Potential value of pretreatment neutrophil-to-lymphocyte ratio in patients with bone sarcomas

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Abstract

Background Increasing evidence indicates the important value of the neutrophil-to-lymphocyte ratio (NLR) in various cancers. In this meta-analysis, we will explore the potential role of pretreatment NLR in patients with bone sarcomas. Methods A systematic literature search of the PubMed, Embase and Web of Science databases for relevant articles was performed with the deadline of December 29, 2019. The hazard ratio (HR) and its 95% confidence interval (CI) were calculated to evaluate the association between NLR and overall survival (OS) in patients with bone sarcomas. Results A total of 1131 patients in 6 studies were included in this meta-analysis. The pooled HR of 2.26 (95%CI: 1.83-2.69, p<0.001) indicated that an elevated NLR had an unfavourable effect on OS. Subgroup analyses showed that elevated NLR was related to poor OS in patients with bone sarcomas, regardless of the type of cancer, ethnicity, sample size (≥200 or <200), the cut-off value for NLR (≥3 or <3), follow-up time (≥30 or <30) and paper quality (NOS scores ≥8 or <8). Additionally, the results of diagnosis analysis suggested that NLR had a relatively high diagnostic accuracy for bone sarcoma patients. Conclusion The results of this meta-analysis suggest that an elevated NLR is associated with poor survival of patients with bone sarcomas. Moreover, NLR had a relatively high diagnostic accuracy for bone sarcoma patients. All these findings suggest NLR might be a promising biomarker in the management of bone sarcomas.

1. Background

Bone sarcomas, dominated by osteosarcoma, Ewing sarcoma, and chondrosarcoma, are rare primary malignant tumors represent less than 1 percent of all malignancies [1]. Osteosarcoma and Ewing's sarcoma predominantly occur in children and adolescents, whereas chondrosarcoma most commonly affects older adults [2]. Despite the significant advance in diagnosis and treatment in the past decades, the overall 5-year survival rates of bone sarcomas remain unsatisfactory for local recurrence or metastasis after surgical resection. High mortality rates caused by cancer are attributed in part to the lack of efficiently prognostic biomarkers [3]. Therefore, there is an urgent need for more effective and reliable biomarkers to provide additional prognostic information.

Mounting evidence shows that systemic inflammation plays an essential role in tumor growth, development and metastasis [4]. Several inflammatory indicators in peripheral blood have been investigated to predict the prognosis in various cancers, such as C-reactive protein (CRP) [5], NLR [6], platelet-lymphocyte ratio (PLR) [7], lymphocyte-monocyte ratio (LMR) [8] and Glasgow prognostic score (GPS) [9]. NLR, calculated as the absolute neutrophil count divided by the absolute lymphocyte count, has been reported to be an accurate and reliable prognostic biomarker in various cancers such as gastric cancer [10], hepatocellular carcinoma [11], lung cancer [12], and colorectal cancer [13]. Of note, NLR serves as an easily accessible and cost-effective blood test that does not need any additional resources for routine use. However, the exact value of NLR in bone sarcomas has not yet been fully elucidated. Therefore, we sought to perform a meta-analysis based on relevant studies to investigate the potential role of pretreatment NLR in patients with bone sarcomas.

2. Methods

2.1. Materials and methods

2.1. 1. Search strategies

A systematic literature search of the PubMed, Embase and Web of Science databases for relevant articles was performed with the deadline of December 29, 2019. Search terms used in the search strategy included the keywords “bone sarcoma”, “bone cancer”, “bone neoplasms”, “chondrosarcomas”, “sarcoma, Ewing's”, “sarcoma, Ewings”, “Ewing's sarcoma”, “Ewings sarcoma”, “Ewing's tumor”, “Ewings tumor”, “tumor, Ewing's”, “Ewing sarcoma”, “Ewing tumor”, “tumor, Ewing”, “osteosarcomas”, “osteosarcoma tumor, “osteosarcoma tumors”, “tumor, osteosarcoma”, “tumors, osteosarcoma”, “sarcoma, osteogenic”, “osteogenic sarcomas”, “sarcomas, osteogenic”or“osteogenic sarcoma” combined with “neutrophil to lymphocyte ratio”, “neutrophil-lymphocyte ratio” or “NLR” and“prognosis” or “outcome” or“survival”. In addition, the reference lists of the relative articles were carefully scanned for potentially eligible studies.

2.1.2. Selection criteria

The following eligibility criteria were as follows: (1) the diagnosis of all patients with bone sarcomas was confirmed depended on histological evidence; (2) studies investigated the association of pretreatment NLR with overall survival (OS); (3) reported a cut-off value for NLR; (4) the study provided sufficient information to calculate the HR and 95% CI. The exclusion criteria were as follows: (1) articles that were letters, conference abstracts, case reports, editorials, laboratory studies, expert opinions and reviews; (2) lack of sufficient data for further analysis; (3) repeated analyses and duplicate publications; (4) non-English articles.

2.1.3. Data extraction and quality assessment

Studies were assessed for eligibility and quality and the data extracted by three independent reviewers (HZH, XH and WBY), and any conflicts between them was resolved by discussion. The following information was were collected from the 6 included studies: first author's name, the year of publication, country, ethnicity, number of patients, age, gender, cut-off values, stage, time of follow-up, the survival data and the and the relevant information regarding the bone sarcomas.

The quality of the eligible studies was assessed according to the Newcastle-Ottawa quality assessment scale (NOS) [14]. The NOS scores ≥6 were defined as high-quality studies.

2.1.4. Statistical analysis

All statistical analyses were carried out by STATA software version 12.0 (STATA Corporation, College Station, TX, USA). The combined HR and 95% CIs were used to evaluate the association between NLR and OS based on the imformation extracted from the eligible studies. The between-study heterogeneity was assessed by using the chi-square test and the I^2 statistic. An I^2 value of >50% indicated a significant heterogeneity. We further conducted sensitivity analyses and publication bias to assess the stability of results.

2.2. Results

2.2.1. Study characteristics

The study selection process is shown in the flow diagram (Fig. 1). A total of 256 potential articles were acquired from the three databases (PubMed, Embase and Web of Science) through expanding the search strategy. 168 studies were left after duplicates removed. Of these studies, 92 were excluded by reviewing the titles and abstracts, leaving 76 articles for the full-text review. In the review, 70 studies were excluded for the reasons as follows: 3 were not relevant to NLR or bone tumor, 28 were eliminated for no relevant outcomes reported, 13 studies were letter, reviews or meta-analysis, 6 were animal experiments, and 8 were of insufficient data for analysis. Finally, 6 eligible studies involving 1131 patients that met the inclusion criteria were enrolled into our meta-analysis [15-20].

All the included studies were published between 2016 and 2017. The sample sizes ranged from 100 to 359. Of the 6 studies, four studies came from China, one in Peru, and one in Denmark. All the included studies regarded the OS as the endpoint, and two studies presented progression-free survival (PFS) and disease-specific mortality (DSM) respectively. Quality assessment results of the eligible studies varied from 7 to 8, with average 7.5 (Supplementary Table 1). The detailed information of the eligible studies is shown in Table 1.

2.2.2. Meta-analysis

2.2.3. Overall survival

The present results revealed that high NLR was significantly related with a poor prognosis for patients with bone sarcoma (OS: HR=2.26, 95%CI: 1.83-2.69, p<0.001) (Fig. 2), and the fixed-effect model was utilized for no significant heterogeneity among the studies (I^2=0.0%, p=0.691). We made subgroup-analysis to further explore the relationship between high NLR and OS

based on the following parameters: type of cancer, ethnicity, sample size (≥200 or <200), cut-off values for NLR (≥3 or <3), follow-up time (≥30 months or <30) and paper quality (NOS scores ≥8 or <8). The subgroup-analysis illustrated the same outcomes that the significant relationship between high NLR and poor OS was not altered with all the factors above (Table 2). Moreover, no significant heterogeneity was detected across studies.

2.2.4. Diagnosis analysis

Forest plots of the sensitivity and specificity of NLR for predicting overall survival of patients with bone sarcoma are shown in Fig. 3. A random effect model was utilized with an obvious heterogeneity (I^2=68.31% for sensitivity and I^2=37.81% for specificity). The summary outcomes are as follows: sensitivity (SEN), 0.63 (95%CI 0.55-0.70); specificity (SPE), 0.80 (95%CI 0.75-0.84); positive likelihood ratio (PLR), 3.10 (95%CI 2.30-4.20); negative likelihood ratio, 0.46 (95%CI 0.36-0.58); and overall diagnostic odds ratio (DOR), 7.0 (95%CI 4.0-11.0). Furthermore, we made a summary receiver operator characteristic (SROC) curve (Fig. 4) and calculated the area under the curve (AUC) (0.80, 95%CI 0.76-0.83). To sum up, the study suggested that NLR had a relatively high diagnostic accuracy for the prognosis of malignant bone tumor patients. Whereas, more studies were warranted to verify our findings.

2.2.5. Sensitivity analysis and publication bias

In the present study, we quantitatively performed Begg's and Egger's tests to assess the publication bias. No evidence of publication bias was observed from Begg's funnel plot (p=0.260) (Supplementary Figure 1) and Egger's test (p=0.223) (Supplementary Figure 2). Accordingly, the possibility of publication bias could be excluded. Furthermore, the sensitivity analysis revealed that the outcomes did not change greatly when omitting studies one by one (Supplementary Figure 3). We made a Deeks' funnel plot asymmetry test and no evidence of publication bias (p=0.27) existed (Supplementary Figure 4).

3. Discussion

The relationship between inflammation and the development of tumorigenesis has been well established [21]. The inflammatory reaction, which involves the repair of the tissue destruction caused by tumors, is a vital factor in the microenvironment of tumor cells [22, 23]. Furthermore, inflammation plays an essential role in the occurrence, development and metastasis of tumor by promoting proliferation, angiogenesis and antiapoptosis [24]. Neutrophils, as inflammatory cells, could be drawn to the tumor microenvironment as varieties of chemokines secreted by tumor cells, and then neutrophils stimulate the growth of tumor cells by producing a set of cytokines, such as interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor α (TNF-α) and vascular endothelia growth factor (VEGF) [25, 26]. Of note, the increased TNF-α and IL-10 cause a decrease in lymphocyte count and lymphocyte dysfunction [27]. In general, impaired T-lymphocyte-mediated antitumor response might be related with lymphocyte depletion. Accordingly, the relative ratio of neutrophils and lymphocytes seems to reflect the systemic inflammatory response to cancer progression [28].

Growing evidence has demonstrated that the predictive value of the NLR in various cancers [5-9], the underlying mechanism might be correlated with the infiltrated neutrophils and lymphocytes. Numerous studies have shown that NLR could be valuable as a prognostic indicator of solid tumors, such as breast cancer [29], melanoma [30], prostate cancer [28]. The present study aimed to investigate the role of pretreatment NLR as a prognostic biomarker in bone sarcoma. As we all know, our meta-analysis is the first to evaluate the potential role of NLR in bone sarcomas.

In this meta-analysis, we combined the outcomes of 1131 patients from 6 articles, indicating that high NLR was in associated with poor OS in patients with bone sarcoma. Subgroup analysis showed that an elevated NLR was related to worse OS in patients with bone sarcomas, regardless of the type of cancer, ethnicity, sample size (≥200 or <200), the cut-off value for NLR(≥3 or <3), follow-up time (≥30 or <30) and paper quality (NOS scores ≥8 or <8). Additionally, we also performed diagnosis analysis, and the results suggested that NLR had a relatively high diagnostic accuracy for bone sarcoma patients.

There were several limitations of the current study should be clarified. First, only 6 studies were included and all of them were retrospective studies. Second, the included studies applied different NLR cut-off values since the lacking of unified standards

which may be a potential source of heterogeneity. Thirdly, there might be some important literatures that are omitted because of language prejudice. Last, the focus of our study purely on the NLR level of pretreatment, in order to further validate its prognostic value, the levels of CRP at various stages, such as after surgery and at recurrence, should also be taken into account. Thus, further investigations need to present more reliable results about the prognostic value of NLR in bone sarcoma.

4. Conclusions

In conclusion, our meta-analysis demonstrated that an elevated NLR is associated with poor survival of patients with bone sarcomas. Moreover, NLR had a relatively high diagnostic accuracy for bone sarcoma patients. All these findings suggest NLR might be a promising biomarker in the management of bone sarcomas. However, further investigations involving multicenter prospective studies and large sample size are warranted to validate the role of the NLR in bone sarcoma.

List Of Abbreviations

NLR: neutrophil-to-lymphocyte ratio; HR: hazard ratio; CI: confidence interval; OS: overall survival; CRP: C-reactive protein; PLR: platelet-lymphocyte ratio; LMR: lymphocyte-monocyte ratio; GPS: Glasgow prognostic score; NOS: Newcastle-Ottawa quality assessment scale; PFS: progression-free survival; DSM: disease-specific mortality; Sen: sensitivity; Spe: specificity; AUC: the area under the curve; DOR: overall diagnostic odds ratio; SROC: summary receiver operator characteristic.

Declarations

Authors' contributions: HZH, XH and WBY designed the study. QWZ and YBL performed the systematic literature search. HZH, XH and BCW analyzed the data. WBY and SYW prepared the manuscript. HZH, XH and ZWS revised the manuscript critically. All authors read an approved the final manuscript.

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Tables

Table 1. Main characteristics of included studies.

Study	Year	Country	Sample size	NLR		Cancer type	Cut-off values	Out-comes	Follow-up (months)	Sen	Spe	AUC
				High	Low							
Li et al. a	2017	China	122	57	65	Ewing sarcoma	2.38	OS	35.0	0.74	0.85	0.618
Li et al. b	2017	China	216	93	123	Osteosarcoma	2.65	OS	31.5	0.64	0.83	0.644
Vasquez et al.	2017	Peru	100	60	40	Osteosarcoma=55; Ewing sarcoma=23; Other=22	2.00	OS	Osteosarcoma =22; Ewing sarcoma =17	NA	NA	NA
Liu et al.	2016	China	162	53	109	Osteosarcoma	2.57	OS	28.2	0.5	0.86	0.663
Xia et al.	2016	China	359	164	195	Osteosarcoma	3.43	OS PFS	40	0.57	0.73	0.705
Aggerholm-Pedersen et al.	2016	Denmark	172	11	152	Ewing sarcoma/ Osteosarcoma=19; Chondrosarcoma=55	5.30	OS DSM	NA	NA	NA	NA

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PFS, progression-free survival; DSM, disease-specific mortality; Sen, sensitivity; Spe, specificity; AUC, the area under the curve; NA, not available.

Table 2. Subgroup analysis of pooled HRs for OS in patients with high NLR.

Subgroup analysis	No. of studies	Pooled HRs	95%CI	Heterogeneity	
				I^2	*p*-value
Type of cancer					
Ewing sarcoma	2	2.10	0.91-3.28	0.0%	0.903
Osteosarcoma	4	2.29	1.82-2.76	0.0%	0.399
Ethnicity					
Asian	4	2.25	1.81-2.70	0.4%	0.390
Non-Asian	2	2.34	0.77-3.91	0.0%	0.843
Sample size					
≥200	2	2.22	1.70-2.73	60.4%	0.112
<200	4	2.36	1.59-3.13	0.0%	0.931
Cut-off values					
≥3	2	2.60	1.90-3.30	0.0%	0.692
<3	4	2.06	1.51-2.60	0.0%	0.691
Follow-up time					
≥30	3	2.19	1.72-2.67	22.2%	0.277
<30	2	2.62	1.52-3.72	0.0%	0.927
NOS score					
≥8	4	2.28	1.81-2.74	0.0%	0.404
<8	2	2.17	1.05-3.28	0.0%	0.743

Supplemental File Legends

Table S1: Quality assessment of eligible studies (Newcastle-Ottawa Scale).

Figure S1: Begg's funnel plot for NLR in patients with bone sarcomas.

Figure S2: Egger's funnel plot for NLR in patients with bone sarcomas.

Figure S3: Sensitivity analysis for NLR in patients with bone sarcomas.

Figure S4: Deeks' funnel plot asymmetry test for NLR in patients with bone sarcomas.

Figures

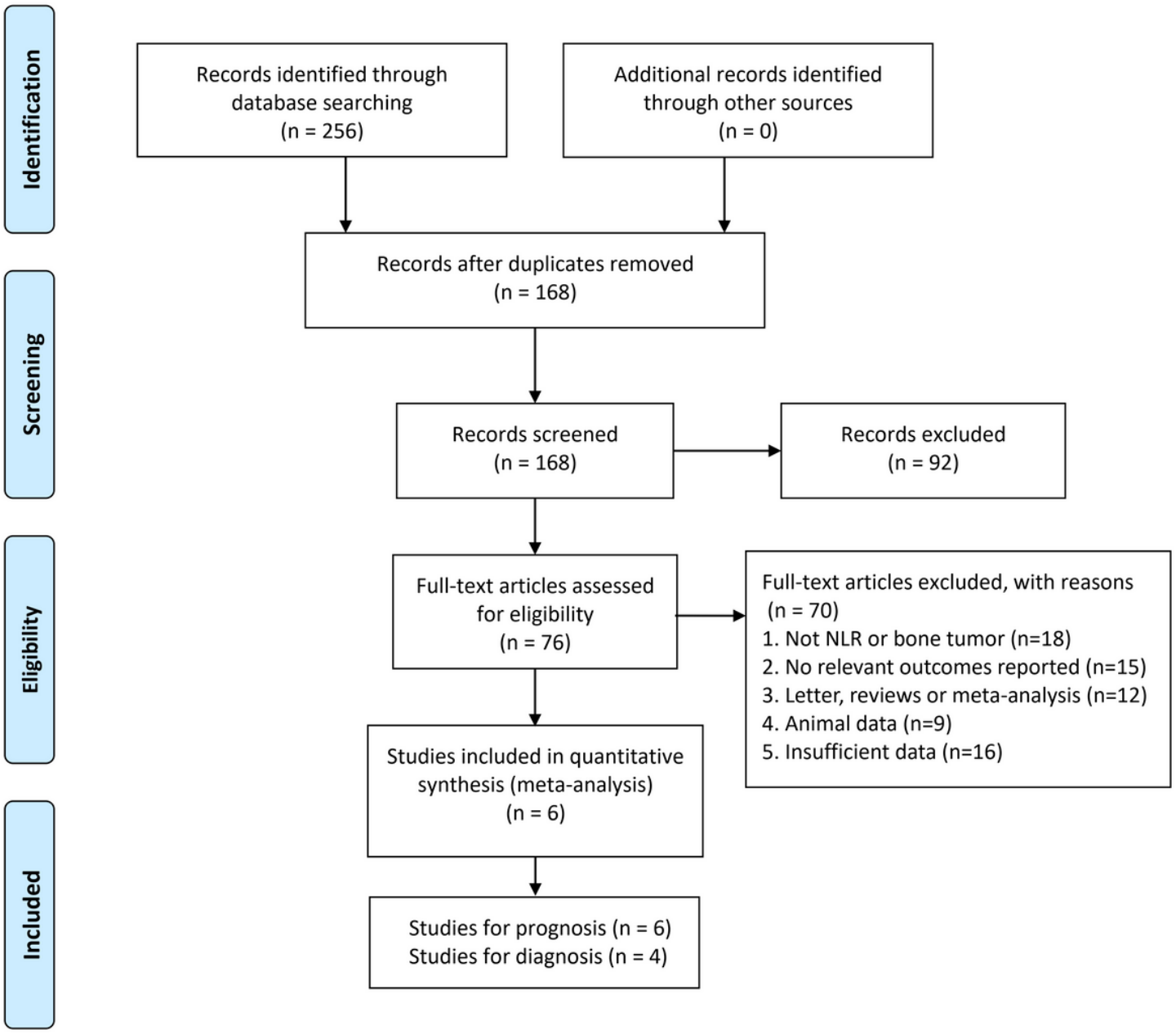

Figure 1

Flowchart of the study selection process.

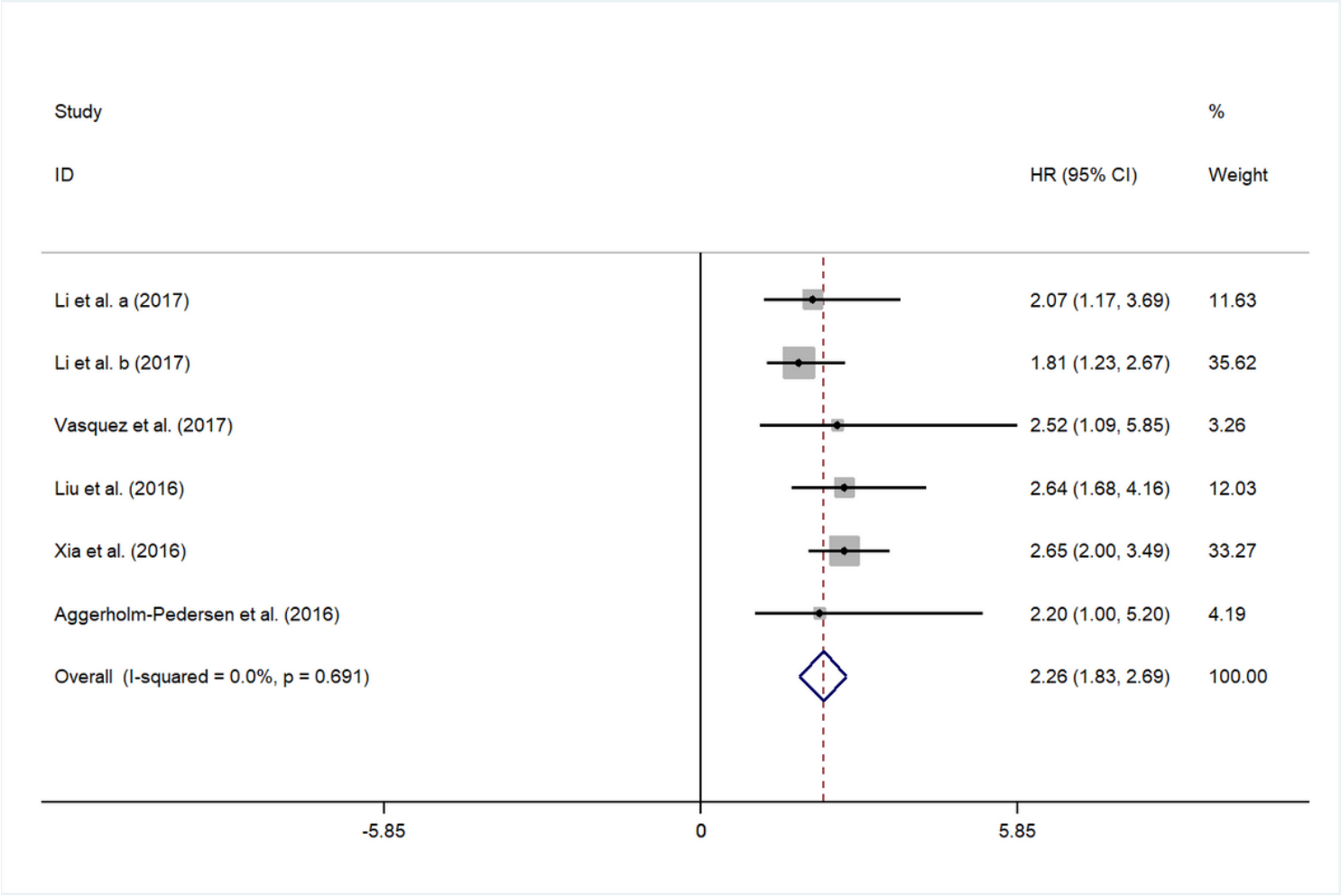

Figure 2

Forest plots for OS in patients with bone sarcomas.

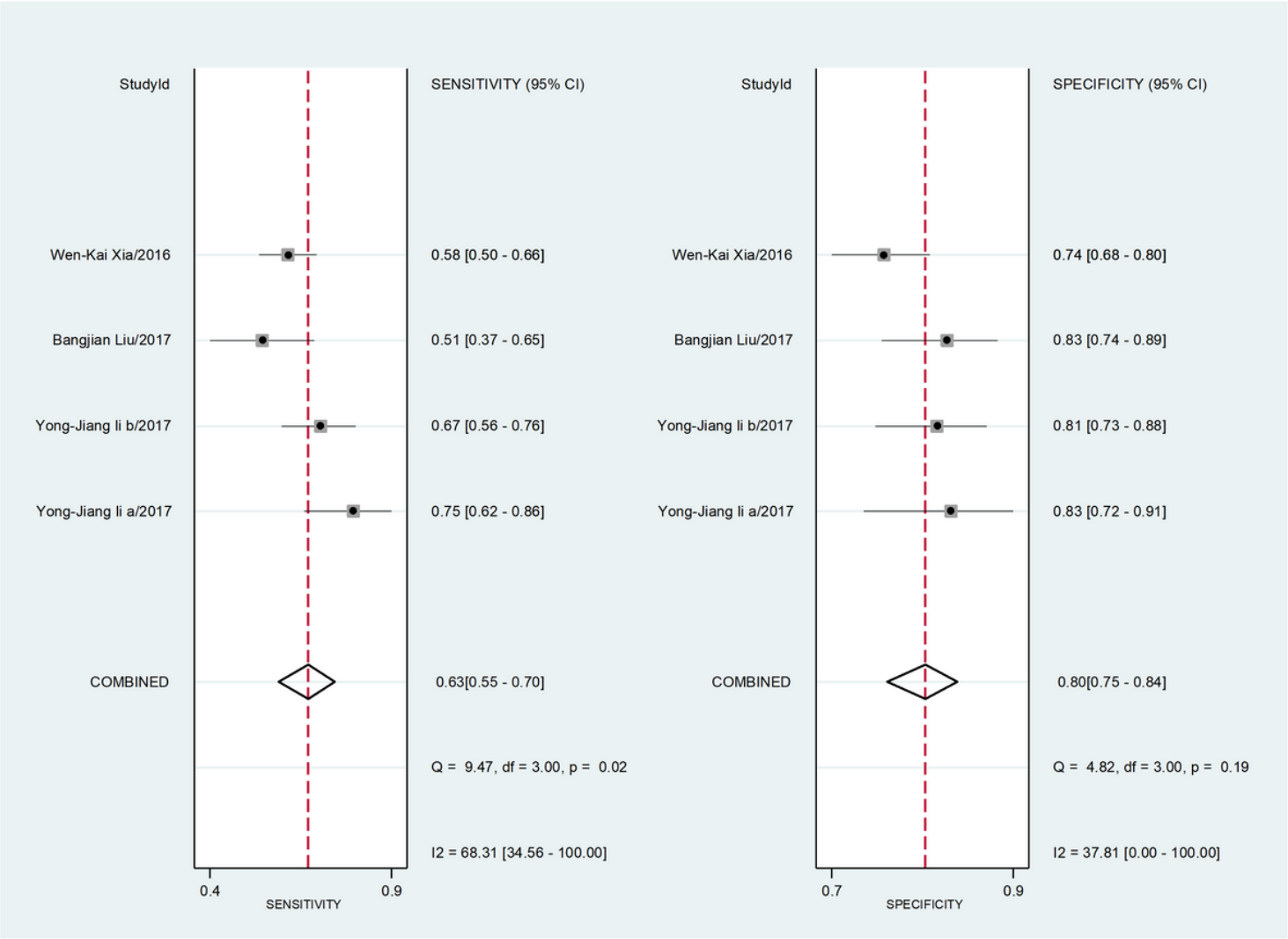

Figure 3

Forest plot of sensitivity and specificity of high NLR for predicting the prognosis of patients with bone sarcomas.

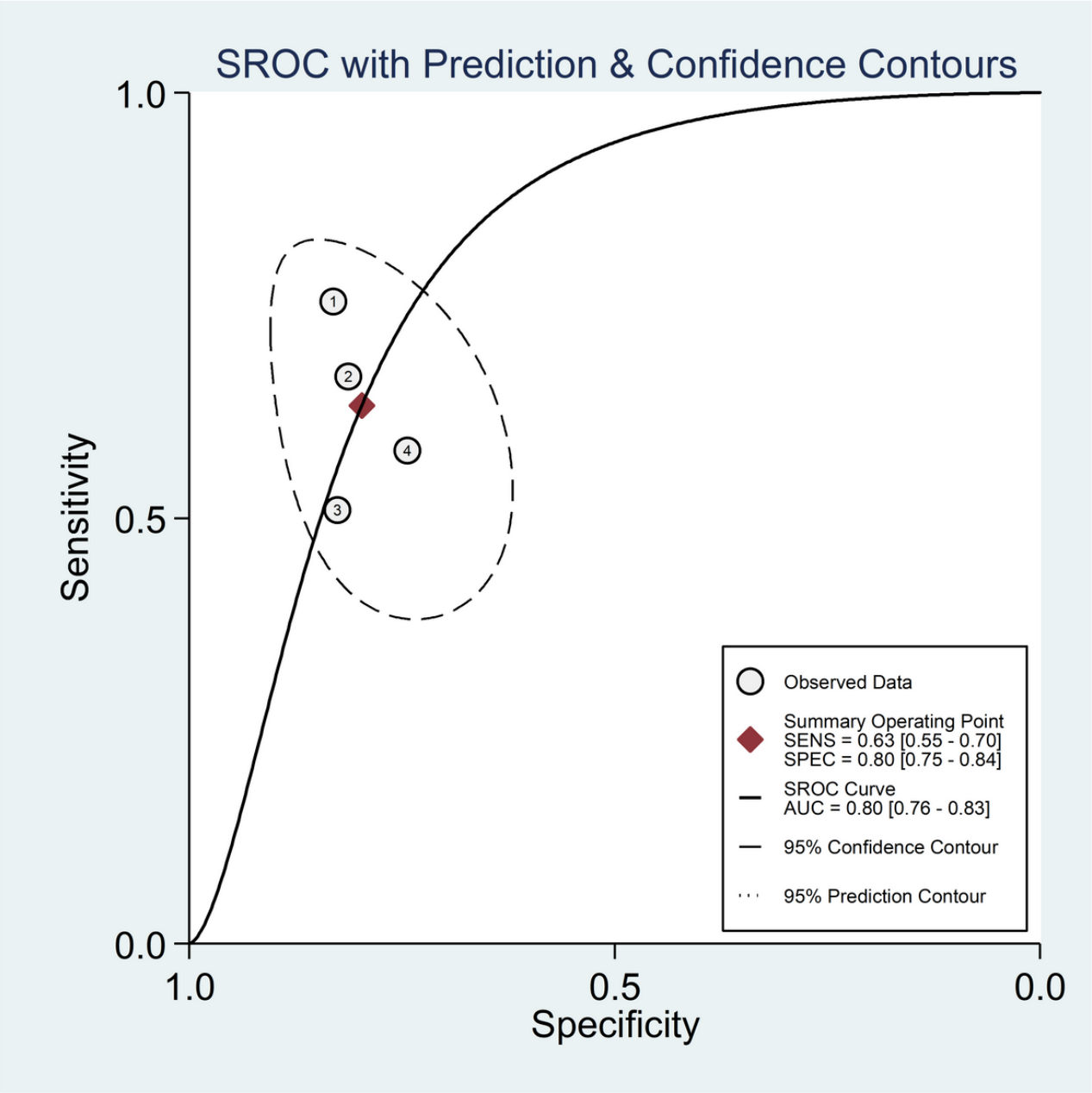

Figure 4

The summary receiver operator characteristic (SROC) curve.

Supplementary Files

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