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Meta-Analysis of Hematological Biomarkers as Reliable Indicators of Soft Tissue Sarcoma Prognosis

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Background: Several recent studies have reported the reliable prognostic effect of hematological biomarkers in various tumors. Yet, the prognostic value of these hematological markers in soft tissue sarcoma (STS) remains inconclusive. Thus, the aim of this meta-analysis was to check the effect of hematological markers on the prognosis of STS.

Methods: We systematically searched for relevant papers published before October 2019 in the PubMed and EMBASE databases. Overall survival (OS) and disease-specific survival (DSS) were the primary outcome, whereas disease-free survival was the secondary outcome. A thorough study of hazard ratios (HR) and 95% of confidence intervals (CIs) was done for determining the prognostic significance.

Results: We performed 23 studies that comprised of 4,480 patients with STS. The results revealed that higher neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), and platelet-to-lymphocyte ratio (PLR) were associated with poor OS/DFS (HR = 2.08/1.72, for NLR; HR = 1.92/1.75, for CRP, and HR = 1.86/1.61, for PLR). In contrast, a low lymphocyte-to-monocyte ratio (LMR) was relate to worse OS/DFS (HR = 2.01/1.90, for LMR). Moreover, pooled analysis illustrated that elevated NLR and CRP represents poor DSS, with HRs of 1.46 and 2.06, respectively. In addition, combined analysis revealed that higher Glasgow prognostic score (GPS) was linked to an adverse OS/DSS (HR = 2.35/2.77).

Conclusion: Our meta-analysis suggested that hematological markers (NLR, CRP, PLR, LMR, and GPS) are one of the important prognostic indicators for patients affected by high-grade STS and patients with the STS being located in the extremity.

Keywords: soft tissue sarcoma, meta-analysis, hematological markers, prognosis, biomarker, inflammation

INTRODUCTION

Rationale

Soft tissue sarcoma (STS) is a relatively rare, heterogeneous tumor derived primarily from the mesodermal layer. Approximately 12,750 new cases and 5,270 deaths were reported in 2019 (1, 2). Several prognostic factors including tumor size, depth, histologic tumor grade, and patient age have proven effective in guiding the design of treatment regimens for STS (3). Nevertheless, mortality in

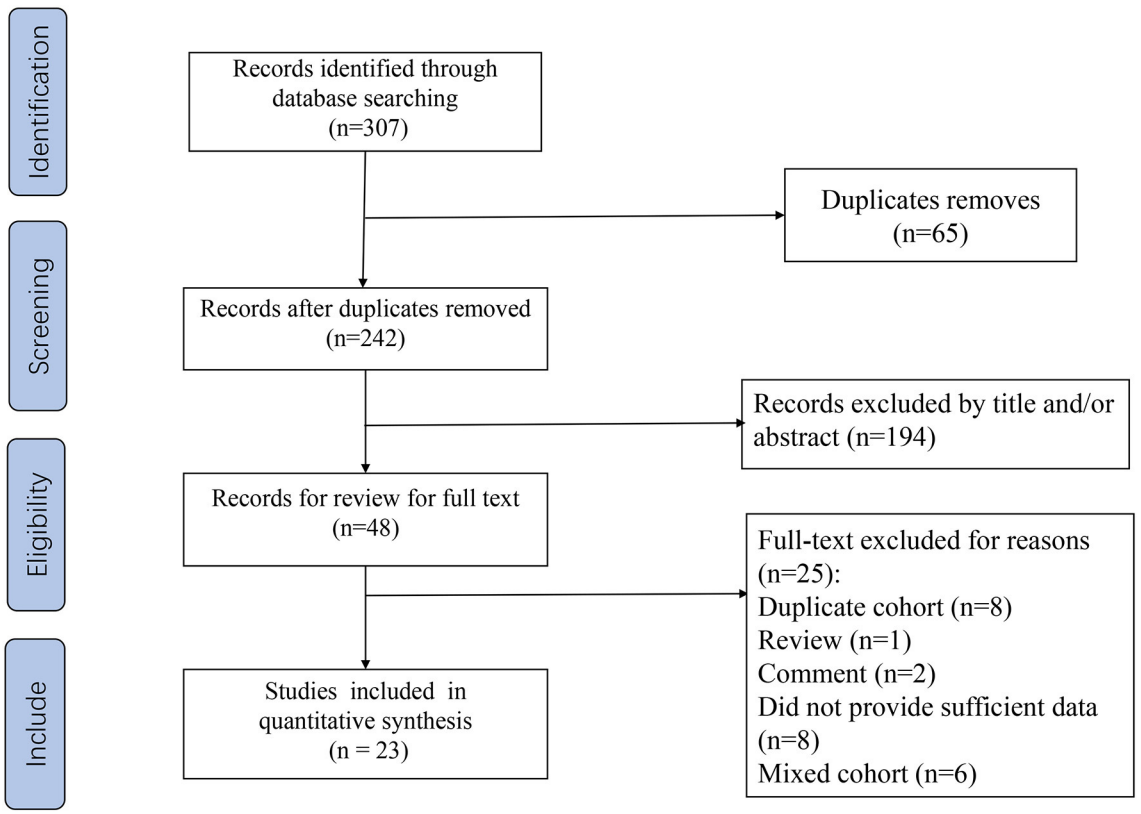

FIGURE 1 | Flow chart of the included studies.

patients with high-grade tumors is nearly 50%, primarily due to development of locally relapsed or metastatic tumors. Hence, more accurate predictive factors are required to allow for development of personalized treatment plans for high risk patients (4). Identifying accurate and novel biomarkers will provide improved treatment options and surveillance methods for STS.

For these novel biomarkers to provide more accurate diagnosis of patients with high risk of recurrence and metastasis, they must be readily accessible via non-invasive procedures and cost-effective. Accumulating evidence suggests that inflammatory cells and proteins play a key role in tumor development (5). Inflammation in the tumor microenvironment promotes angiogenesis, tumor invasion, and metastasis, subverts both the adaptive and innate immune responses while also increasing tumor cell proliferation and enhanced survival (5, 6). Fortunately, clinical routine tests, many of which are readily available and consist of inexpensive hematological markers, such as the NLR, CRP, PLR, LMR, and Glasgow prognostic score (GPS), can reflect the systemic inflammatory status. Notably, the aforementioned markers show reliable prognostic value for various tumors (7–13).

Objectives and Research Question

Inflammatory hematological biomarkers that have proven effective as prognostic factors in other tumors, may offer similar prognostic roles for STS. Although, several recent retrospective studies have demonstrated prognostic significance for some of these biomarkers in STS patients, the prognostic efficacy of several other markers have yet to be fully characterized. Therefore, the primary purpose of this meta-analysis was to explore the prognostic role of hematological biomarkers in STS.

METHODS

Search Strategies

Published reports before October 2019 and available in PubMed and EMBASE were retrieved through a systematic literature search. The keywords were as follows: hematologic markers, neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), GPS, STS, prognosis, survival, and mortality. Since this is a meta-analysis and all data are collected from previously published studies, no ethical approval is required.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) diagnosis of STS based on pathological examination; (2) the study assessed the prognostic value for a minimum of one hematologic marker through overall survival (OS), disease-specific survival (DSS), and/or disease-free survival (DFS); (3) hazard ratio (HR) was

employed with a 95% confidence interval (CI) to represent the prognostic value of biomarkers; (4) studies published in English.

Studies were excluded if: (1) reviews, letters, comments, and case reports; (2) subjects include patients with osteogenic tumors; (3) studies did not follow standard treatment guidelines (4) overlapping or duplicate studies; (5) studies not in English.

Data Extraction and Quality Assessment

Two investigators (LL and ZB) independently selected these studies. Discrepancies were resolved by consensus, and the following information was extracted from each study: first author's name, publication year, country, number of patients, treatment method, tumor stage, cut-off value, and survival outcomes. HRs were primarily collected from multivariate analysis; in the case of no relevant data, univariate analysis was adopted. Two investigators used the Newcastle-Ottawa scale (NOS) to examine the quality of the reference articles. Studies with NOS scores ≥ 6 were included in our meta-analysis since they are considered as high-quality studies (14).

Data Analysis

Considering the similar survival outcomes, we combined DSS, sarcoma-specific survival (SSS), cancer-specific survival (CSS), and regarded them as DSS. In addition, recurrence-free survival (RFS), progression-free survival (PFS), and DFS were combined as DFS. The hematological biomarkers-survival outcome relationship was assessed by means of studying hazard ratio and 95% CI. The Cochrane *Q-test* and I^2 statistics were used to assess the heterogeneity among the studies. A random effects model (Der Simonian-Laird method) was employed in the case of any significant heterogeneity ($P < 0.05$ and $I^2 > 50\%$) (15), otherwise the fixed-effect model (Mantel-Haenszel method) was applied (16). In addition, subgroup analysis by treatment method, tumor stage, and ethnicity of NLR, CRP, and PLR was conducted. With the help of Stata software, version 12.0 (Stata corporation, College Station, TX, USA), publication bias was performed, whereas evaluation was completed by means of Begg's funnel plots, Egger's tests as well as the trim and fill method (17). Data analyses were conducted by RevMan5.3 (Cochrane Collaboration) and two-side $P < 0.05$ was considered to be statistically significant.

RESULTS

Study Selection and Characteristics

Our flow chart for data retrieval from publications is shown in **Figure 1**. The search strategy identified 307 potential records

TABLE 1 | Baseline characteristics of studies included in the meta-analysis.

References	Year	Country	Sample size	Treatment	Stage	Cut-off value	Makers	Outcome
Idowu et al. (18)	2012	UK	83	Surgery	Non-metastatic	5	NLR	OS RFS
Marshall et al. (19)	2017	Japan	75	Mixed	Mixed	NA	CRP	OS
Nakamura et al. (20)	2012	UK	312	Surgery	Non-metastatic	10	CRP	DSS RFS
Szkandera et al. (21)	2014	Austria	170T/170V*	Surgery	Non-metastatic	5/200/2.85	NLR/PLR/LMR	OS DFS CSS
Panotopoulos et al. (22)	2015	Austria	85	Surgery	Mixed	NA/8.7	NLR/CRP	OS DSS
Jiang et al. (23)	2015	China	142	Mixed	Metastatic	1	NLR	OS PFS
Nakamura et al. (24)	2017	Japan	47	Mixed	Metastatic	5,3,2	CRP	DSS
Chan et al. (25)	2018	Singapore	529L/183M†	Surgery/Mixed	Non/Metastatic	2.5/184/2.4	NLR/PLR/LMR	OS RFS
Park et al. (26)	2019	Korea	99	Surgery	Non-metastatic	1.95/1.4	NLR/CRP	OS DFS
Sasaki et al. (27)	2018	Japan	103	Mixed	Mixed	5/NA/1	NLR/PLR/GPS	OS
Liang et al. (28)	2017	China	206	Surgery	Mixed	1.64/151.9/1	NLR/PLR/GPS	OS DFS
Maretty-Kongstad et al. (29)	2017	Denmark	818/403‡	Mixed	Non-metastatic	NA/NA/1	NLR/CRP/GPS	DSS
Nakamura et al. (30)	2015	Japan	139	Surgery	Non-metastatic	1	GPS	DSS EFS
Szkandera et al. (31)	2013	Austria	304	Surgery	Mixed	6.9	CRP	OS DFS CSS
Choi et al. (32)	2014	Korea	162	Surgery	Non-metastatic	2.5/2	NLR/CRP	DSS
García-Ortega et al. (33)	2017	Mexico	169	Mixed	Mixed	3.5	NLR	OS
Chen et al. (34)	2019	China	42	Surgery	Mixed	2.73/103.89/4.2	NLR/PLR/LMR	OS DFS
Willegger et al. (35)	2017	Austria	132	Surgery	Mixed	8.7	CRP	OS SSS RFS
Tsuda et al. (36)	2017	Japan	202	Surgery	Non-metastatic	1	GPS	SSS EFS
Vasquez et al. (37)	2017	Peru	22	Mixed	Mixed	2/150	NLR/PLR	OS
Nakamura et al. (38)	2017	Japan	81	Surgery	Mixed	2.8/14	NLR/CRP	DSS
Nakamura et al. (39)	2012	Japan	102	Mixed	Non-metastatic	3	CRP	DFS
Cheng et al. (40)	2019	China	103	Mixed	Mixed	2.7/154.99/4.16	NLR/PLR/LMR	OS/PFS

NA, not available; OS, overall survival; DSS, disease-specific survival; SSS, sarcoma-specific survival; CSS, cancer-specific survival; DFS, disease-free survival; PFS, progression-free survival; RFS, recurrence-free survival.

**This study has validation set and training set, each set has 170 patients.*

† This study has non-metastatic and metastatic group.

‡ Four hundred and three patients have data on CRP.

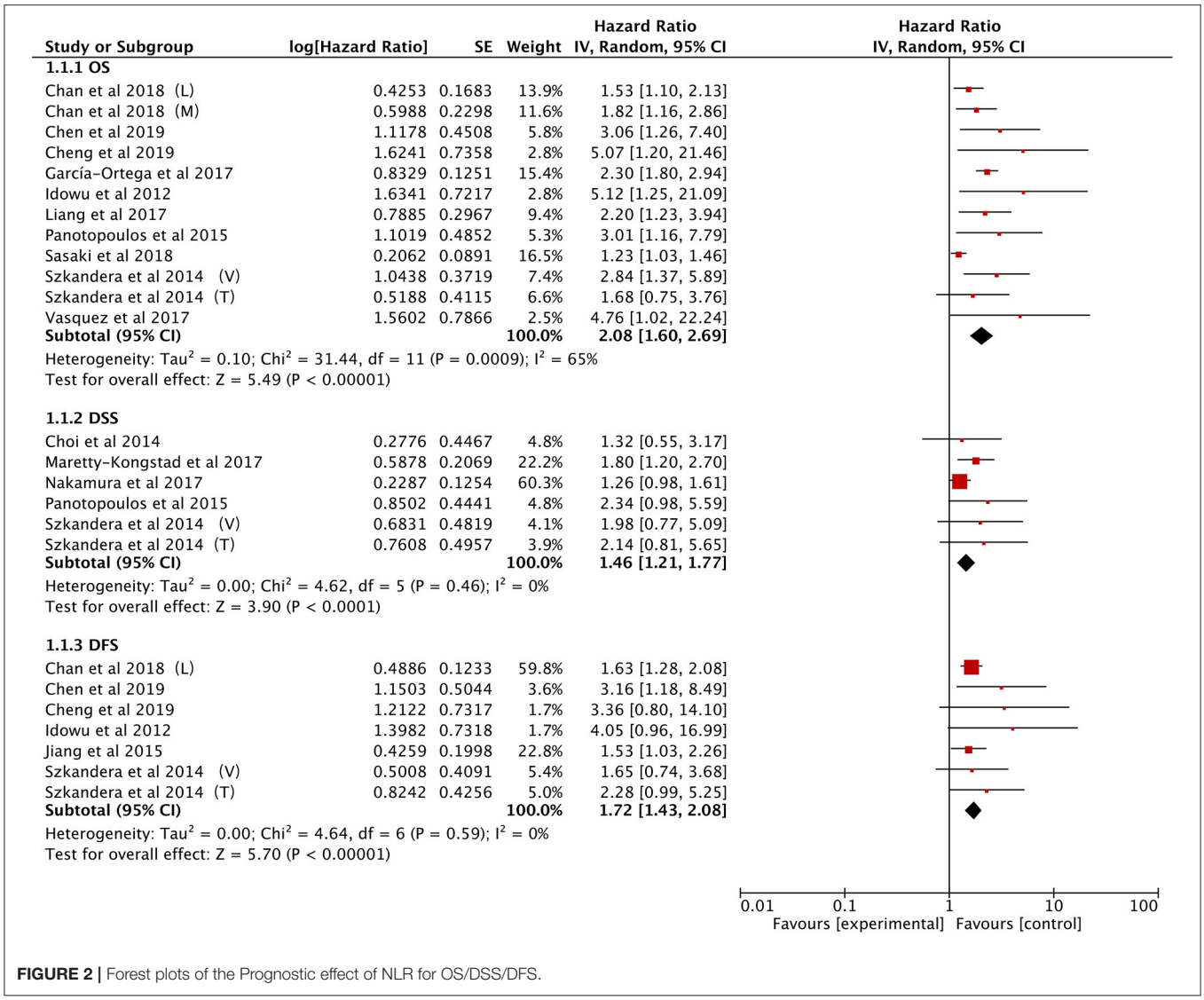

FIGURE 2 | Forest plots of the Prognostic effect of NLR for OS/DSS/DFS.

from the database. Ultimately, 23 studies involving 4,480 patients with STS met the inclusion criteria and were added into our meta-analysis. There were 15 studies for NLR, 11 for CRP, 7 for PLR, 4 for LMR, and 5 for GPS. The size of the samples ranged from 22 to 818. All studies collected data retrospectively. The mean NOS score was 6.95 and individual values ranged from 6 to 8. Further details of the studies are shown in **Table 1**.

Synthesized Findings

Correlation Between NLR and OS/DSS/DFS in STS

The data on prognostic value of NLR for OS were reported in 10 studies holding 1,964 STS patients (18, 21, 22, 25, 27, 28, 33, 34, 37, 40). Overall, elevated NLR was significantly associated with poor OS (HR: 2.08, 95% CI: 1.60–2.69, $P < 0.00001$), and due to the moderate heterogeneity observed, a random effect model was used ($I^2 = 65\%$; **Figure 2**). The NLR-OS correlation in synovial sarcoma and liposarcoma was shown in three studies and two studies, respectively (HR: 2.39, 95% CI: 1.89–3.02, $P <$ 0.00001 for synovial sarcoma; HR: 2.94, 95% CI: 1.81–4.77, $P < 0.0001$ for liposarcoma); no heterogeneity was detected ($I^2 = 0\%$; **Figure 3**). Only one study provided data on leiomyosarcoma, undifferentiated pleomorphic sarcoma, angiosarcoma, clear cell sarcoma, and rhabdomyosarcoma (HR: 1.62, 95% CI: 0.97–2.69, $P = 0.087$ for leiomyosarcoma; HR: 2.17, 95% CI: 1.49–3.16, $P = 0.0002$ for undifferentiated pleomorphic sarcoma; HR: 2.15, 95% CI: 1.29–3.59, $P = 0.0056$ for angiosarcoma; HR: 3.06, 95% CI: 1.26–7.40, $P = 0.013$ for clear cell sarcoma; HR: 4.76, 95% CI: 1.01–22.24, $P = 0.024$ for rhabdomyosarcoma).

The correlation between NLR and DSS was demonstrated in five studies comprising 1,486 STS patients (21, 22, 29, 32, 38). Collected data showed that poor prognosis of DSS was associated with high NLR (HR: 1.46, 95% CI: 1.21–1.77, $P < 0.0001$) without heterogeneity ($I^2 = 0\%$; **Figure 2**).

Six studies provided the data of NLR and DFS in STS (18, 21, 23, 25, 34, 40). The combined analysis indicated that NLR had a significant prognostic effect on DFS (HR: 1.72, 95% CI:

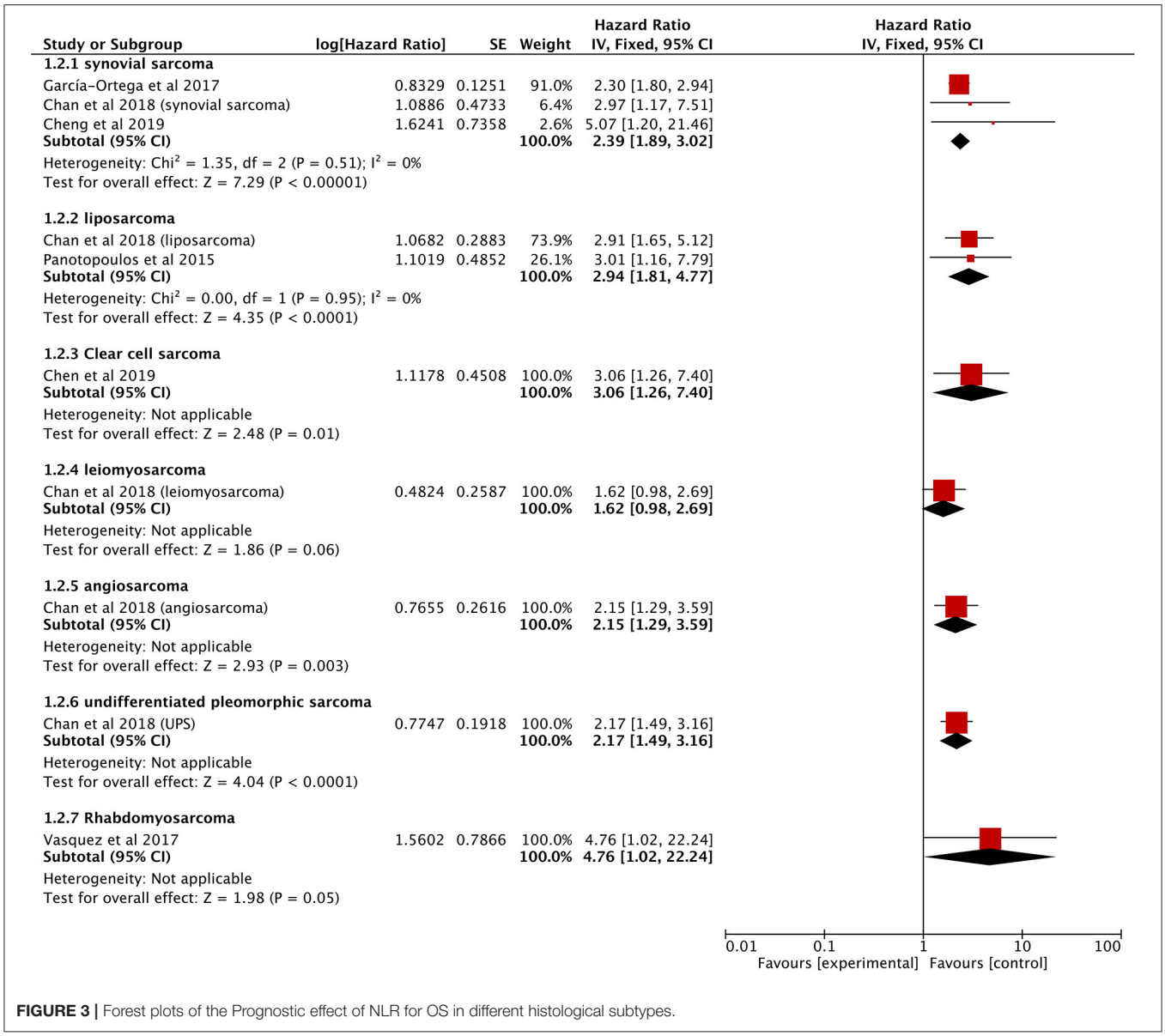

FIGURE 3 | Forest plots of the Prognostic effect of NLR for OS in different histological subtypes.

1.43–2.08, $P < 0.00001$), and no heterogeneity was detected ($I^2 = 0\%$; **Figure 2**).

Subgroup analysis illustrated that NLR was association with poor OS, DSS, and DFS in most subgroups, while the DSS Asia group had no significant prognostic value (**Table 2**).

Prognostic Value of Elevated CRP for OS/DSS/DFS

The effect of CRP on the STS prognosis was demonstrated in five studies (19, 22, 26, 31, 35). The analysis showed that a higher CRP level is a useful prognostic marker for predicting survival rate (HR: 1.92, 95% CI: 1.52–2.42, $P < 0.00001$) with no heterogeneity between studies ($I^2 = 0\%$; **Figure 4**). Seven studies reported the data on CRP and DSS (20, 22, 24, 29, 31, 32, 35). The random-effects model demonstrated that an elevated CRP levels had significantly prognostic value for DSS (HR: 2.06; 95% CI: 1.32–3.22; $P = 0.002$), but with significant heterogeneity ($I^2 = 84.0\%$; **Figure 4**). The correlation between CRP and DFS was demonstrated in five studies, and the pooled data illustrated that an elevated CRP level was associated with poor DFS (HR: 1.75; 95% CI: 1.38–2.23; $P < 0.00001$) (20, 26, 31, 35, 39). No heterogeneity ($I^2 = 0\%$; **Figure 4**) was observed. Subgroup analysis is shown in **Table 3**. The non-metastatic group did not show significant significance with regard to OS; the mixed treatment group and Asian ethnicity group did not show significant significance with respect to DSS.

Prognostic Effect of PLR for OS/DFS

The association between PLR and OS was demonstrated in seven studies (21, 25, 27, 28, 34, 37, 40). Elevated PLR was clearly

TABLE 2 | Subgroup analysis of the prognostic value of NLR.

Survival analysis	No. of studies	I^2 (%)	HR (95% CI)	*P*
OS				
Total	10	65%	2.08 (1.60–2.69)	$P < 0.00001$
Treatment				
Surgery	6*	14%	1.97 (1.56–2.48)	$P < 0.00001$
Mixed	5	82%	1.98 (1.27–3.08)	$P = 0.002$
Stage				
Non-metastatic	3†	33%	1.77 (1.34–2.33)	$P < 0.0001$
Metastatic	2	0%	2.06 (1.45–2.92)	$P < 0.0001$
Mixed	6	80%	2.33 (1.45–3.75)	$P = 0.0005$
Ethnicity				
Asian	5	59%	1.72 (1.29–2.31)	$P = 0.0003$
Latinos	2	0%	2.34 (1.84–2.98)	$P < 0.00001$
Caucasian	3	0%	2.60 (1.66–4.06)	$P < 0.0001$
DSS				
Total	5	0%	1.46 (1.21–1.77)	$P < 0.0001$
Treatment				
Surgery	4	0%	1.38 (1.11–1.71)	$P = 0.004$
Mixed	1	NA	1.80 (1.20–2.70)	$P = 0.004$
Stage				
Non-metastatic	3	0%	1.78 (1.29–2.46)	$P = 0.0005$
Mixed	2	45%	1.32 (1.04–1.67)	$P = 0.02$
Ethnicity				
Asian	2	0%	1.26 (1.00–1.60)	$P = 0.05$
Caucasian	3	0%	1.92 (1.39–2.66)	$P < 0.0001$
DFS				
Total	6	0%	1.72 (1.43–2.08)	$P < 0.00001$
Treatment				
Surgery	4	0%	1.76 (1.42–2.18)	$P < 0.00001$
Mixed	2	7%	1.62 (1.11–2.36)	$P = 0.01$
Stage				
Non-metastatic	3	0%	1.71 (1.37–2.13)	$P < 0.00001$
Metastatic	1	NA	1.53 (1.03–2.26)	$P = 0.03$
Mixed	2	0%	3.22 (1.43–7.27)	$P = 0.005$
Ethnicity				
Asian	4	0%	1.67 (1.37–2.04)	$P < 0.00001$
Caucasian	2	0%	2.14 (1.25–3.65)	$P = 0.005$

NA, not available.
**Chan 2018's study has both surgery cohort and mixed treatment cohort.*
† Chan 2018's study has both metastatic group and non-metastatic group.

associated with poor OS (HR: 1.86, 95% CI: 1.32–2.64, $P = 0.0004$), however, significant heterogeneity was observed ($I^2 = 85\%$; **Figure 5**).

The effect of PLR and DFS was reported in five studies (21, 25, 28, 34, 40). The fixed-effect model illustrated that an elevated PLR correlated with poor DFS (HR: 1.61, 95% CI: 1.32–1.95, $P < 0.00001$) with no heterogeneity among the studies ($I^2 = 0\%$; **Figure 5**).

Subgroup analytical studies illustrated that PLR had significant prognostic effect for OS and DFS in most subgroups, while the mixed treatment group on OS and DFS Caucasian ethnicity group had no significant prognostic value (**Table 4**).

Association Between LMR and OS/DFS in STS

A total of four studies provided LMR data on OS in STS patients (21, 25, 34, 40). The pooled data demonstrated that a low LMR had a visible prognostic effect on OS with an HR of 2.01 (95% CI: 1.65–2.45, $P < 0.00001$). No heterogeneity was observed ($I^2 = 0\%$; **Figure 6**).

The same four studies illustrated that LMR was also associated with DFS (21, 25, 34, 40). Alternatively, pooled data indicated that a low LMR had strong association with DFS (HR: 1.90, 95% CI: 1.49–2.43, $P < 0.00001$) and heterogeneity was not observed between studies ($I^2 = 0\%$; **Figure 6**).

Value of GPS for OS/DSS

Only two eligible studies explored the correlation between the GPS and OS (27, 28), and the combined data indicated that higher GPS scores correlated with much poorer OS (HR: 2.35; 95% CI: 1.64–3.36, $P < 0.00001$), without heterogeneity ($I^2 = 0\%$; **Figure 7**).

Three other studies show that high GPS is associated with poor DFS (29, 30, 36). The analysis showed that a higher GPS score is a useful prognostic marker for predicting DFS (HR: 2.77, 95% CI = 1.39–5.53, $P = 0.004$) with significant heterogeneity ($I^2 = 69\%$; **Figure 7**).

DISCUSSION

We performed a meta-analysis of 23 studies that were identified from multiple databases to examine the prognostic effect of hematological markers for STS. In our study, majority were high-grade and extremity tumors. The most common histological subtype was liposarcoma accounting for ∼830 cases, followed by malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma with ∼780 cases, and ∼550 cases of synovial sarcoma. The pooled data indicated that hematological markers, comprising NLR, CRP, PLR, LMR, and GPS, were associated with survival outcomes of STS; while high NLR, CRP, PLR, and GPS as well as low LMR were correlated with poorer prognosis. The results of the subgroup analysis also support our conclusions. Yet, many of the patients in our study were high grade patients with tumors located in the extremities, hence, these results should not be applied to all patients with STS. Patients with non-extremity and low-grade tumors require further analysis. Collectively, our findings suggest that these established markers, which can be tested using inexpensive, readily available assays, may serve as important biomarkers for the prognosis of high grade and extremity STSs.

Recently, the treatment for STS has changed allowing for improved overall prognosis. Despite some limitations, the clinical and pathological features have served as the primary prognostic factors for STS in recent decades. Innovative methodology has to must be applied to achieve improved early diagnosis of patients at risk of a specific outcome with acceptable cost (41). Molecular markers have shown reliable prognostic value in numerous types of cancer, some of which, including MDM2, MMP2, and P53, also exhibit a certain prognostic value in STSs. The MDM2 gene has been widely used in the diagnosis of STSs. A number of clinical trials targeting MDM2 gene drugs have recently

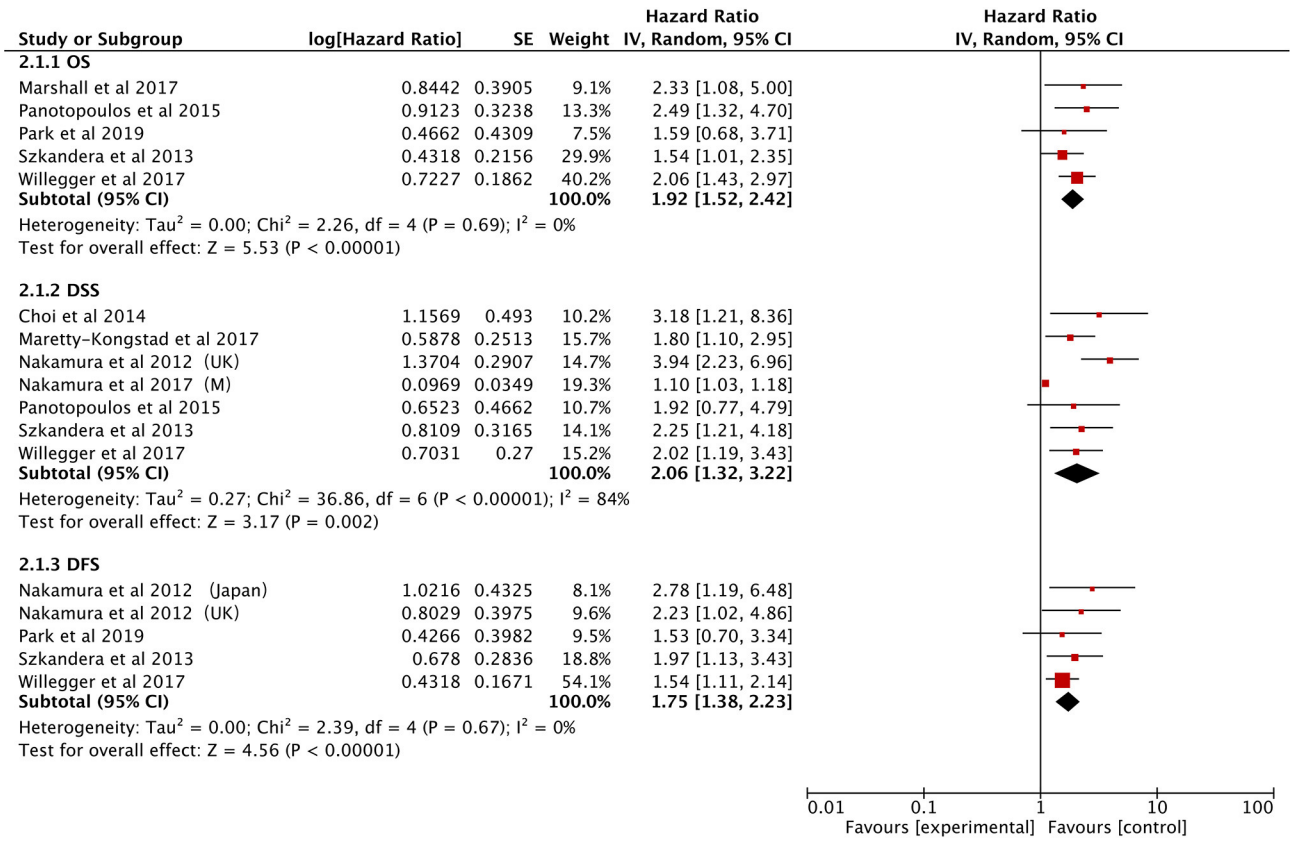

FIGURE 4 | Forest plots of the Prognostic effect of CRP for OS/DSS/DFS.

been conducted. Unfortunately, a meta-analysis shows that the MDM2 gene has a very limited role in prognosis (42, 43). Moreover, molecular detection technology must be improved to allow for reduced costs associated with evaluation (44, 45). Other markers, such as tumor necrosis, 18F-fluorodeoxyglucose positron emission tomography, and PD-1/PD-L1 have also demonstrated prognostic effects in STS. However, the clinical use of these markers is very limited (46, 47). Hence, none of these biomarkers are ready for clinical use.

In cancer patients, hematological markers serve as sensitive prognostic indicators, with inflammatory markers being the most reliable (7–13). The belief that a relationship exists between inflammation and tumor development can be traced back to the nineteenth century. As early as 1863, Rudolf Virchow observed leukocytes in tumor tissues and established this hypothesis. Due to the limitations of the times and technology, this speculation has been silent for many years. However, currently, our knowledge of inflammation in the tumor microenvironment has supported this hypothesis (48, 49). In fact, evidence now suggests that inflammation of the tumor microenvironment promotes tumorigenesis, growth, and metastasis, with a very prominent link between inflammation and tumors (5, 6, 49).

NLR is currently the most common hematological inflammation marker. Neutrophils can remodel the extracellular matrix and promote angiogenesis, which may stimulate tumor cell migration and metastasis. Furthermore, neutrophils significantly impact immunity by inhibiting cytolytic activity of lymphocytes, whereas tumor-infiltrating lymphocytes may restrict the metastatic outgrowth of cancer cells (50–52). In a previous study, Liu et al. (53) indicated that NLR may serve as a prognostic marker in both localized bone and STSs. However, osteoblastic tumors differ markedly from STSs in terms of treatment and prognosis. We, therefore, separated STS from osteogenic tumors and included a larger sample size.

The prognostic effect of CRP has been established in a variety of cancers. Tumor growth can lead to inflammation of tissues, thereby elevating the CRP level. Previous studies have preliminarily demonstrated the prognostic value of CRP in STS, however, there are certain limitations to these studies. For example, Li et al. (54) did not separate DSS from the OS even though these variable constitute two unique concepts by definition, especially when considering tumor prognosis. This can be observed from our conclusion. Compared to Xiaolin Wang's research (55), we have included more papers to provide a more comprehensive endpoint.

Previous studies have also shown that PLR exhibits reliable prognostic value in various tumors, such as those of ovarian cancer, pancreatic cancer, and bladder cancer. Platelets can mediate tumor cell growth, angiogenesis, and proliferation by

TABLE 3 | Subgroup analysis of the prognostic value of elevated CRP.

Survival analysis	No. of studies	I^2 (%)	HR (95% CI)	*P*
OS				
Total	5	0%	1.92 (1.52–2.42)	$P < 0.00001$
Treatment				
Surgery	4	0%	1.88 (1.48–2.40)	$P < 0.00001$
Mixed	1	NA	2.33 (1.08–5.00)	$P = 0.03$
Stage				
Non-metastatic	1	NA	1.59 (0.68–3.71)	$P = 0.28$
Metastatic	4	0%	1.95 (1.53–2.48)	$P < 0.00001$
Ethnicity				
Asian	2	0%	1.96 (1.11–3.46)	$P = 0.02$
Caucasian	3	0%	1.91 (1.48–2.46)	$P < 0.00001$
DSS				
Total	7	84%	2.06 (1.32–3.22)	$P = 0.001$
Treatment				
Surgery	5	0%	2.57 (1.91–3.45)	$P < 0.00001$
Mixed	2	73%	1.32 (0.83–2.10)	$P = 0.24$
Stage				
Non-metastatic	3	54%	2.72 (1.57–4.69)	$P = 0.0003$
Metastatic	1	NA	1.10 (1.03–1.18)	$P = 0.005$
Mixed	3	0%	2.08 (1.44–3.01)	$P < 0.0001$
Ethnicity				
Asian	2	77%	1.68 (0.62–4.54)	$P = 0.30$
Caucasian	5	16%	2.29 (1.76–2.97)	$P < 0.00001$
DFS				
Total	5	0%	1.75 (1.38–2.23)	$P < 0.00001$
Treatment				
Surgery	4	0%	1.68 (1.31–2.16)	$P < 0.0001$
Mixed	1	NA	2.78 (1.19–6.48)	$P = 0.02$
Stage				
Non-metastatic	3	0%	2.09 (1.31–3.31)	$P = 0.002$
Mixed	2	0%	1.64 (1.24–2.18)	$P = 0.0006$
Ethnicity				
Asian	2	2%	2.01 (1.13–3.57)	$P = 0.02$
Caucasian	3	0%	1.70 (1.30–2.22)	$P < 0.0001$

NA, not available.

TABLE 4 | Subgroup analysis of the prognostic value of PLR.

Survival analysis	No. of studies	I^2 (%)	HR (95% CI)	*P*
OS				
Total	7	85%	1.86 (1.32–2.64)	$P < 0.00001$
Treatment				
Surgery	4	0%	1.90 (1.53–2.35)	$P < 0.00001$
Mixed	4	84%	1.55 (0.93–2.58)	$P = 0.09$
Stage				
Non-metastatic	2	0%	1.76 (1.38–2.26)	$P < 0.00001$
Metastatic	1	NA	1.70 (1.28–2.26)	$P = 0.0002$
Mixed	5	80%	2.09 (1.08–4.04)	$P = 0.03$
Ethnicity				
Asian	5	88%	1.72 (1.17–2.52)	$P = 0.006$
Caucasian	1	0%*	1.97 (1.20–3.25)	$P = 0.008$
Latinos	1	NA	4.73 (1.01–22.17)	$P = 0.05$
DFS				
Total	5	0%	1.61 (1.32–1.95)	$P < 0.00001$
Stage				
Non-metastatic	2	40%	1.56 (1.24–1.97)	$P = 0.0002$
Mixed	3	0%	1.71 (1.19–2.44)	$P = 0.003$
Ethnicity				
Asian	4	0%	1.67 (1.36–2.06)	$P < 0.00001$
Caucasian	1	NA	1.01 (0.50–2.04)	$P = 0.98$

NA, not available.
**Szkandera 2014's study has validation set and training set, each set has 170 patients.*

releasing vascular endothelial growth factor, hepatocyte growth factor, basic fibroblast growth factor, angiopoietin-1 together with other angiogenesis and tumor growth factors. Furthermore, platelets have a defined role in protecting tumor cells from immune elimination and supporting tumor metastasis (56–58). In this meta-analysis, we observed that elevated PLR was clearly related with poor OS and DFS, consistent with the findings of previous studies. To our knowledge, this study is the first meta-analytical study that conducted research on the prognostic effect of PLR in STS patients.

Recent studies have also provided insights into the prognostic value of LMR. In fact, it has been suggested that LMR is a better prognostic indicator. Further, studies have highlighted the importance of tumor-associated macrophages. Hence, TMA derived from peripheral blood monocytes may support tumor progression and angiogenesis through secretion of growth factors and cytokines (59). This is also the first meta-analytical study, to our knowledge, to investigate LMR prognostic value in STS patients. However, only three studies were qualified for our analytical study, and subsequent studies are required.

There is also an increasing interest in scoring based on the inflammatory biomarkers. GPS is now used to predict various tumor prognoses (12). Glasgow's prognosis score consists of CRP and albumin as albumin levels in plasma reflect both the patient's nutritional level and systemic inflammation. However, most high scores are caused by abnormalities in CRP. Implying that the score is based on systemic inflammation. The significant correlation between GPS and STS is what our study demonstrated, with no similar meta-analysis previously performed.

Our study also has several limitations. First, we need to acknowledge that we cannot correct the histological subtype, a confounding factor that may affect outcomes. We have done our best to analyze histological subtypes. However, only three studies provided data on synovial sarcoma, two studies provided data on liposarcoma, and one provided data on clear cell sarcoma, angiosarcoma, undifferentiated pleomorphic sarcoma, rhabdomyosarcoma, and leiomyosarcoma. Results for a single subtype suggest that NLR has prognostic value in most subtypes, however, it is not possible to predict the prognosis of leiomyosarcoma. Thus, more research on specific subtypes is needed to further validate our results. Second, since some studies did not include multivariate analysis data, we included a portion of univariate analysis. Third, the same blood markers have different cut-off values. However,

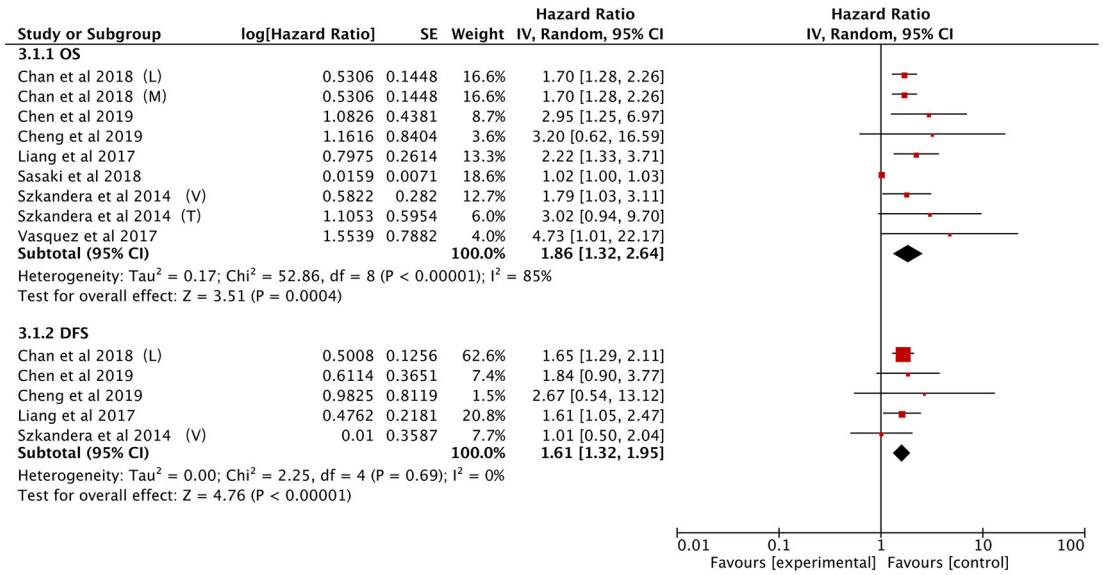

FIGURE 5 | Forest plots of the Prognostic effect of PLR for OS/DFS.

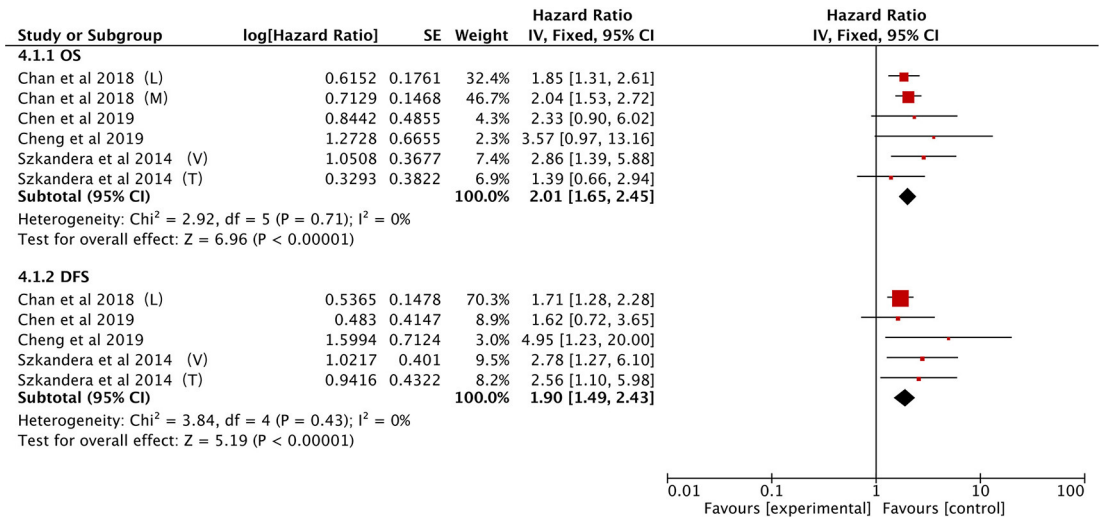

FIGURE 6 | Forest plots of the Prognostic effect of LMR for OS/DFS.

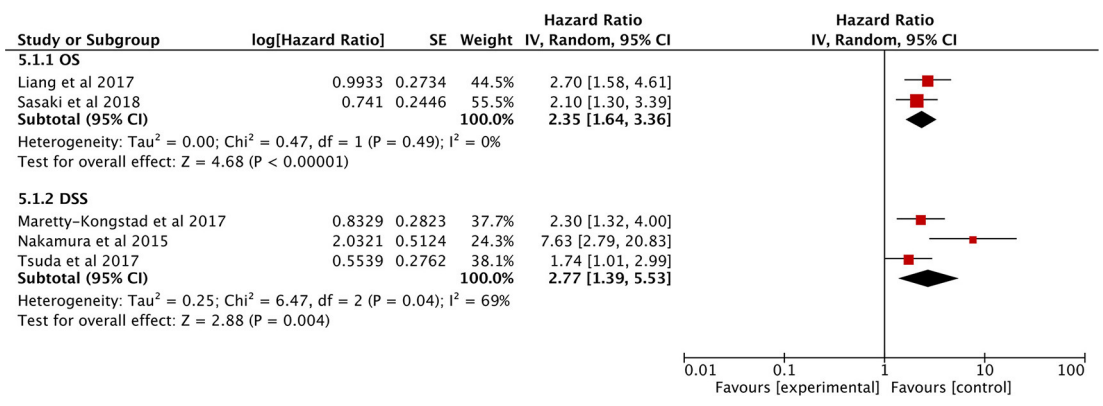

FIGURE 7 | Forest plots of the Prognostic effect of GPS for OS/DSS.

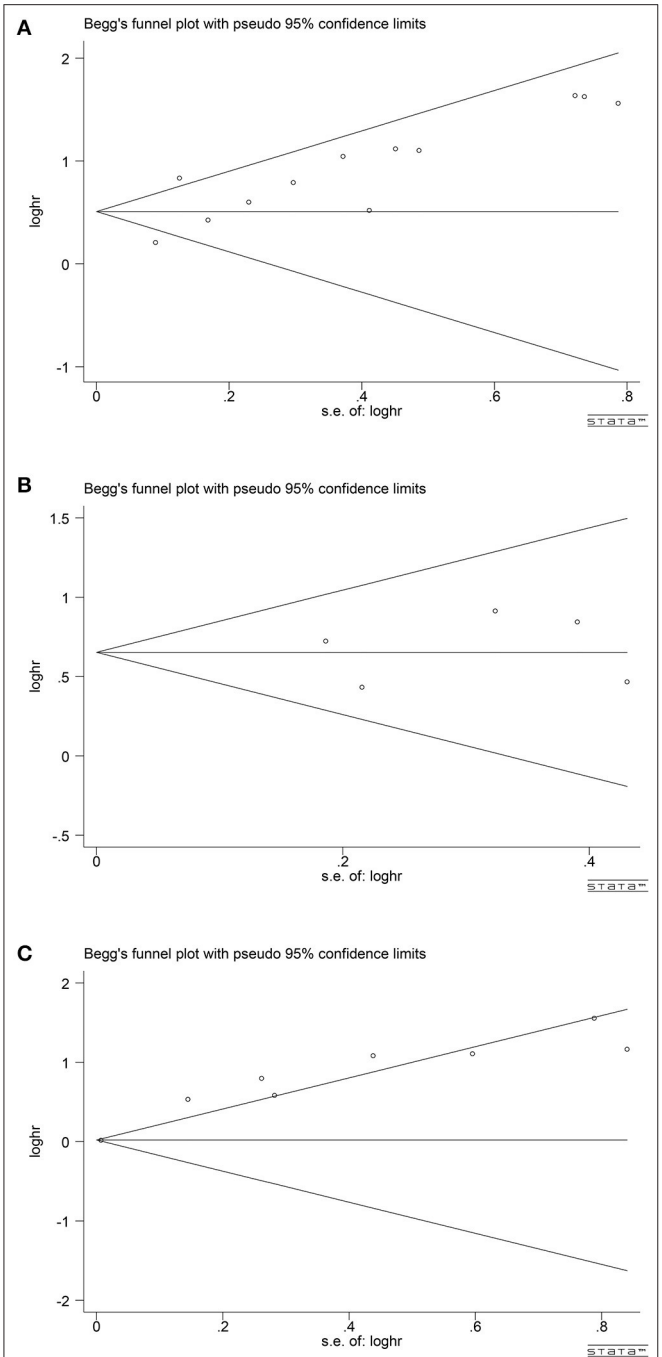

FIGURE 8 | Analyses of publication bias for the relationship between NLR/CRP/PLR and OS **(A)** Begger's funnel plot for NLR. **(B)** Begger's funnel plot for CRP. **(C)** Begger's funnel plot for PLR.

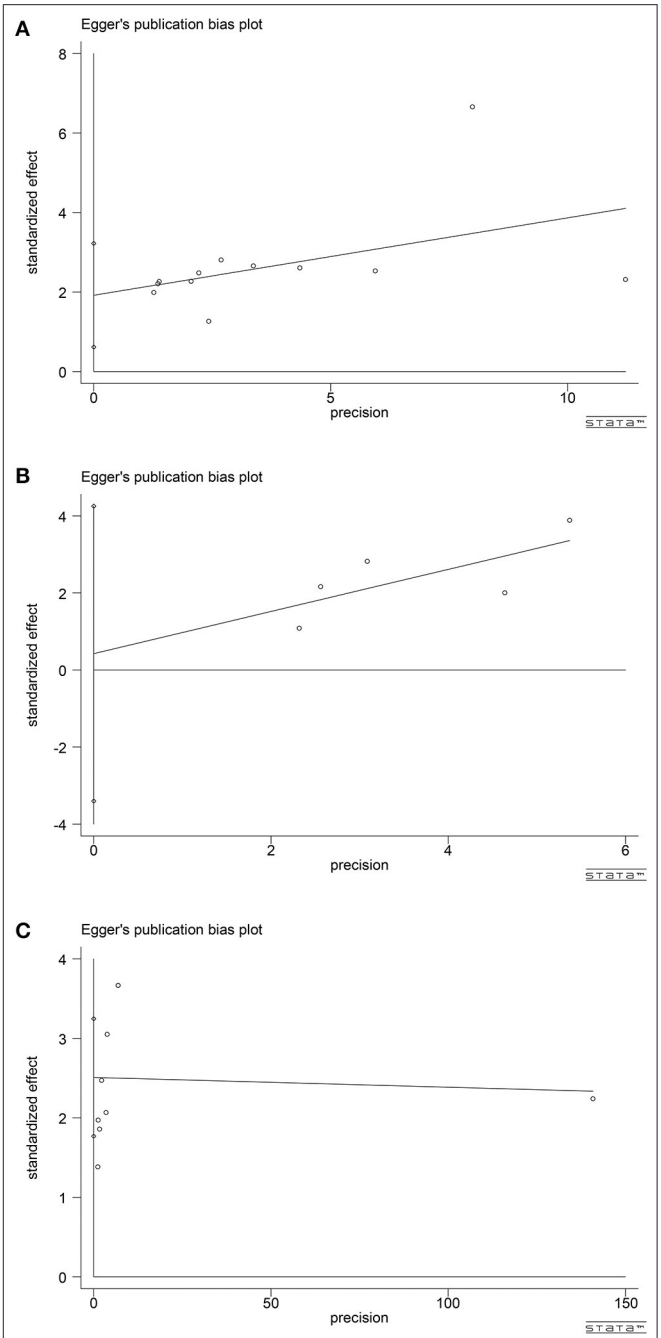

FIGURE 9 | Analyses of publication bias for the relationship between NLR/CRP/PLR and OS **(A)** Egger's publication bias plot for NLR. **(B)** Egger's publication bias plot for CRP. **(C)** Egger's publication bias plot for PLR.

since there have been no studies to compare the prognostic effects of different cutoff values, the optimal value cannot be evaluated. Nevertheless, our meta-analysis is the largest study to investigate the prognostic value of hematological markers in STSs. Compared to previous studies, we have included a larger sample size and excluded confounding factor of osteogenic tumors. Moreover, we are the first, to our knowledge, to investigate the prognostic value of multiple markers in STSs. These factors reinforce the strengths of our meta-analysis.

PUBLICATION BIAS

According to the publication-bias-plot shown in **Figures 8**, **9**, the bias was insignificant with regards to the prognostic value of NLR/CRP/PLR for OS. The Begg's p and Egger's p for OS were 0.115 and 0.008, respectively. Calculate new

HR using trim and fill methods (HR: 1.80; 95% CI: 1.42–2.28; $p < 0.001$; random effects). No publication bias was observed in the prognostic value of CRP for OS. The Begg's p and Egger's p for OS were 1.000 and 0.748. Among the seven included studies for PLR on OS, the Egger's test depicted proof of publication bias ($p = 0.000$), whereas the Begg's test did not ($p = 0.144$). Therefore, we used the trim and fill method allowing the new HRs to retain statistical significance (HR: 1.58; 95% CI: 1.17–2.13; $p < 0.001$; random effects).

CONCLUSIONS

Our research shows that hematological markers are one of the important prognostic indicators for patients affected by high-grade STS and patients with the STS being located in the extremity. Large-scale prospective studies are needed, especially studies targeting specific STS subtypes, to further validate our results.

AUTHOR CONTRIBUTIONS

L-QL collected and analyzed the data and wrote the paper. Z-HB and L-HZ assisted in collecting the data and participated in the writing. YaZ, X-CL, YiZ, JW, and Y-KL assisted in the design of this study. J-ZL was responsible for all the integrity of data and the accuracy of data analysis. All authors have thoroughly revised the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.