelet-to-lymphocyte ratio.

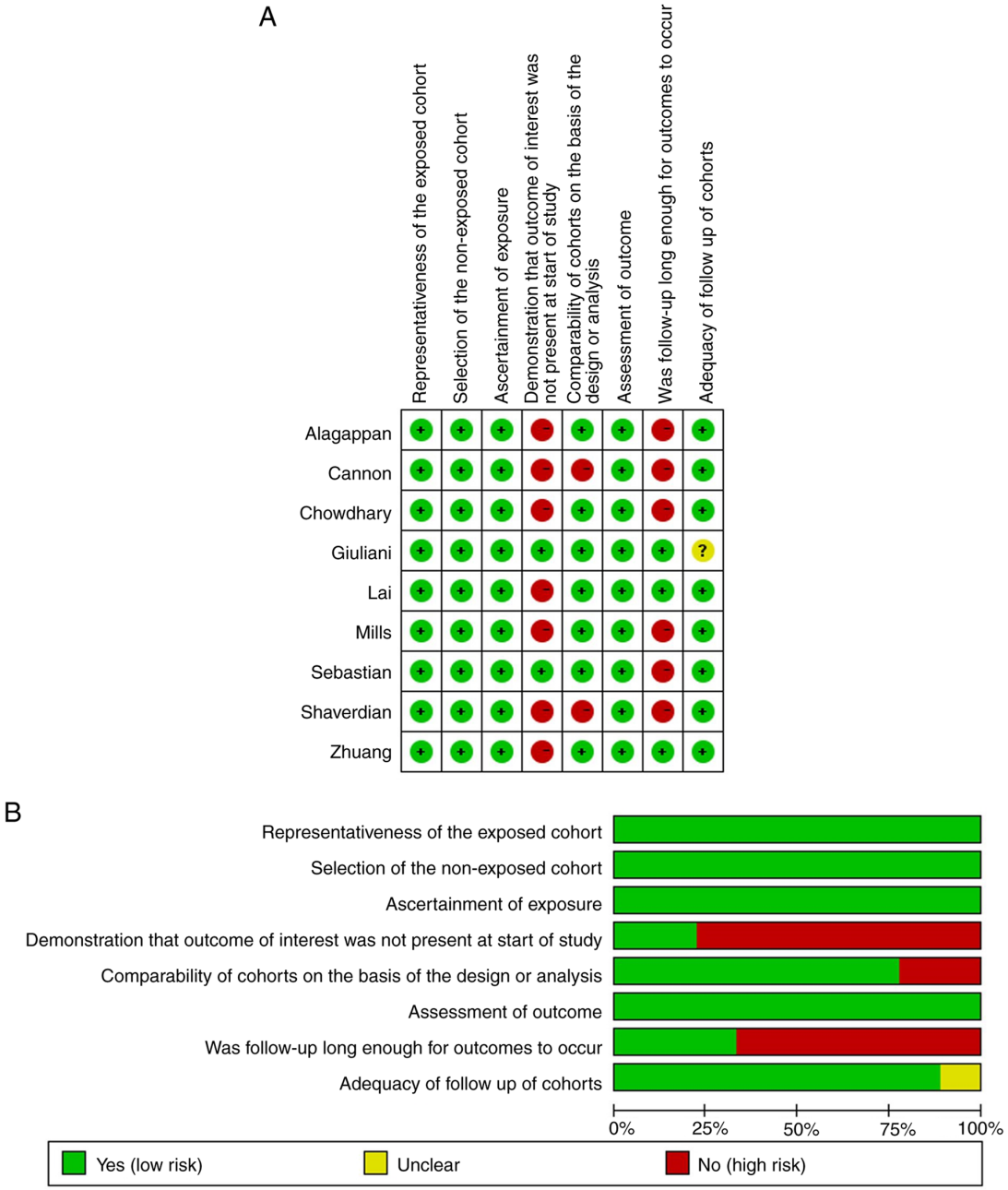

Figure 2. Risk of bias summary. (A) Judgements about each risk of bias item for each included study. (B) Judgements about each risk of bias item presented as percentages across all included studies. Green circle, items conform to Newcastle-Ottawa Scale; red circle, non-conforming items; yellow circle, unclear items.

results demonstrated that increased NLR was associated with a poorer OS (HR, 1.29; 95% CI, 1.16-1.44; P<0.001), without significant heterogeneity (I^2=10.1%; P=0.352) (Fig. 4). Subgroup analysis by pre- or post-SBRT NLR revealed the pooled HR was 1.27 (95% CI, 1.14-1.42; P<0.001; Fig. 4A) and 1.56 (95% CI, 1.07-2.29; P<0.005; Fig. 4B).

Subgroup analysis to explore sources of heterogeneity. Subgroup analysis of univariate analysis was performed based on the extracted data (Table II). Subgroup analysis of retrospective or prospective data demonstrated that the pooled HRs were 1.47 (95% CI, 1.17-1.84) and 1.25 (95% CI, 1.10-1.40), respectively, and the prospective group showed more significant heterogeneity (I^2=57.7%; P=0.124) than overall (I^2=47.5%). The cut-off values applied in the studies were not consistent, ranging between 1.88 and 6. Five studies had a NLR cut-off value of ≤3, whereas four studies had a NLR cut-off value of >3. Heterogeneity was not detected between cut-off value ≤3 and cut-off value >3 groups (P=0.051), although the P-value was close to significance, and the pooled HRs were 1.22 (95% CI, 1.08-1.38) and 1.58 (95% CI, 1.26-1.98), respectively.

In addition, subgroup analyses were performed according to treatment methods (treatment by SBRT and combined), disease stage (early stage, advanced stage and all stages), tumor type (NSCLC, HCC and others), ethnicity (Caucasian and Asian) and sample size (≤100 and >100), but no significant differences were identified.

Publication bias. Begg's funnel plot and Egger's linear regression test were performed to evaluate publication bias. The

Table II. Summary of the subgroup meta-analysis.

Analysis	N	References	Random-effects model HR (95% CI)	Fixed-effects model HR (95% CI)	Heterogeneity		
					I^2, %	P-value	P-value (between groups)
Subgroup 1: Study design							0.210
Retrospective	7	(26,27,29,30,32-34)	1.47 (1.17-1.84)	1.47 (1.17-1.84)	0.00	0.817	
Prospective	2	(28,31)	1.40 (0.93-2.10)	1.25 (1.10-1.40)	57.70	0.124	
Subgroup 2: Therapy							0.158
SBRT only	5	(27,28,30,31,33)	1.25 (1.11-1.40)	1.25 (1.11-1.40)	0.00	0.577	
Combined	4	(26,29,32,34)	1.52 (1.18-1.95)	1.52 (1.18-1.95)	0.00	0.575	
Subgroup 3: Stage							0.147
Early	4	(27,30,31,33)	1.22 (1.08-1.38)	1.22 (1.08-1.38)	0.00	0.914	
Advanced	3	(29,32,34)	1.56 (1.21-2.02)	1.56 (1.21-2.02)	0.00	0.553	
All stages	2	(26,28)	1.56 (0.84-2.90)	1.64 (1.00-2.69)	23.90	0.252	
Subgroup 4: Cut-off value							0.051
NLR ≤3	5	(26,27,30,31,33)	1.22 (1.08-1.38)	1.22 (1.08-1.38)	0.00	0.914	
NLR >3	4	(28,29,32,34)	1.58 (1.26-1.98)	1.58 (1.26-1.98)	0.00	0.639	
Subgroup 5: Tumor location							0.230
NSCLC	4	(27,28,31,33)	1.25 (1.11-1.41)	1.25 (1.11-1.41)	0.00	0.440	
HCC	2	(26,30)	1.04 (0.58-1.84)	1.04 (0.58-1.84)	0.00	0.849	
Others	3	(29,32,34)	1.56 (1.21-2.02)	1.56 (1.21-2.02)	0.00	0.553	
Subgroup 6: Ethnicity							0.447
Caucasian	7	(27-29,31-34)	1.33 (1.17-1.51)	1.30 (1.17-1.45)	4.00	0.396	
Asian	2	(26,29)	1.04 (0.58-1.84)	1.04 (0.58-1.84)	0.00	0.849	
Subgroup 7: Sample size							0.941
≤100	4	(26,29,30,33)	1.31 (0.81-2.12)	1.31 (0.81-2.12)	0.00	0.448	
>100	5	(27,28,31,32,34)	1.31 (1.16-1.48)	1.29 (1.16-1.44)	4.90	0.379	

CI, confidence interval; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; SBRT, stereotactic body radiation therapy; NSCLC, non-small cell lung cancer; HCC, hepatocellular carcinoma.

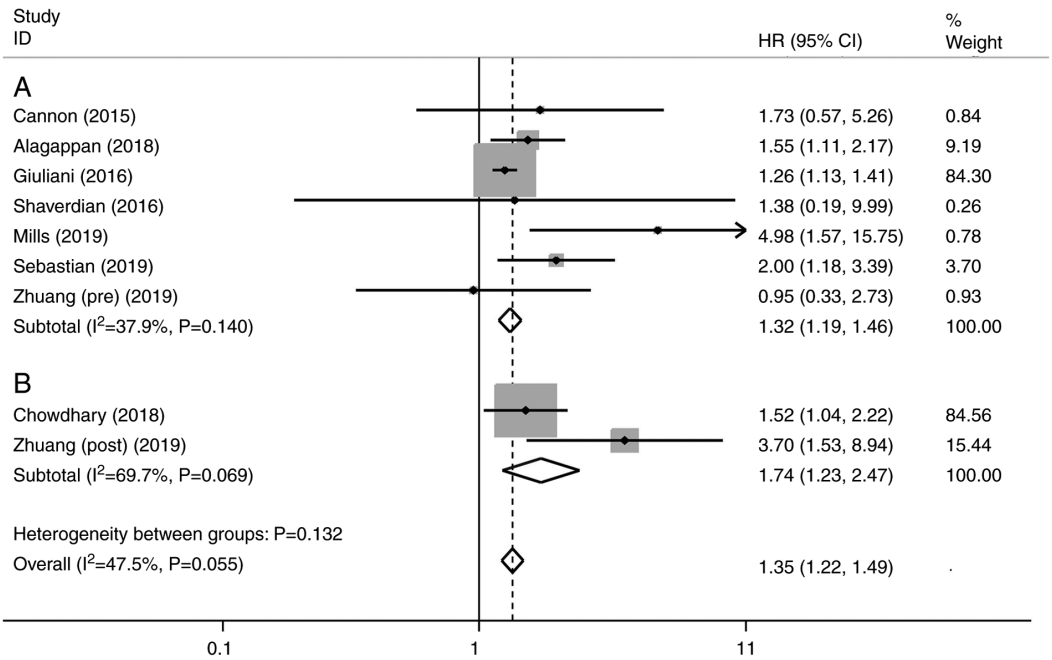

Figure 3. Forest plot of univariate analysis of (A) pre-treatment and (B) post-treatment neutrophil-to-lymphocyte ratio. Results are presented as individual and pooled HRs, and 95% CIs. Grey square indicates weight of study. CI, confidence interval; HR, hazard ratio.

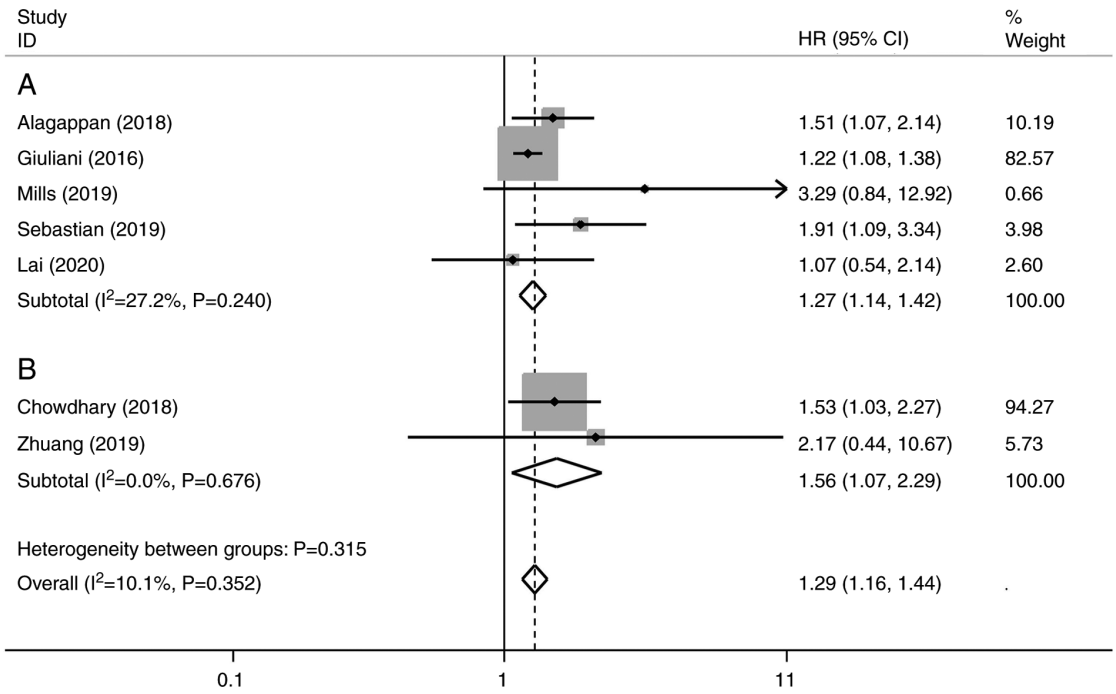

Figure 4. Forest plot of multivariate analysis of (A) pre-treatment and (B) post-treatment neutrophil-to-lymphocyte ratio. Results are presented as individual and pooled HRs, and 95% CI. Grey square indicates weight of study. CI, confidence interval; HR, hazard ratio.

publication biases were Pr>|z|=0.917 for Begg's test (Fig. 5A) and P>|t|=0.131 for Egger's test (Fig. 5B). The size of the circle indicates the weight of the article. No publication bias was found.

Discussion

The present meta-analysis demonstrated that elevated NLR was a significant predictor of poor survival outcomes in patients that underwent SBRT alone or in combination with chemotherapy or surgery. The results were consistent in both univariate and multivariate analyses, thus indicating that NLR may be an independent predictor for prognosis. Notably, the weights of Giuliani *et al* (31) and Chowdhary *et al* (32) were particularly large (>80%), because these studies yielded CIs of a smaller range and are thus considered more accurate. Subgroup analyses showed that both elevated pre- and post-treatment NLR could significantly reduce the survival

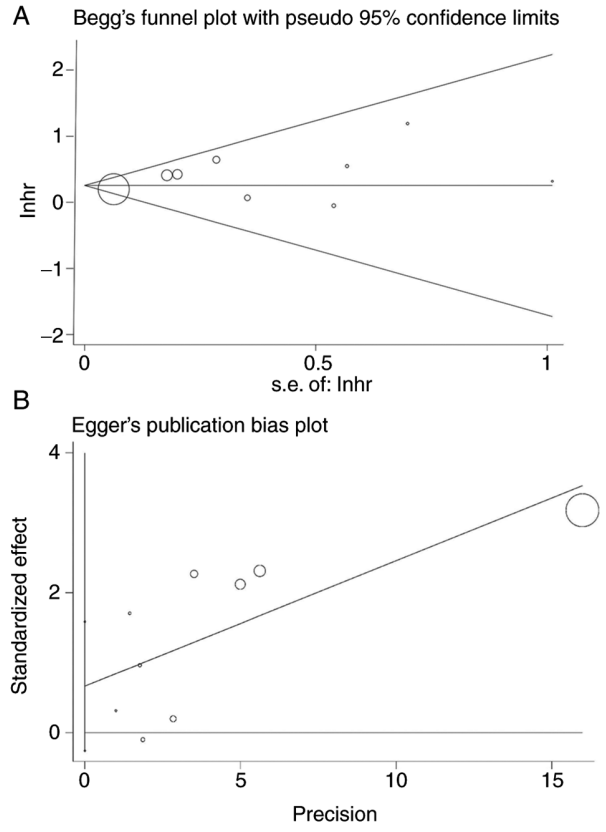

Figure 5. Publication bias. (A) Begg's funnel plot and (B) Egger's linear regression test. Circle size indicates weight of study. lnhr, logarithm of hazard ratio; s.e, standard error.

of patients treated with SBRT. Meanwhile, post-treatment NLR predicted poorer survival than pre-treatment. Although there was no significance between pre- and post-treatment groups, the induction of a leukocyte-predominant inflammatory response after SBRT may predict a worse prognosis. Moreover, heterogeneity was not found between cut-off value ≤3 and cut-off value >3 groups (P=0.051), although the P-value was close to significance. This may be caused by an insufficient sample size.

The association of elevated NLR with a worse prognosis may be based on the immune/inflammatory response. Inflammation affects all stages of tumorigenesis; not only have researchers confirmed that inflammation and immunity govern the development of tumors (35), but they have also verified the therapeutic value when targeting the inflammasome for the prevention and treatment of cancer (36). The association between increased NLR and poor outcome is not yet understood; however, the potential mechanism may involve the association between NLR and inflammation. Notably, previous studies have revealed that neutrophils may be indicative of inflammation, which can induce production of chemokines and cytokines, and suppress the cytolytic activity of immune cells, such as activated T cells and natural killer cells (37,38). Cancer cells together with its host cells can produce inflammatory cytokines and chemokines that contribute to malignant progression (39). Neutrophils can produce an inflammatory response, which may stimulate the change of tumor microenvironment, thus resulting in the proliferation and metastasis of cancer cells. In addition, it has been reported that elevated NLR can lead to elevated tumor growth-promoting factors, such as TGF-β (40). Furthermore, inflammatory factors can increase the number of neutrophils and decrease the number of lymphocytes; in some reports, primary tumor infiltration was revealed to be positively linked with lymphopenia (41,42). Other studies have also reported that tumor-infiltrating lymphocytes (TIL) serve an essential role in guiding prognosis. Notably, $CD3^+$ TILs have been reported to exert a positive effect on survival of patients with breast cancer and the importance of lymphocytes has been highlighted (43-45). Formerly regarded as a merely immunosuppressive treatment, pre- and clinical observations have indicated that radiotherapy can elicit an immune response against tumors (46,47). The response was first observed as infrequent abscopal effects emerged from the phenomenon of tumor remission outside the radiation field in satellite secondary tumors (48). Elevated lymphocytes and low NLR may be positive signs of abscopal effects.

There are some limitations in the present study. Firstly, the number and sample size of the included eligible studies were small. In addition, two (27,33) of the HRs and 95% CIs were extracted from Kaplan-Meier survival curves due to the unavailability of original data using Engauge Digitizer, which could lead to imprecise risk estimates. Secondly, among the included studies, only three studies were followed up for >2 years. Insufficient follow-up may overestimate the survival and prognosis of patients with cancer in the cohort to some extent. Thirdly, the NLR cut-off value for the present study was inconsistent; each study varied from another. The optimal NLR cut-off value for various tumors needs to be investigated in further large-scale prospective cohort studies. In addition, it is well known that SBRT processing has an impact on NLR; however, with the exception of Sebastian *et al* (28), the original studies did not provide the specific measurement time of NLR. Sebastian *et al* (28) mentioned that all patients had an available CBC with differential within 6 months of completion of treatment. Therefore, we cannot know whether the post-NLR value given in these studies was obtained after the first SBRT or measured after all SBRT was completed; this affects the accuracy of the results to a certain extent. Finally, the discrepancies between pre- and post-SBRT NLR require further research; although the present results revealed there was no statistical significance, this may be caused by insufficient sample size.

Notably, more well-designed, large-scale studies with a longer follow-up are required in the future. Furthermore, further research is needed to clarify the mechanism underlying the systemic inflammatory response to SBRT based on the change of pre- and post-SBRT NLR.

In conclusion, both pre- and post-SBRT elevated NLR may be considered an independent predictor of poor survival in patients with cancer who received SBRT; the higher level of NLR predicts a worse outcome. Therefore, NLR may be considered a promising index for appropriately individualizing SBRT and assessing prognosis.

Acknowledgements

Not applicable.

Funding

This work was supported by grants from the China Postdoctoral Science Foundation (grant no. 2020M682578), the Science and Technology Innovation Program of Hunan Province (grant no. 2020RC2061), the Hunan Cancer Hospital Climb Plan (grant no. YF2020006), the Hunan Cadres Health Care Department (grant no. NCC2017A17), the Hunan Provincial Health Commission (grant no. B2019098) and the Chinese National Cancer Center (grant no. NCC2017A17, No NCC2017L01).

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

YY, DT and HL designed the research and extracted data. CL, ZH and PY performed the statistical analysis, and the data visualization and interpretation. YY and DT drafted the first manuscript. HL, PY and ZH made critical revisions to the manuscript for key intellectual content and reviewed the data analysis. YY and DT confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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