The Prognostic Value of A Preoperative Lymphocyte Count and C-Reactive Protein Ratio In Osteosarcoma

Shu-Yu Ji

The First Affiliated Hospital of Guangxi Medical University

Hai-Jun Tang

Affiliated MinZu Hospital of Guangxi Medical University

Xiao-Ting Luo

The First Affiliated Hospital of Guangxi Medical University

Wei-Feng Liang

The First Affiliated Hospital of Guangxi Medical University

Xian-Ying Huang

First Affiliated Hospital of Guangxi University of Traditional Chinese Medicine

Shi-Jie Liao

The First Affiliated Hospital of Guangxi Medical University

Wen-Yu Feng

The First Affiliated Hospital of Guangxi Medical University

Qing-Jun Wei

The First Affiliated Hospital of Guangxi Medical University

Yun Liu (✉ 976267410@qq.com)

The First Affiliated Hospital of Guangxi Medical University

Ju-Liang He

Guangxi Medical University Cancer Hospital

Research

Keywords: osteosarcoma, lymphocyte count and C-reactive protein ratio, prognostic nutritional index

Posted Date: January 29th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-154092/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: Systemic inflammatory response and nutritional status are closely related to tumor development, and both have been recognized as predictors of tumors. Our study investigated the effect on the prognosis of osteosarcoma by analyzing the ratio of lymphocytes to C-reactive protein (LCR) before surgery.

Methods: Patients who were diagnosed with osteosarcoma and underwent surgery in the First Affiliated Hospital of Guangxi Medical University from 2012 to 2019 were included in this retrospective study. The albumin (g/L) +5 × total lymphocyte count (PNI), neutrophil/lymphocyte count (NLR), platelet/lymphocyte count (PLR) and platelet × neutrophil/lymphocyte count (SII) were calculated from preoperative peripheral white blood cells, C-reactive protein and serum albumin. The optimal cutoff values of LCR, PNI, NLR, PLR and SII were determined by receiver operating characteristic (ROC) analysis. According to the Optimal cutoff values, LCR, PNI, NLR, PLR and SII were divided into high and low groups. The Kaplan-Meier method was used to compare the overall survival (OS) between the high and low LCR groups. Univariate analysis was used to determine the influence of age, gender, tumor size, Enneking stage and neoadjuvant chemotherapy on the prognosis of osteosarcoma.

The independent predictors of OS were determined by Cox multivariate analysis.

Results: The optimal cutoff values for LCR, PNI, NLR, PLR and SII were 0.093, 48.4, 1.23, 157.03 and 314.27, respectively. A low preoperative LCR was significantly correlated with tumor metastasis, stage, NLR, PLR and SII. However, a low preoperative PNI was significantly associated with tumor metastasis, stage, and PLR.

Kaplan-Meier survival analysis indicated that the postoperative OS was significantly correlated with preoperative LCR and PNI ($P < 0.05$). Univariate analysis showed that Enneking stage, metastasis and preoperative LCR, PNI, NLR, PLR and SII were important factors affecting OS ($P < 0.05$). For multivariate analysis, the results revealed that the preoperative LCR (HR, 0.401; 95% CI, 0.199-0.807; $P = 0.01$) and Enneking stage (HR, 2.717; 95%CI, 1.067-6.919; $P = 0.036$) is an independent prognostic factor affecting the postoperative OS of osteosarcoma.

Conclusions: The high preoperative LCR is strongly associated with longer survival time in patients with osteosarcoma. Enneking stage and preoperative LCR may be important parameters for the prognosis of osteosarcoma.

Introduction

Osteosarcoma is a common malignant bone tumors, mainly occurring in children and adolescents, with an annual incidence of approximately 4/1000000, accounting for approximately 45% of all bone and joint tumors^[1]. Although surgery combined with chemotherapy and other multidisciplinary therapies can significantly improve the prognosis of patients compared with that of the previous treatments alone, The

5-year survival rate for patients with osteosarcoma is still less than 70%.The latest study found that the prognostic factors of osteosarcoma include tumor grade, histological subtypes, metastasis, alkaline phosphatase and lncRNAs, tp73-as1, circRNAs, calcitonin 3 (CNN3) and other proteins^[2, 3].Although these factors have some advantages in predicting the prognosis of osteosarcoma, they also have some disadvantages, such as a complicated process, expensive price or being difficult to monitor continuously. Therefore, finding effective prognostic indicators for patients with osteosarcoma has been the focus of researchers in recent years.

The systemic inflammatory response has been recognized as the seventh characteristic of cancer^[4]. Inflammatory cells and inflammatory factors widely exist in the microenvironment of osteosarcoma, which can induce the expression of various cytokines and chemokines, promote the proliferation of tumor cells and induce angiogenesis, and change the body's response to hormones and chemotherapy drugs, thus promoting the development, metastasis and drug resistance of tumors^[5].Taking the relationship between inflammation and tumor into consideration, in recent years, more and more studies have found that inflammation-related markers are prognostic factors for colorectal cancer, gastric cancer, pancreatic cancer and other malignant tumors ^[6-9]. Recently, some scholars have found that inflammatory indicators such as NLR, PLR and SII are correlated with the prognosis of osteosarcoma. However, there are still few reports on the influence of preoperative a LCR on the prognosis of patients with osteosarcoma. Therefore, in this study, preoperative LCR and PNI were analyzed in patients with osteosarcoma to investigate the effect of preoperative LCR on the prognosis of patients.

Methods

Patients

Patients with osteosarcoma diagnosed and operated on in the First Affiliated Hospital of Guangxi Medical University from 2012 to 2019 were included in this retrospective study. Inclusion criteria are as follows: (1) postoperative histopathological diagnosis of osteosarcoma, (2) no anticancer treatment, such as chemotherapy, radiotherapy or blood transfusion, was received before surgery, and (3) with detailed medical data and laboratory results. Exclusion criteria are as follows: (1) preoperative infection, high fever, autoimmune disease or blood system disease, (2) history of other malignant tumors, (3) receipt of nonsteroidal anti-inflammatory drugs or antibiotics, or (4) incomplete medical records. Finally, 101 patients met the above criteria to be included. Our study was conducted with the consent of Ethics Committee of Guangxi Medical University and the informed consent of each patient.

Data Collection And Definition

Through the hospital information system, we collected the gender, age, tumor size, stage, metastasis, neoadjuvant chemotherapy, pathological fracture, laboratory examination and other basic clinical data of all patients. The results of blood routine and liver function tests were obtained by drawing blood within 1

week before the operation. The definitions of LCR, PNI, NLR, PLR and SII were shown as follows: LCR = lymphocyte counts/ C-reactive protein; PNI = albumin (g/L) + 5 × total lymphocyte count (10^9 /L); NLR = neutrophil/lymphocyte-count; PLR = platelet/lymphocyte count; SII = platelet × neutrophil/lymphocyte count. According to receiver operating characteristic curve (ROC), the optimal truncation values of the LCR, NLR, PLR, SII and PNI are obtained when the Youden index is the largest. LCR and PNI values greater than the corresponding cutoff values were defined as high LCR, high PNI, high NLR, high PLR, and high SII (HLCR, HPNI, HNLR, HPLR, and HSII respectively).

Follow-up

After the operation, all patients were followed up regularly by re-examination and telephone calls. Overall survival (OS) was defined from the time of definite histopathological diagnosis until the date of last follow-up or death in this study. Follow-up was conducted every 3 months for the first 4 years, followed by every 6 months to the most recent follow-up. Follow-up included a thorough history, physical examination, laboratory tests (routine blood, blood biochemistry, tumor markers, etc.), MRI, chest CT, etc.

Statistical analysis

SPSS 24.0 Software was used for data analysis. ROC analysis was used to obtain the optimal cutoff values for continuous prognostic variables (LCR, PNI, NLR, PLR, and SII) by the maximal Youden index. The χ^2 test was used to compare the differences between groups, the Kaplan-Meier was used to draw the survival curve, and the log-rank test was used to compare the survival differences between the two groups. In terms of prognostic analysis, both a univariate analysis and multivariate analysis were investigated by Cox hazard regression model. The factors were supposed to be remarkably significant. A two-tailed $p < 0.05$ was considered to be statistically significant.

Results

Clinical Parameters Of Patients With Osteosarcoma

Table 1 presents the clinical parameters of the patients. Among 101 patients with osteosarcoma, 67 patients were male (66.3%) and 34 patients were female (33.7%). The median age was 18 years. A total of 90 tumors (89.1%) were located in the extremities, and 11 tumors (10.9%) were located in other parts of the body. There were 73 tumors with tumor size ≥ 5 cm. All patients underwent surgical treatment, of which 84 (83.2%) and 17 cases (16.8%) had tumor resection and amputation, respectively. According to the Enneking stage, 62 patients (61.4%) were in stages I and II, and 39 patients (38.6%) were in stage III. There were 15 patients (14.9%) with pathological fractures. Thirty patients (29.7%) had tumor metastasis, and 21 patients (20.8%) received neoadjuvant chemotherapy.

Table 1
Association of the patients' clinical parameters with LCR and PNI

LCR PNI							
Variables	Cases	Low (36)	Hight (65)	P	Low (27)	Hight (74)	P
Gender	101	25	42	0.623	17	50	0.665
Male	67	11	23		10	24	
Female	34						
Age(years)	41	12	29	0.269	9	32	0.369
<17	60	24	36		18	42	
≥ 17							
Tumor location	90	33	57	0.539	25	65	0.497
Extremities	11	3	8		2	9	
Non extremities							
Tumor size	28	8	20	0.358	4	24	0.080
<5	73	28	45		23	50	
≥ 5							
Surgical approach	84	28	56	0.281	21	63	0.382
Tumor resection	17	8	9		6	11	
Amputation							
Enneking stage	62	16	46	0.009	12	50	0.035
I + II	39	20	19		15	24	
III							
Pathological fracture	86	29	57	0.334	24	62	0.523
No	15	7	8		3	12	
Yes							

Abbreviations: LCR: lymphocyte count and C-reactive protein ratio; PNI: prognostic nutritional index; NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio; SII: systemic immune-inflammation index.

LCR PNI							
Local recurrence	91	31	62	0.318	23	68	0.318
No	10	5	5		4	6	
Yes							
Metastasis	71	16	55	0.000	14	57	0.014
No	30	20	10		13	17	
Yes							
Neoadjuvant chemotherapy	80	27	53	0.438	19	61	0.186
No	21	9	12		8	13	
Yes							
NLR				0.019			0.058
<1.23	9	0	9		0	9	
≥ 1.23	92	36	56		27	65	
PLR				<0.001			
<157.03	61	13	48		9	52	0.001
≥ 157.03	40	23	17		18	22	
SII				0.017			0.099
<314.27	18	2	16		2	16	
≥ 314.27	83	34	49		25	8	
Abbreviations: LCR: lymphocyte count and C-reactive protein ratio; PNI: prognostic nutritional index; NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio; SII: systemic immune-inflammation index.							

The optimal cutoff values of LCR, PNI, NLR, PLR and SII

The death of patients with osteosarcoma was used as the endpoint. Figure 1 shows the results of ROC analysis of LCR, PNI, NLR, PLR and SII. The area under the ROC curve (AUC) of LCR and PNI was 0.727 ($P < 0.001$) and 0.671 ($P = 0.003$), respectively, while the AUC of NLR, PLR and SII was 0.577, 0.579 and 0.603, respectively. The optimal cutoff value of LCR was 0.093 (sensitivity was 52.6%, specificity was 86.4%),

While the optimal cutoff value of PNI was 48.4 (sensitivity 40.4%, specificity 90.9%). The optimal cutoff value of NLR was 1.23 (sensitivity 98.2%, specificity 18.2%). The optimal cutoff value of PLR was 157.03 (sensitivity 47.4%, specificity 70.5%). The optimal cutoff value of SII was 314.27 (sensitivity 93.0%, specificity 31.8%). According to the optimal cutoff values, patients were divided into the HLCR group (≥ 0.093 , $n = 65$) and the low LCR group (LLCR < 0.093 , $n = 36$); the HPNI group (≥ 48.4 , $n = 74$) and low PNI group (LPNI < 48.4 , $n = 27$); the HNLR group (≥ 1.23 , $n = 92$) and low NLR group (LNLR < 1.23 , $n = 9$); the HPLR group (≥ 157.03 , $n = 40$) and low PLR group (LPLR < 157.03 , $n = 61$); HSII group (≥ 314.27 , $n = 83$) and low SII group (< 314.27 , $n = 18$). (Table 2)

Table 2
ROC curve and cut-off values analysis of LCR,PNI,NLR,PLR and SII.

Variable	AUC	95%CI	P	Yoden index	Cutoff values	Sensitivity	Specificity
LCR	0.727	0.627–0.826	<0.001	0.390	0.093	52.6%	86.4%
PNI	0.671	0.567–0.776	0.003	0.313	48.4	40.4%	90.9%
NLR	0.577	0.463–0.691	0.186	0.164	1.23	98.2%	18.2%
PLR	0.579	0.465–0.693	0.173	0.178	157.03	47.4%	70.5%
SII	0.603	0.490–0.717	0.076	0.248	314.27	93.0%	31.8%

Relationship between LCR and PNI and clinical indicators of patients

The relationship between LCR, PNI and the basic clinical features of patients with osteosarcoma is shown in Table 1. Compared with the HLCR group, the LLCR group was significantly associated with advanced Enneking stage ($P = 0.009$) and more metastasis ($P < 0.001$). However, there were no significant differences between the two groups in age, sex, pathological fracture, modality, tumor size, local recurrence or neoadjuvant chemotherapy.

In addition, the LPNI group tended to get more metastasis ($P = 0.014$) and, advanced Enneking stage ($P = 0.035$) compare with those in the HPNI. However, there was no significant relationship between the HLCR group and LCR group in terms of internal age, sex, pathological fracture, modality, tumor size, local recurrence or neoadjuvant chemotherapy.

Univariate And Multivariate Survival Analyses

The median follow-up time of the 101 patients with osteosarcoma was 25 months (range,2–96 months), and 57 patients died. Kaplan-meier was used to analyze the difference of postoperative overall survival rate between HLCR group and LLCR group, HPNI group and LPNI group. The results suggest that the OS

of the LLCR group was significantly lower than that of the HLCR group (median OS, 17 VS 54 months, $P=0.001$, 95% CI 27.32–44.68; Fig. 2a). Compared with the HPNI group, the OS of the LPNI group was significantly worse (median OS, 22 VS 52 months, $P=0.001$, 95% CI 27.32–44.68; Fig. 2b).

Univariate Cox regression analysis showed that tumor stage ($P < 0.001$), metastasis ($P < 0.001$), LCR ($P < 0.001$), PNI ($P = 0.001$), NLR ($P = 0.018$), PLR ($P = 0.002$) and SII ($P < 0.001$) were significantly associated with OS. Therefore, these factors were incorporated into a Cox regression analysis for multifactor analysis. The results showed that the tumor stage (HR, 2.717; 95%CI, 1.067–6.919; $P = 0.036$) and preoperative LCR (HR, 0.401; 95% CI, 0.199–0.807; $P = 0.01$) is an independent prognostic factors for OS after surgery. (Table 3)

Table 3

Analysis of the factors influencing the postoperative prognosis of patients with osteosarcoma

Univariate analysis				Multivariate analysis		
Variables	HR	95% CI	P	HR	95% CI	P
Gender	1	0.408–1.302	0.286			
Male	0.729					
Female						
Age (years)	1	0.665–2.008	0.607			
<17	1.156					
≥ 17						
Tumor location	1	0.654–2.949	0.393			
Extremities	1.388					
Nonextremities						
Tumor size	1	0.711–2.464	0.377			
<5	1.323					
≥ 5						
Surgical approach	1	0.456–1.795	0.774			
Tumor resection	0.904					
Amputation						
Enneking stage	1	1.801–5.171	< 0.001	2.717	1.067–6.919	0.036
I + II	3.052					
III						
Pathological fracture	1	0.566–2.760	0.581			
No	1.250					
Yes						
Local recurrence	1	0.785–3.514	0.185			
No	1.661					
Yes						

Univariate analysis		Multivariate analysis				
Metastasis	1	1.601–4.620	< 0.001	0.703	0.261–1.890	0.485
No	2.720					
Yes						
Neoadjuvant chemotherapy	1	0.721–2.624	0.333			
No	1.376					
Yes						
LCR	1	0.153–0.449	< 0.001	0.401	0.199–0.807	0.01
Low	0.262					
High						
PNI	1	0.225–0.660	0.001	0.846	0.429–1.667	0.628
Low	0.385					
High						
NLR	1	1.519–80.07	0.018	2.816	0.318–24.966	0.352
Low	11.02					
High						
PLR	1	1.339–3.908	0.002	0.922	0.483–1.762	0.806
Low	2.287					
High						
SII	1	2.250–17.759	< 0.001	3.134	0.974–10.087	0.055
Low	6.322					
High						

Discussion

It is well-known that NLR, PLR, LCR and SII are important factors in the systemic inflammatory response, and PNI is an important indicator to evaluate both the nutritional and immune status of patients. A large number of studies have shown that inflammatory and nutritional indicators in the peripheral blood are significantly correlated with the prognosis of breast cancer, rectal cancer and other tumors. LLCR and HPNI have certain effects on the assessment and prediction of the survival rate and postoperative management^[7, 8, 10, 11]. However, the effect of preoperative LCR and PNI on the prognosis of patients with osteosarcoma is not yet clear, and there are few relevant reports. In this study, preoperative peripheral

blood inflammatory and nutritional indicators were used to evaluate the prognosis of patients with osteosarcoma in order to obtain a comprehensive and objective predictor and provide relevant theoretical basis for timely treatment. We detected and analyzed the preoperative peripheral blood count and albumin levels of all patients with osteosarcoma, and finally found that LCR and PNI were important factors affecting the postoperative survival rate of patients with osteosarcoma, among which LCR and tumor stage were independent predictors of prognosis.

There is increasing evidence that systemic immune inflammation and nutrition are related to clinical indicators and prognosis of tumor patients^[12–14]. Our study found that LLCR and LPNI were related to late Enneking stage and more prone to tumor metastasis, which was the same as previous studies. Inflammatory responses can lead to increased neutrophils, thrombocytopenia, lymphocytopenia, elevated C-reactive protein, and decreased serum albumin. As a leukocyte subgroup, both neutrophils and platelets can promote tumorigenesis, proliferation and metastasis by secreting chemokines and vascular endothelial factors, such as vascular endothelial growth factor (VEGF)^[4, 15, 16]. The rapid increase in CRP is mainly related to pro-inflammatory factors, such as interleukin (IL)-1, TNF- α , IL-6 and IL-8, and these pro-inflammatory factors regulate cell proliferation and angiogenesis by activating intracellular pathways, such as the pathway mediated by the nuclear factor NF- κ B that activates B cells, thereby promoting the development and metastasis of malignant tumors^[17–19]. Serum albumin, which is produced by the liver, is an important nutritional indicator of the body and plays an important role in improving the body's immunity, suppressing the inflammatory response and anti-tumor effects^[20]. However, an increase of CRP is often accompanied by a decrease of serum albumin concentration, an increase of tissue consumption, and the continuous loss of body weight, which leads to malnutrition of the body and further aggravation of the disease^[21, 22]. In contrast, lymphocytes are crucial in the body's immunity. During the development of tumor cells, lymphocytes suppress tumor growth and invasion by secreting cytokines such as TNF- α and interferon. Therefore, lymphocytosis often indicates that the host's immune response to tumor is impaired^[23–25]. In summary, patients with LLCR and LPNI who had an immunosuppressed state and malnutrition had shorter OS time. In addition, our results suggest that patients with LLCR may have HNL, HPL and HSII, and the degree of inflammation *in vivo* may be more severe. At present, it has been reported that systemic inflammatory markers such as preoperative LCR, PNI, NLR, PLR and SII can be independent predictors of prognosis of gastric cancer, colorectal cancer, lung cancer and osteosarcoma^[26–29]. As the most prevalent malignant bone tumor, the prognostic factors of osteosarcoma, such as local recurrence, metastasis, tumor stage and pathological fracture, have been reported in a large number of clinical studies.^[1, 28, 30–32] However, there are few studies on the correlation between preoperative LCR and PNI and the prognosis of patients with osteosarcoma. In this paper, the relationship between preoperative LCR, PNI, NLR, PLR and SII and the postoperative OS rate of 101 patients with osteosarcoma was analyzed to explore the important factors affecting the postoperative OS of patients with osteosarcoma. Univariate analysis by the Cox hazard regression model showed that tumor stage ($P < 0.001$), metastasis ($P < 0.001$), LCR ($P < 0.001$), PNI ($P = 0.001$), NLR ($P = 0.018$), PLR ($P = 0.002$) and SII ($P < 0.001$) were significantly associated with postoperative OS in patients with osteosarcoma. However, after multivariate analysis by the Cox hazard regression model, only tumor stage

(HR, 2.717;95%CI, 1.067–6.919; P = 0.036) and preoperative LCR (HR, 0.401;95% CI,0.199–0.807; P = 0.01) were independent prognostic factors for OS after surgery. However, Huang et al.^[28] considered that PNI and SII were also independent prognostic factors for patients with osteosarcoma, which was different from the results of this study. These differences may be due to the small sample size and heterogeneity of the study population. For example, of the 126 patients with osteosarcoma included in the study by Huang et al, 31.7% received neoadjuvant chemotherapy. In our study according to the results of the univariate analysis, NLR, PLR, SII, PNI and metastasis were the important factors influencing the postoperative OS in patients with osteosarcoma, but by the multivariate Cox hazards regression model analysis to eliminate confounding factors, the effect of the above factors on the postoperative OS of patients with osteosarcoma decreased obviously.

There are differences in research results related to osteosarcoma in recent years^[1, 28, 30–32]. The reasons for this result may be as follows: 1. the sample size included in this study is small, 2. The included indicators are too few, 3. the mutual influence of different indicators. There are some limitations to our study. First, the number of cases included in this study is small, with only 101 cases. Second, our study is a single-center retrospective study, which may have a large selection bias, which needs to be further confirmed by a multicenter, large sample size study or prospective study. In addition, there are many factors affecting the prognosis of osteosarcoma, and still need more studies to determine the correlation between different influencing factors. It is still necessary to further explore the relationship between systemic inflammation and nutritional immunity and the prognosis, recurrence and metastasis of osteosarcoma.

Conclusion

The higher preoperative LCR is strongly associated with the longer survival time in patients with osteosarcoma. Tumor staging and preoperative LCR may be important parameters for the prognosis of osteosarcoma.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

YL and JLH contributed to the study concepts. SYJ and HJT contributed to the study design. XTL and WFL contributed to the data acquisition. XYH contributed to the quality control of data. SJL and FWY contributed to the data analysis and interpretation. XYH and SJL contributed to the statistical analysis. QJW and YL reviewed the manuscript. All authors read and approved the final manuscript.

Founding

The study was partly supported by Natural Science Foundation of Guangxi Province (2019JJA140408), Youth Science and Technology Project of the First Affiliated Hospital of Guangxi Medical University (201903038), Guangxi Health Department self-raised funds project (Z20170424), and Science and Technology Base and Talent Project in Qingxiu District, Nanning City (2020068).

Availability of data and materials

All data used in the study are available from the corresponding authors.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University.

Consent for publication

All participants consented to the publication.

Competing interests

The authors declare that they have no competing interests.

Author details

¹ General Medicine Ward of the First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China.² Department of Orthopaedics, the Minzu Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China.³ Department of Pharmacy,

First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China.⁴Department of Orthopaedics, First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China.⁵Spinal Surgery Department, First Affiliated Hospital of Guangxi University of Traditional Chinese Medicine.

⁶Department of Bone and Soft Tissue Surgery, Guangxi Medical University Cancer Hospital.

References

1. Yang Q, Chen T, Yao Z, et al. *Prognostic value of pre-treatment Naples prognostic score (NPS) in patients with osteosarcoma*, World Journal of Surgical Oncology. 2020. 18(1).
2. Liu M, Yang P, Mao G, et al. Long non-coding RNA MALAT1 as a valuable biomarker for prognosis in osteosarcoma: A systematic review and meta-analysis. 72. London: International Journal of Surgery; 2019.
3. Xu S, Gong Y, Yin Y, et al. The multiple function of long noncoding RNAs in osteosarcoma progression, drug resistance and prognosis. Biomed Pharmacother. 2020;127:110141.

4. Colotta F, Allavena P, Sica A, et al. *Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability*, Carcinogenesis. 2009.
5. Alberto M. Paola, et al. *Cancer-related inflammation*, Nature. 2008.
6. Hirahara T, Arigami T, Yanagita S, et al. Combined neutrophil-lymphocyte ratio and platelet-lymphocyte ratio predicts chemotherapy response and prognosis in patients with advanced gastric cancer. BMC Cancer. 2019;19(1):672.
7. Shinsuke S, Takashi A, Koji O, et al. *Comprehensive Comparative Analysis of Prognostic Value of Systemic Inflammatory Biomarkers for Patients with Stage II/III Colon Cancer*, Annals of Surgical Oncology. 2020. 27(3):844–852.
8. Yoshinaga O, Yuji T, Akira Y, et al. *Lymphocyte-C-reactive Protein Ratio as Promising New Marker for Predicting Surgical and Oncological Outcomes in Colorectal Cancer*, Annals of Surgery. 2019.
9. Pointer DT, Roife D, Powers BD, et al. Neutrophil to lymphocyte ratio is predictive of patient survival after resection of pancreatic adenocarcinoma. HPB. 2019;21(1):128.
10. Okugawa Y, Toiyama Y, Fujikawa H, et al. *Prognostic Potential of Lymphocyte–C-Reactive Protein Ratio in Patients with Rectal Cancer Receiving Preoperative Chemoradiotherapy*, Journal of Gastrointestinal Surgery. 2020(1).
11. He H, Guo W, Song P, et al. Preoperative systemic immune-inflammation index and prognostic nutritional index predict prognosis of patients with pulmonary neuroendocrine tumors after surgical resection. Annals of Translational Medicine. 2020;8(10):630–0.
12. Wang Y, Zhu Z, Li C, et al. *Prognostic significance of preoperative albumin-to-globulin ratio and prognostic nutritional index combined score in Siewert type 3 adenocarcinoma of esophagogastric junction*, Cancer Management and Research. 2019. 11.
13. Carr BI, Guerra V *Serum albumin levels in relation to tumor parameters in hepatocellular carcinoma patients*, Int J Biol Markers. 2017. 32(4).
14. Ikeda S, Yoshioka H, Ikeo S, et al. Serum albumin level as a potential marker for deciding chemotherapy or best supportive care in elderly, advanced non-small cell lung cancer patients with poor performance status. BMC Cancer. 2017;17(1):797.
15. Tecchio C. Neutrophil-derived cytokines involved in physiological and pathological angiogenesis. Chemical Immunology Allergy. 2014;99:123.
16. Mantovani A. Cassatella, et al. *Neutrophils in the activation and regulation of innate and adaptive immunity*, Nature Reviews Immunology. 2011.
17. Gabay C, Kushner, et al. *Acute-Phase Proteins and Other Systemic Responses to Inflammation*, New England Journal of Medicine. 1999.
18. Ilhan N, Ilhan N, Ilhan Y, et al. C-reactive protein, procalcitonin, interleukin-6, vascular endothelial growth factor and oxidative metabolites in diagnosis of infection and staging in patients with gastric cancer. World J Gastroenterol. 2004;10(008):1115–20.

19. Pasqualesansone, Marcu. K *IL-6 triggers malignant features in mammospheres from human ductal breast carcinoma and normal mammary gland*. Journal of Clinical Investigation. 2007;117(12):3988.
20. Seaton K. Albumin concentration controls cancer. J Natl Med Assoc. 2001;93(12):490–3.
21. Mcmillan DC. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. Cancer Treat Rev. 2013;39(5):534–40.
22. Roxburgh CSD, Mcmillan DC *Cancer and systemic inflammation: treat the tumour and treat the host*. Br J Cancer. 2014;110(6):1409–12.
23. Giorgi UD, Mego M, Scarpi E, et al. *Relationship Between Lymphocytopenia and Circulating Tumor Cells as Prognostic Factors for Overall Survival in Metastatic Breast Cancer*, Clinical Breast Cancer. 2012. 12(4).
24. Ownby HE, Roi LD, Isenberg RR, et al. Peripheral lymphocyte and eosinophil counts as indicators of prognosis in primary breast cancer. Cancer. 1983;52(1):126–30.
25. Chen L, Yan Y, Zhu L, et al. Systemic immune-inflammation index as a useful prognostic indicator predicts survival in patients with advanced gastric cancer treated with neoadjuvant chemotherapy. Cancer Management Research. 2017;9:849–67.
26. Tiainen S, Rilla K, Hmlinen K, et al. *The prognostic and predictive role of the neutrophil-to-lymphocyte ratio and the monocyte-to-lymphocyte ratio in early breast cancer, especially in the HER2 + subtype*, Breast Cancer Research and Treatment. 2020:1–10.
27. Li X, Yao Z, Wan Y, et al. Prognostic impact of prognostic nutritional index in advanced (stage IIIB/IV) non-small cell lung cancer patients. Neoplasma. 2019;66(6):971–7.
28. Xin, Huang H, et al. *Prognostic value of prognostic nutritional index and systemic immune-inflammation index in patients with osteosarcoma*, Journal of Cellular Physiology. 2019.
29. Okugawa Y, Toiyama Y, Yamamoto A, et al. *Lymphocyte-to-C-reactive protein ratio and score are clinically feasible nutrition-inflammation markers of outcome in patients with gastric cancer*, Clinical Nutrition. 2019.
30. Yong-Jiang L, Kai Y, Min-Xun L, et al. Prognostic value of the C-reactive protein to albumin ratio: a novel inflammation-based prognostic indicator in osteosarcoma. Oncotargets Therapy. 2017;10:5255–61.
31. Liu B, Huang Y, Sun Y, et al. Prognostic value of inflammation-based scores in patients with osteosarcoma. Sci Rep. 2016;6(1):39862.
32. Liu T, Fang X-C, Ding Z, et al. Pre-operative lymphocyte-to-monocyte ratio as a predictor of overall survival in patients suffering from osteosarcoma. Febs Open Bio. 2015;5(1):682–7.

Figures

Figure 1

Receiver operating characteristic curves for pretreatment LCR and PNI based on OS. OS: overall survival; LCR: lymphocyte count and C-reactive protein ratio; PNI: prognostic nutritional index.

Figure 2

Kaplan–Meier survival curves for OS according to LCR and PNI in osteosarcoma patients. (a) OS of patients in the LLCR group was significantly worse than those in the HLCR group ($p < 0.001$). (b) OS of patients in the HPNI group was significantly better than those in the LPNI group ($p < 0.001$).