Systematic Review and Meta-Analysis

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Prognostic value of pretreatment neutrophil-to-lymphocyte ratio in patients with soft tissue sarcoma

A meta-analysis

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Abstract

Background: The neutrophil-to-lymphocyte ratio (NLR) has been reported to possess significant prognostic value in multiple types of cancer. We conducted a meta-analysis to evaluate the prognostic value of pretreatment NLR in soft tissue sarcoma (STS).

Methods: A systematic literature search through April 2018 was conducted to identify studies evaluating the prognostic value of the pretreatment NLR in STS patients. The end points were overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), and clinicopathological parameters. All statistical analyses were conducted with Stata 13.0.

Results: Fourteen cohorts with 2820 patients were analyzed. Elevated NLR was significantly correlated with worse OS [hazard ratio (HR): 1.59, 95% confidence interval (95% CI): 1.28–1.97, $P < .001$] and DFS/PFS (HR = 1.28; 95% CI = 1.12–1.47; $P < .001$). In addition, elevated NLR was highly correlated with age (≥ 65 years), tumor size (>5 cm), tumor depth (deep), Grade (G3), and TNM stage (III-IV).

Conclusion: Overall, pretreatment NLR could be an adverse prognostic biomarker for STS.

Abbreviations: CI = confidence interval, CRP = C-reactive protein, DFS = disease-free survival, GPS = Glasgow Prognostic Score, HR = hazard ratio, IL-2 = interleukin-2, NLR = neutrophil-to-lymphocyte ratio, NOS = Newcastle–Ottawa Scale, OR = odds ratio, OS = overall survival, PFS = progression-free survival, STS = soft tissue sarcoma, TILs = tumor-infiltrating lymphocytes, TNF-α = tumor necrosis factor α, VEGF = vascular endothelia growth factor.

Keywords: meta-analysis, neutrophil-to-lymphocyte ratio, prognosis, soft tissue sarcoma

1. Introduction

Soft tissue sarcomas (STSs) comprise a heterogeneous collective of rare tumors arising from almost any embryonic mesodermal tissue and accounting for approximately 1% of adult malignancies.[1,2] Surgical resection combined with radiation therapy is the standard of care for patients with STS.[3] Nevertheless, some 50% of all patients with adequate local control experience local recurrence and distant metastasis,[4] with 5-year survival rates of approximately 50%.[5,6] Therefore, it is necessary to find a suitable biomarker that can identify risk classification and even guide the treatment.

There is increasing evidence that cancer-related inflammation leads to worse prognosis. Increasing evidence shows that inflammation can largely influence several stages of tumorigenesis, from tumor initiation to promotion and metastatic progression.[7] Several indicators in peripheral blood often reflect the inflammatory response in the tumor microenvironment.[8] Inflammation-based prognostic indicators, such as the plasma fibrinogen, Glasgow prognostic score (GPS), and C-reactive protein (CRP), have been investigated in different type of cancers.[9,10] The pretreatment NLR has been demonstrated as significant predictors in patients with STS.[11–13] However, due to the inconsistent results, the prognostic role of NLR in STS remains controversial.[14–16] We therefore conducted a meta-analysis to quantify the prognostic effect of NLR and analyze the relationship between NLR and clinicopathological parameters in patients with STS.

2. Materials and methods

2.1. Search strategies

A systematic search of the association between NLR and survival was conducted up to April 2018 in this research. Essays were searched through EMBASE, PubMed, and the Cochrane library. Search terms included "sarcoma" and "NLR" or "neutrophil lymphocyte ratio" and "prognosis" or "survival" or "outcome." The whole process of search was conducted by 2 reviewers, independently. All analyses were based on previous published

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GL and L-CK contributed equally to this work.

The authors report no conflicts of interest in this work.

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studies. Thus, this study did not require the ethic approval and informed consent.

2.2. Selection criteria

The inclusion criteria for this study were as follows: all selected literatures investigated NLR and survival in STS; patients with STS were pathologically confirmed; hazard ratio (HR) with its 95% confidence intervals (95% CIs) was reported from the original paper or can be calculated by Kaplan–Meier curve; and reporting a cut-off value for NLR. Articles were excluded from the analyses if they were letters, reviews, or conference abstracts; studies with sample size less than 20; unable to extract relevant metrics data; and duplicate publication.

2.3. Data extraction and quality assessment

All eligible studies were reviewed and extracted independently by 2 reviewers. Data needed to be recorded was as follows: first author's name, publication year, area, ethnicity, number of patients, age, follow-up period, survival analysis methods, treatment, cut-off values, tumor size, tumor depth, tumor grade, TNM stage, and HR as well as corresponding 95% CI.

The quality of each study was assessed according to the Newcastle–Ottawa Scale (NOS).[17] We applied the NOS scale generally used for evaluating cohort studies. This scale consists of 3 primary domains: Selection, Comparability, and Outcome, which were scored separately. One star for each item can be given within the Selection and Outcome categories, while 2 stars for Comparability. Studies with a score of 6 or more were defined as high quality.

2.4. Statistical analysis

All statistical analyses were performed with Stata 13.0 statistical software (StataCorp, College Station, TX). Odds ratio (OR) and their 95% CI were used to assess the association between NLR and clinicopathological factors. If the statistical variables were not given in the study, we calculated them with Kaplan–Meier survival curves, which were read by Engauge Digitizer version 4.1 (free software downloaded from http://sourceforge.net) according to the methods described by and Parmar et al[18] and Tierney et al.[19] The between-study heterogeneity was evaluated with Chi-squared test and I^2 statistics. A Chi-squared test of $P < .10$ or $I^2 > 50\%$ showed the existence of heterogeneity. Subgroup analysis was furtherly performed to explore the source of existing heterogeneity. Sensitivity analysis to test the credibility of the result was performed by sequential omission of individual studies. Publication bias was estimated by Begg and Egger test. A P value less than .05 was considered to be statistically significant.

3. Results

3.1. Study selection and study characteristics

The search strategy identified 152 potentially relevant records, among which 38 were excluded, as they were duplicates. The remaining 114 manuscripts were subject to title and abstract screening. We further removed 85 publications because they were unrelated studies or studies without survival information. Hence, 29 articles were eligible for full-text review and data extraction. Finally, 16 articles were excluded due to letter, conference abstract, or duplicate data, and the remaining 13 studies were enrolled in the meta-analysis as it presents in Fig. 1. The major characteristics of the 14 eligible cohorts are listed in Table 1[11–16,20–26] (the study of Yanagisawa et al[25] was divided into 2 cohorts.) The sample size of the studies ranged from 25 to 818. Thirteen cohorts reported the outcomes of OS, and 11 cohorts presented DFS/PFS as primary outcome. HRs were reported directly in all included cohorts.

3.2. Quality assessment

The quality of all eligible studies varied from 6 to 9, with average 7.5 according to NOS. Therefore, all studies were included subsequent analysis.

3.3. Meta-analysis

3.3.1. Correlation of NLR with clinicopathological features.

The association between NLR and several clinicopathological parameters is illustrated in Table 2. The elevated NLR was highly correlated with age (≥ 65 vs <65; HR = 1.56, 95% CI: 1.10–2.21, $P = .01$), tumor size (> 5 vs <5 cm; HR = 2.02, 95% CI: 1.24–3.29, $P = .005$), tumor depth (deep vs superficial; HR = 2.26, 95% CI: 1.60–3.20, $P < .001$), Grade (G3 vs G2/G1; HR = 1.61, 95% CI: 1.16–2.25, $P = .004$), and TNM stage (III-IV vs I-II; HR = 3.16, 95% CI: 2.16–4.61, $P < .001$). However, elevated NLR was not related to gender (male vs female; HR = 1.02, 95% CI: 0.80–1.30, $P = .85$).

3.4. Overall survival

The main results of this meta-analysis are listed in Fig. 2. As the studies evaluating OS were of obvious statistical heterogeneity ($I^2 = 75.8\%$, $P < .001$), we used a random-effects model to pool the HR. Meta-analysis of the 13 cohorts showed that elevated NLR was associated with poor OS (HR: 1.59, 95% CI: 1.28–1.97, $P < .001$). The correlation between NLR and OS was further assessed by subgroup analysis based on several related clinicopathological parameters (Table 3). The results demonstrated that elevated NLR was associated with worse OS both in Asian (HR = 1.59; 95% CI = 1.28–1.97; $P = .001$) and Caucasian populations (HR = 1.44; 95% CI = 1.03–2.00; $P = .031$). Pooled HRs for OS were stratified by disease stage, the negative effect of elevated NLR on OS was observed in patients with nonmetastatic (HR = 1.64; 95% CI = 1.06–2.56; $P = .028$), and mixed disease subgroups (HR = 1.53; 95% CI = 1.17–2.01; $P = .002$). Moreover, subgroup analyses showed that elevated NLR predicted worse OS in patient with STS, regardless of the treatment (surgery and mixed), analysis method (univariate and multivariate), and the cut-off value for NLR (≥3.0 and <3.0).

3.5. Disease-free survival/progression-free survival

Seven cohorts explored the association between elevated NLR and DFS/PFS. Elevated NLR was significantly associated with poor DFS/PFS (HR = 1.28; 95% CI = 1.12–1.47; $P < .001$; Fig. 3) and significant heterogeneity was observed ($I^2 = 60.4\%$; $P = .005$).

3.6. Sensitivity analysis and publication bias

We found that the result was not obviously impacted by any single study, therefore indicating that our results were statistically robust (Fig. 4). Significant publication bias was observed in OS

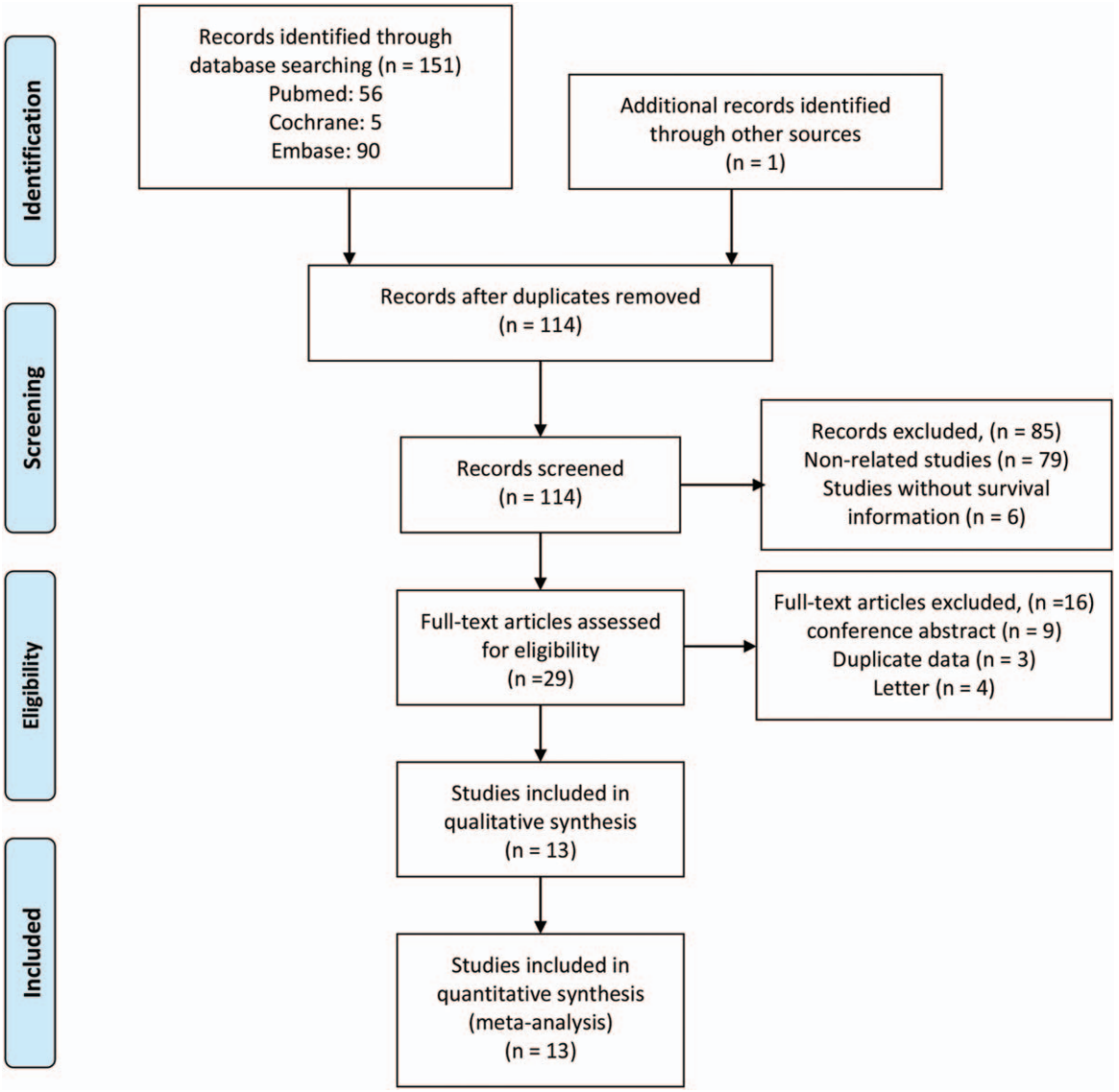

Figure 1. Flow diagram of the study selection process.

Table 1

Characteristics of the studies included in the meta-analysis.

Ref.	Year	Area	Ethnicity	Follow-up, mo	Treatment	No. of patients	Stage	Cut-off value	Survival analysis	Analysis	NOS score
Yanagisawa et al[25]	2018	USA	Caucasian	31.8	Mixed	98	II-III	2.8	OS/RFS	MV	7
Kobayashi et al[15]	2018	Japan	Asian	5.5 (2.0–45.2)	Mixed	25	Metastatic	3.8	OS/PFS	UV	8
Idowu et al[20]	2012	UK	Caucasian	28.0 (3.0–75.0)	Mixed	83	Nonmetastatic	5	OS/RFS	MV	7
Li et al[11]	2017	China	Asian	35.0	Mixed	122	Mixed	2.38	OS	UV	7
Szkandera et al[21]	2015	Austria	Caucasian	NA	Surgery	340	Mixed	2.39	OS/DFS	MV	8
Nakamura et al[14]	2017	Japan	Asian	45.0 (5.0–136.0)	Surgery	81	Nonmetastatic	2.8	OS/PFS	UV	7
Choi et al[22]	2018	Korea	Asian	46.7 (6–144)	Mixed	162	Nonmetastatic	2.5	DFS/RFS	UV/MV	9
Que et al[16]	2015	China	Asian	74.0 (1.0–176.0)	Mixed	222	Mixed	2.5	OS/DFS	MV	8
Xia et al[23]	2016	China	Asian	40.0 (36.0–60.0)	Mixed	359	Mixed	3.43	OS/PFS	MV	9
Liu et al[12]	2016	China	Asian	28.2 (3.1–124.1)	Mixed	162	Mixed	2.57	OS	MV	6
Jiang et al[13]	2015	China	Asian	71.05 (2.97–476.17)	NA	142	Metastatic	1.0	OS/PFS	MV	8
Liang et al[24]	2017	China	Asian	75.5 (8–136)	Surgery	206	Mixed	1.64	OS/DFS	UV	7
Maretty-Kongstad et al[26]	2017	Denmark	Caucasian	68.4 (12–264)	Mixed	818	Nonmetastatic	2.3	OS	MV	7

DFS = disease-free survival, MV = multivariate, NA = not available, OS = overall survival, PFS = progression-free survival, RFS = recurrence-free survival, UV = univariate.

Table 2

Meta-analysis of the association between NLR and clinicopathological features of STS.

Characteristics	No. of studies	No. of patients	OR (95% CI)	*P*	Heterogeneity	
					I^2 (%)	P_h
Age (≥ 65 vs < 65)	4	749	1.56 (1.10–2.21)	.01	0	.70
Gender (male vs female)	6	1250	1.02 (0.80–1.30)	.85	0	.69
Tumor size (> 5 vs < 5 cm)	3	724	2.02 (1.24–3.29)	.005	41	.18
Tumor depth (deep vs superficial)	4	602	2.26 (1.60–3.20)	<.001	36	.20
Grade (G3 vs G2/G1)	4	429	1.61 (1.16–2.25)	.004	0	.42
TNM stage (III-IV vs I-II)	2	232	3.16 (2.16–4.61)	<.001	0	.65

CI = confidence interval, OR = odds ratio.

(P=.951 for Begg test and P=.001 for Egger test, Fig. 5) and DFS/PFS (P=.533 for Begg test and P=.003 for Egger test, Fig. 6).

4. Discussion

To date, the relationship between NLR and the outcome of STS remains inconclusive. Our current study chiefly assessed the prognostic role of pretreatment NLR and the relationship between NLR and clinical features in patients with STS. Pooled results from 13 studies with 2820 patients showed that elevated NLR was significantly associated with poor OS and DFS/PFS. In addition, subgroup analyses indicated that elevated NLR was associated poor OS in patient with STS, regardless of the ethnicity, treatment, stage, analysis method, and the cut-off value for NLR. In addition, elevated NLR was highly correlated with age (≥ 65 years), tumor size (> 5 cm), tumor depth (deep), Grade (G3), and TNM stage (III-IV).

The actual mechanisms of the prognostic impact of the NLR for a patient with a STS are unclear. Cancer-related inflammation is an emerging hallmark of cancer.[27] Accumulating evidence suggested a strong link between inflammation and tumor development.[7,28,29] High densities of tumor tissue infiltrating neutrophil provides a favorable tumor environment for cancer progression by secreting many inflammation mediators such as tumor necrosis factor α (TNF-α), vascular endothelia growth factor (VEGF), interleukin-2 (IL-2), interleukin-6 (IL-6), and interleukin-10 (IL-10).[30–32] Moreover, infiltration of neutro-

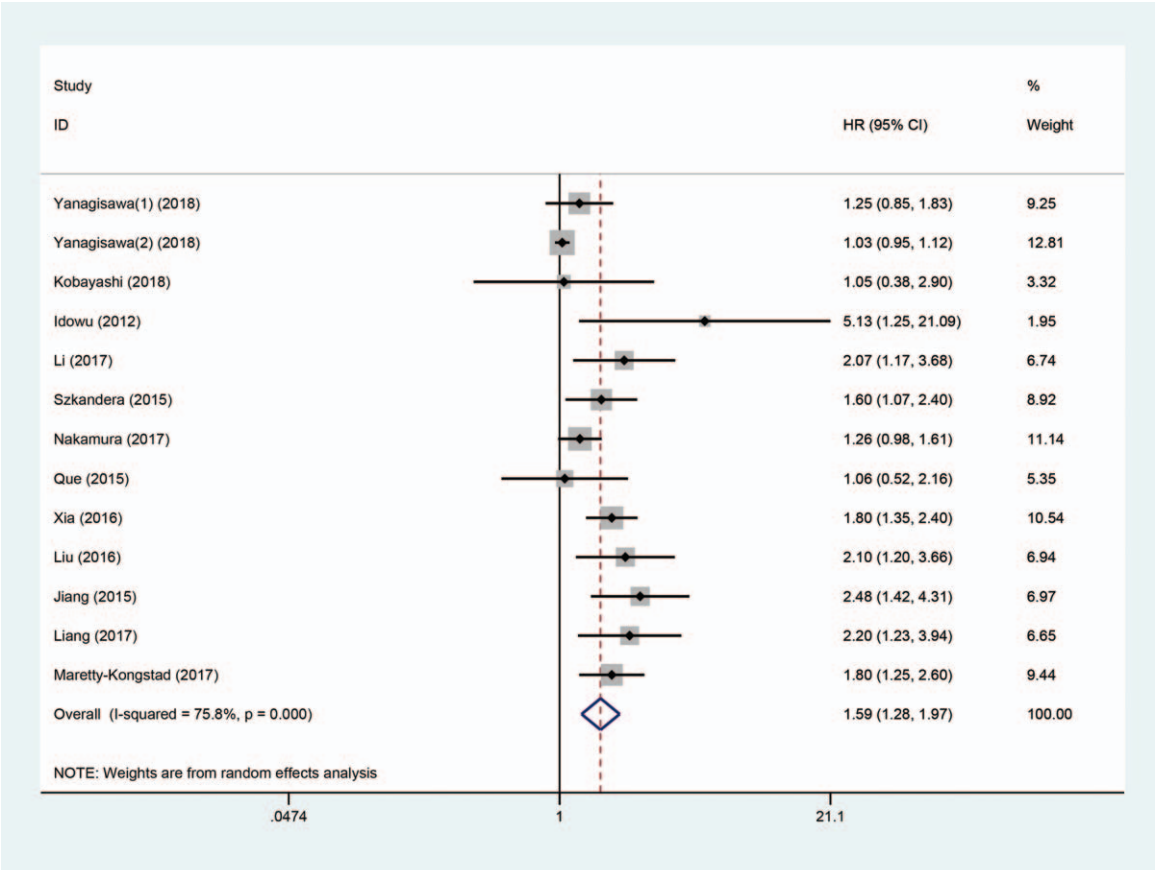

Figure 2. Forest plots for the association between NLR and OS.

Table 3

Pooled hazard ratios (HRs) for DFS/PFS according to subgroup analyses.

Subgroup	No. of cohorts	No. of patients	HR (95% CI)	*P*	Heterogeneity	
					I^2 (%)	P_h
Overall	13	2658	1.59 (1.28–1.97)	<.001	75.8	<.001
Ethnicity						
Asian	8	1319	1.59 (1.28–1.97)	<.001	39.1	.119
Caucasian	6	1339	1.44 (1.03–2.00)	.031	77.2	.002
Treatment						
Surgery	3	627	1.51 (1.13–2.02)	.006	42.1	.178
Mixed	9	2031	1.53 (1.16–2.03)	.003	76.9	<.001
Stage						
Metastatic	2	167	1.80 (0.80–4.06)	.157	52.7	.146
Mixed	8	1509	1.53 (1.17–2.01)	.002	78.1	<.001
Nonmetastatic	3	982	1.64 (1.06–2.56)	.028	64.8	.058
Cut-off						
≥3	3	467	1.84 (1.03–3.27)	.039	37.2	.204
<3	10	2191	1.54 (1.23–1.93)	<.001	75.4	<.001
Analysis method						
Univariate	4	434	1.56 (1.11–2.20)	.010	41.3	.164
Multivariate	9	2224	1.60 (1.22–2.11)	<.001	80.4	<.001

CI = confidence interval, HR = hazard ratio.

phils can suppress the immune activity of lymphocytes and natural killer cells by producing some chemokines and cytokines.[30,33] Lymphocytes play critical roles in the host immune response. They can inhibit the proliferative and metastatic ability of cancer cells via inducing cytotoxic cell death and cytokine production.[34] Tumor-infiltrating lymphocytes (TILs) are involved in several stages of tumor progression.[35,36] A growing body of evidence has reported tumor-infiltrating CD4+ and CD8+ T lymphocytes may be a prognostic biomarker in many types of cancer.[37–39] A low lymphocyte

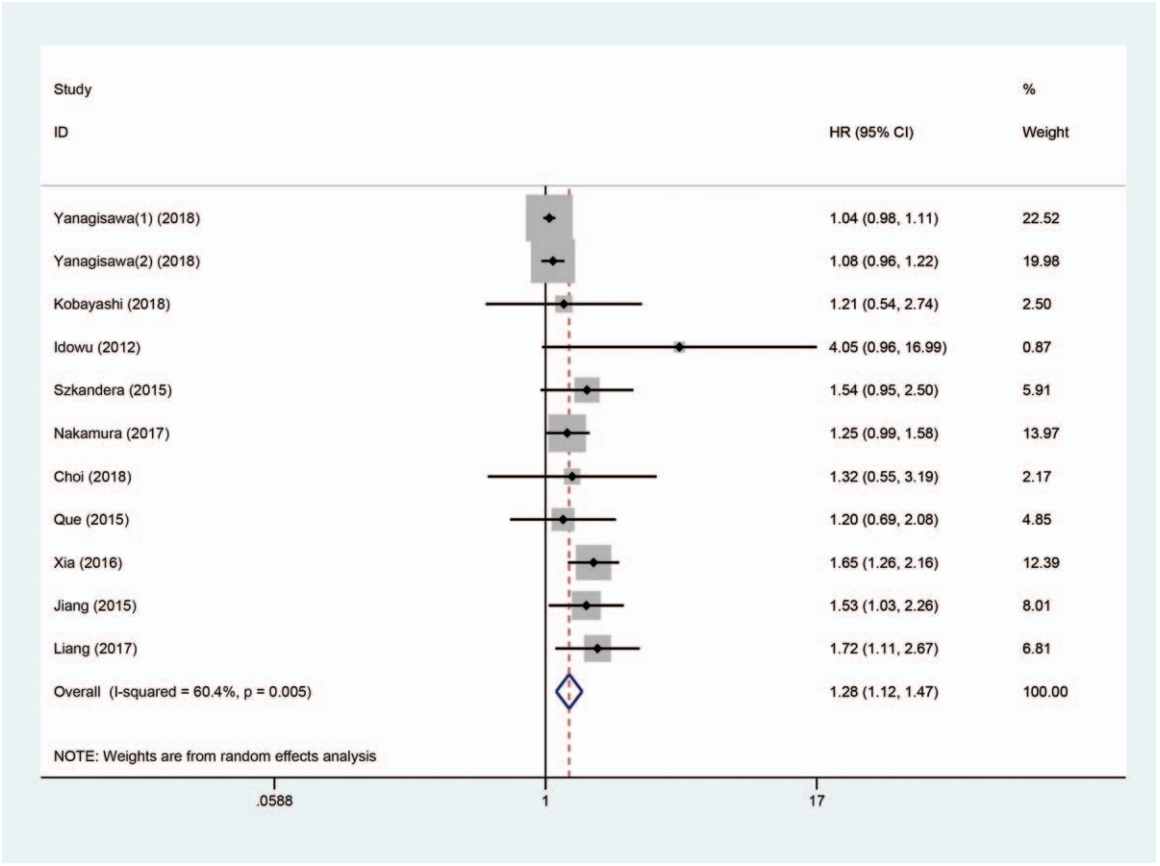

Figure 3. Forest plots for the association between NLR and DFS/PFS.

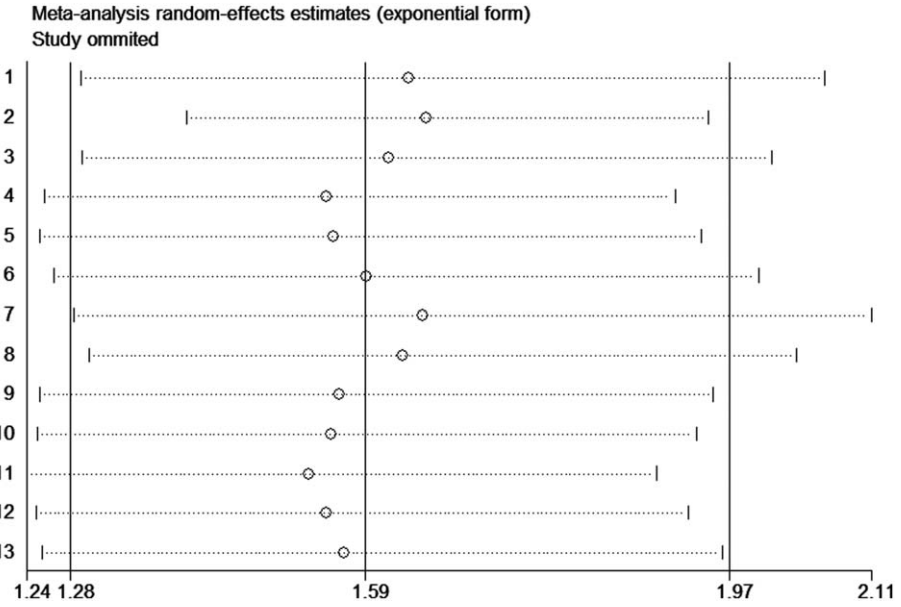

Figure 4. Sensitivity analysis of NLR on OS in STS patients.

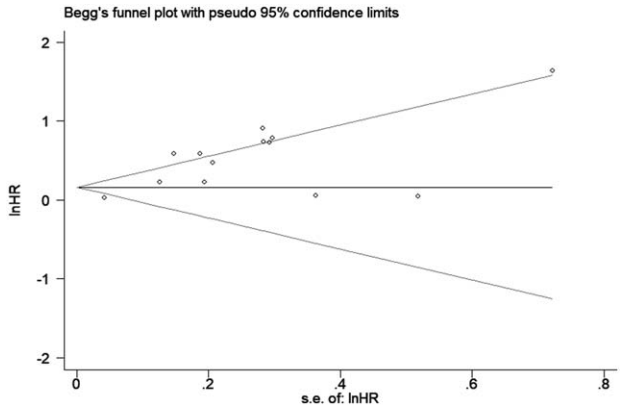

Figure 5. Begg funnel plot of publication bias test for OS in STS.

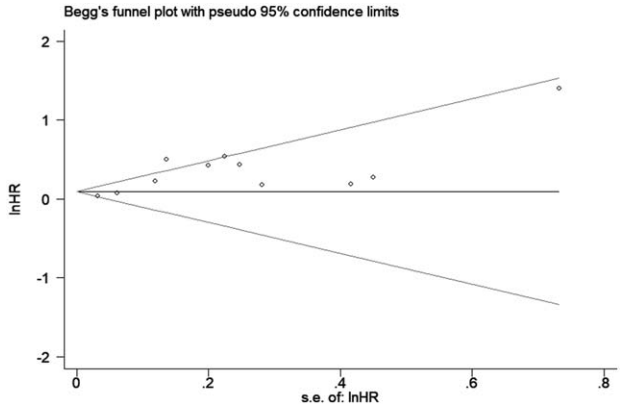

Figure 6. Begg funnel plot of publication bias test for DFS/PFS in STS.

count might result in an inadequate immune response in the control of tumor.[40,41] Thus, NLR may represent a balance between the tumor promotion reaction and antitumor immune function.

There were several limitations of our study. First, the heterogeneity between studies was statistically significant. However, interestingly, subgroup analyses indicated that the heterogeneity diminished in Asian populations, in patients who received surgery and in studies with cut-off ≥ 3. Second, due to the lack of a unified standard, different cut-off values were applied in various studies, which may affect the outcomes of the value that NLR plays as a biomarker in STS prognosis. Third, all included studies were retrospective.

In summary, our findings demonstrated that the pretreatment NLR is associated with unfavorable outcomes in conjunction with advanced clinicopathological features in patients with STS, suggesting that NLR could serve as a predicative biomarker for STS patients.

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Author contributions

Conceived and designed the experiments: GL, LCK, SRS. Performed the experiments: GL, LCK, SRS. Analyzed the data: GL, LCK, SRS. Contributed reagents/materials/analysis tools: GL, LCK, SRS. Wrote the paper: all authors.
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Writing – original draft: Gang Liu, Li-chi Ke, Sheng-rong Sun.
Writing – review & editing: Gang Liu, Li-chi Ke, Sheng-rong Sun.

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