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Lymphocyte-Related Inflammation and Immune-Based Scores Predict Prognosis of Chordoma Patients After Radical Resection

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Abstract

The inflammatory microenvironment plays a critical role in the development and progression of malignancies. In the present study, we aimed to evaluate the prognostic value of lymphocyte-related inflammation and immune-based prognostic scores in patients with chordoma after radical resection, including the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), and systemic immune-inflammation index (SII). A total of 172 consecutive patients with chordoma who underwent radical resection were reviewed. R software was used to randomly select 86 chordoma patients as a training set and 86 chordoma patients as a validation set. Potential prognostic factors were also identified, including age, sex, tumor localization, KPS, Enneking stage, tumor size, and tumor metastasis. Overall survival (OS) was calculated using the Kaplan–Meier method and multivariate Cox regression analyses. NLR, PLR, SII, Enneking stage, tumor differentiation and tumor metastasis were identified as significant factors from the univariate analysis in both the training and validation sets and were subjected to multivariate Cox proportional hazards analysis. The univariate analysis showed that NLR $\geq$1.65, PLR $\geq$121, and SII $\geq 370\times10^9$/L were significantly associated with poor OS. In the multivariate Cox proportional hazard analysis, SII, Enneking stage and tumor metastasis were significantly associated with OS. As noninvasive, low-cost, reproducible prognostic biomarkers, NLR, PLR and SII could help predict poor prognosis in patients with chordoma after radical resection. This finding may contribute to the development of more effective tailored therapy according to the characteristics of individual tumors.

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Introduction

Chordoma, the fourth most common malignant neoplasm arising from notochordal remnant tissue, accounts for 1% to 4% of all bone malignancies [1]. Chordoma preferentially occurs in the axial skeleton and is most commonly found in the sacrum (50%-60%), the spheno-occipital region (25%-30%), cervical (10%) and thoraco-lumbar vertebrae (5%) [2]. Chordoma is insensitive to conventional radiotherapy [3] and chemotherapy [4]. The gold standard of treatment for chordoma is radical resection with the goal of negative margins [5]. However, chordoma tends to be locally aggressive and has a high rate of recurrence [6], and recurrent chordoma is nearly impossible to eradicate [7]. Metastases occur in 5% to 40% of patients [8]. Given the current therapeutic challenges, a better understanding of the factors that influence chordoma prognosis may help guide treatment planning to prolong survival [9].

In previous studies, several prognostic factors such as age, sex, location, resection margins and Enneking stages have been investigated [10]. The abovementioned prognostic markers are mainly based on the clinicopathological findings. It has increasingly

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been recognized that inflammation with the tumor microenvironment plays a critical role in the development and progression of malignancies [11]. Elevated C-reactive protein (CRP), as a marker of systemic inflammation, has been confirmed to be associated with decreased survival in patients with chordoma of the lumbar spine and sacrum [5]. Several inflammatory and immune-based prognostic scores, such as the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), and systemic immune-inflammation index (SII), have also been developed to predict survival and recurrence in hepatocellular carcinoma, gastric cancer and small cell lung cancer [12–15]. However, the prognostic value of these inflammatory and hematological markers in patients with chordoma is still unclear.

In the present study, we aimed to evaluate the prognostic value of lymphocyte-related inflammation and the immune-based scores NLR, PLR, MLR and SII in patients with chordoma after radical resection.

Materials and Methods

Between January 1997 and October 2016, 319 consecutive patients with chordoma confirmed by postoperative histological pathology at Chinese PLA General Hospital were retrospectively reviewed. Treatment-naïve patients who did not receive other treatments before surgery and patients who underwent radical resection were included in this study. Patients with active infection or inflammatory disease within 1 month before blood test were excluded. In all, 172 patients were included in this study. This study has been approved by the Ethics Committee of Chinese PLA General Hospital and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent was obtained from all participants or their legal guardians.

The blood samples for the neutrophil, lymphocyte, monocyte, and platelet counts were obtained within 3 days before surgery. The various ratios were calculated as follows: NLR = N / L; PLR = P / L; MLR = M / L and SII = P ×N/L, where N, L, M and P were the preoperative absolute neutrophil, lymphocyte, monocyte, and platelet counts, respectively. Potential prognostic factors were identified, including age, sex, tumor localization, Karnofsky performance status (KPS), Enneking stage, tumor size, and tumor metastasis. Tumor stage was determined according to the Enneking stage [16], and tumor differentiation was classified as classical (conventional), chondroid or dedifferentiated [17].

The patients were followed up every 3 months during the first postoperative year and every 6 months thereafter. If recurrence was confirmed and the recurrent tumor was localized, a second resection was suggested. The last follow-up date was April 07, 2017. Overall survival (OS) was defined as the interval between the initial surgery and either death or the last follow-up.

Statistical Analysis

For normally distributed continuous data, Student's t-test was used for assessing the significance of the difference between the means of two samples and the one-way ANOVA test was performed to compare mean values of three samples. For non-normally distributed continuous data, Mann-Whitney U-test was applied. Differences were considered statistically significant when $p < 0.05$. OS was calculated using the Kaplan-Meier method. Prognostic parameters associated with OS were assessed using both univariate and multivariate Cox analyses. Only variables proven to be significant in the univariate analysis were included in the multivariate model. R software was used to analyze the results of the regression analyses, receiver operating characteristic (ROC) curve analysis [18–20] to determine the cut-off values of the parameters associated with OS of patients with chordoma. ROC curve analysis was used to compare the sensitivity and specificity of the different models. The Clarke-Pearson test was used to compare the differences of the area under the curve (AUC). The cut-off value was determined by the AUC; the ROC curve with the highest AUC indicated that the corresponding model had the best sensitivity and specificity. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated as estimates of the correlations. Statistical analyses were carried out using IBM SPSS 20.0 statistical software (SPSS Inc., Chicago, IL).

Results

Patient Characteristics

A total of 172 patients with a median age of 50 years (ranging from 8-71 years) who were diagnosed with primary chordoma and underwent radical resection were included in this study. The baseline characteristics of patients and their predictive values on OS are shown in Tables 1 and 2. The mean follow-up period was 73.0 months with a minimum follow-up duration of 2 months. At the time of analysis, 68 (39.5%) patients died, and the median OS was 80 months (95%CI: 63.8-98.6).

Association of NLR, PLR and SII with OS

R software was used to randomly select 86 chordoma patients as a training set and 86 chordoma patients as a validation set. All the clinicopathological features, blood routine parameters, and lymphocyte-related indexes (including the NLR, PLR, MLR and SII) were included in the Cox univariate analyses. In both sets, the following parameters were significantly associated with chordoma

Table 1. The Baseline Characteristics of the Patients

Variables	n	%
Total	172	100
Sex		
Male	114	66.3
Female	58	33.7
Age		
<60 years	121	70.3
≥60 years	51	29.7
KPS		
≥80%	102	59.3
60%–80%	48	27.9
<60%	22	12.8
Enneking stage		
I	96	55.8
II–III	76	44.2
Tumor differentiation		
Classical	118	68.6
Non-classical (chondroid, dedifferentiated)	54	31.4
Tumor size		
≤6 cm	108	62.8
>6 cm	64	37.2
Tumor metastasis		
Without metastasis	107	62.2
With metastasis	65	37.8
Localization		
Cranial	79	45.9
Spine	43	25
Sacrum	50	29.1

KPS, Karnofsky performance status.

Table 2. Kaplan-Meier Analyses (log-rank test) of the Predictive Value of Baseline Characteristics on OS

Variables	OS (months)	95%CI	*P*
Total	80	(63.8-98.6)	
Sex			
Male	77.4	(52.6-88.3)	.913
Female	78.7	(57.3-96.8)	
Age			
<60 years	79.6	(59.5-89.7)	.757
≥60 years	63	(46.4-78.5)	
KPS			
≥80%	78.4	(65.7-94.8)	.033
60%-80%	66.5	(55.8-78.4)	
<60%	43.2	(37.3-54.9)	
Enneking stage			
I	81.3	(73.2-99.1)	<.001
II–III	34.5	(26.7-48.5)	
Tumor differentiation			
Classical	75.7	(65.3-88.4)	.042
Non-classical (chondroid, dedifferentiated)	43.5	(22.4-53.1)	
Tumor size			
<6 cm	70.4	(53.7-80.7)	.633
≥6 cm	48.1	(37.6-53.4)	
Tumor metastasis			
Without metastasis	75.9	(59.7-91.3)	.008
With metastasis	23.5	(17.1-38.9)	
Localization			
Cranial	66.8	(47.5-79.9)	.641
Spine	71.2	(49.9-89.6)	
Sacrum	55.8	(39.9-75.7)	
Lymphocyte cells count			
<1.8*10^10	77.8	(53.8-85.9)	.893
≥1.8*10^10	65	(51.3-77.9)	
Neutrophil cells count			
<3.4*10^9	77.3	(53.5-86.2)	.317
≥3.4*10^9	64	(43.4-78.6)	
NLR			
<1.65	82.3	(73.5-91.9)	.023
≥1.65	56.4	(37.4-78.8)	
PLR			
<121	81.7	(77.3-93.7)	.024
≥121	58.6	(47.9-85.4)	
MLR			
<0.36	81.3	(55.7-91.4)	.635
≥0.36	67.4	(46.7-83.5)	
SII			
<370*10^9	81.6	(73.1-89.4)	.008
≥370*10^9	55.9	(39.8-76.7)	

OS, Overall survival; CI, Confidence interval; KPS, Karnofsky performance status; NLR, Neutrophil-lymphocyte ratio; PLR, Platelet-lymphocyte ratio; MLR, Monocyte-lymphocyte ratio; SII, Systemic immune-inflammation index.

OS: NLR, PLR, SII, Enneking stage, tumor differentiation and tumor metastasis (all $P < .05$). The data are shown in Table 3.

The ROC analyses was used to determine the cut-off values of the NLR, PLR, SII and MLR for predicting OS based on the data in the training set

Table 3. Association Between Routine Blood Test Parameters and Overall Survival in Chordoma Patients Based on Univariate Cox Regression Analyses

	Training Set, n=86		Validation Set, n=86	
	HR (95% CI)	*P*	HR(95% CI)	*P*
Lymphocyte cell counts, per increase of 1000 cells/mm^3	0.52 (0.22-1.5)	.74	0.74 (0.25-1.6)	.86
NLR, per increase of 1 unit	1.4 (0.77-2.2)	.025	1.6 (0.97-2.7)	.037
PLR, per increase of 1 unit	1.4 (0.94-2.5)	.031	1.8 (1.0-2.8)	.044
SII, per increase of 1 unit	2.9 (1.2-3.7)	.009	3.0(1.1-4.9)	.015
MLR, per increase of 1 unit	1.3 (0.97-3.1)	.654	1.6 (1.5-2.9)	.712
Enneking stage, stage I vs. stage II-III	6.9 (3.5-8.9)	<.001	7.1 (5.0-9.8)	<.001
Tumor differentiation, classical vs. non-classical	3.2 (2.8-6.0)	.049	4.2 (3.0-7.2)	.051
Tumor metastasis, with vs. without	4.0 (2.6-6.8)	.013	3.6 (2.3-6.3)	.006

NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; MLR, monocyte-lymphocyte ratio; SII, systemic immune-inflammation index; HR, hazard ratios; CI, confidence intervals.

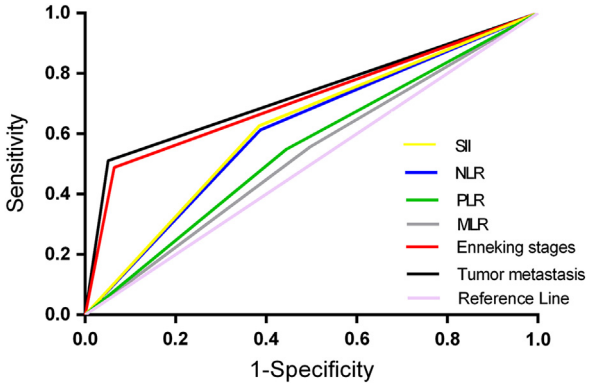

Figure 1. The ROC analyses of the NLR, PLR, SII and MLR. ROC curves of the SII, NLR, PLR, MLR, tumor metastasis and Enneking stage for OS, with a median survival time of 80 months.

(Figure 1). According to these analyses, the AUCs of the NLR, PLR, SII and MLR in predicting OS in the training set were 0.675, 0.619, 0.683 and 0.517, respectively. Based on the ROC curves, the best cut-off value for the NLR was 1.65 with a sensitivity of 62.7% and a specificity of 61.5% for OS; for PLR, the cut-off was 121 with a sensitivity of 59.4% and a specificity of 55.6% for OS; for SII, the cut-off was 370 $\times 10^9$/L with a sensitivity of 61.3% and a specificity of 65.9% for OS. These data are shown in Table 4. Based on the cut-off values, the continuous data were transformed to dichotomous data. Significant factors identified in the univariate analysis in both the training and validation sets, including the NLR, PLR, SII, Enneking stage, tumor differentiation and tumor metastasis, were subjected to multivariate Cox proportional hazards analysis. In this analysis, SII, Enneking stage and tumor metastasis were significantly associated with OS. These data are shown in Table 5.

Additionally, we performed a Kaplan-Meier analysis of the parameters identified as significantly associated and OS. Using the cut-off values of 1.65, 121 and 370 $\times$ 10^9/L, we grouped the NLR, PLR and SII indexes, respectively, into normal groups and elevated groups. Our conclusion was that elevated NLR, PLR and SII indexes were significantly associated with poor OS (log-rank P < 0.05, Figure 2).

Association of the NLR, PLR, SII and MLR with Tumor Metastasis

As is commonly known, tumor metastasis was significantly associated with patient outcome in chordoma; thus, we evaluated the association between the NLR, PLR, SII, MLR and tumor metastasis. We found that the NLR, PLR and SII scores in chordoma patients with metastasis were higher than those in chordoma patients without metastasis (P<0.001, P = 0.021 and P<0.001, respectively,

Table 4. Predictive Value of the NLR, PLR, SII, MLR, New Predictive Variable and 5 Point Scale Variable for Overall Survival of Chordoma Patients

Variables	Cut-off	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV	Accuracy	*P*
NLR	1.65	0.675 (0.553-0.724)	0.627	0.615	0.652	0.589	62.6	.004
PLR	121	0.619 (0.491-0.675)	0.594	0.556	0.606	0.543	58.1	.035
SII	370	0.683 (0.569-0.738)	0.613	0.659	0.674	0.597	63.7	.003
MLR	0.36	0.517 (0.454-0.619)	0.503	0.557	0.566	0.493	52.5	.147

AUC, area under the curve; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SII, systemic immune-inflammation index; MLR, monocyte-lymphocyte ratio; CI, Confidence intervals; PPV, positive predictive value; NPV, negative predictive value.

Table 5. Association Between Routine Blood Test Parameters and Overall Survival of Chordoma Patients Based on Multivariate Cox Regression Analyses

Variables	Category	Overall Survival	
		HR (95% CI)	*P*
SII	<370 vs. ≥370	1.9 (1.2-3.0)	.015
Enneking stage	I vs. II-III	6.2 (3.8-9.8)	<.001
Tumor metastasis	with vs. without	3.2 (2.2-4.5)	.002

SII, systemic immune-inflammation index; HR, hazard ratios; CI, confidence intervals.

Figure 3). Therefore, we suggest that NLR, PLR, and SII may predict the invasiveness and progression of chordoma.

Discussion

Given the low-grade nature of malignant lesions, the overall survival of chordoma patients is still relatively poor. Previous studies have reported five-year and ten-year survival rates ranging from 45% to 77% and 28% to 50%, respectively [1,21,22]. The cumulative probability of local recurrence at five years and ten years after diagnosis was 46% and 54%, respectively [23]. Several studies have analyzed the prognostic factors of chordoma patients. However, the results are inconsistent [10,24,25]. In our research, our data suggested that sex, age, tumor size and localization were not independent prognostic factors for postoperative OS of chordoma. However, Enneking stage, tumor differentiation and metastasis were significantly associated with OS. Consistent with previous study by Meng et al. [10], we also found that a KPS ≥80% had a profound influence on OS but did not affect the recurrence of chordoma. Adequacy of the surgical resection margins is also an important prognostic indicator, and the gold standard of care for chordoma is en bloc resection [26], however, anatomic constraints make achieving this goal technically demanding and difficult. More importantly, total en bloc spondylectomy may lead to significant functional compromise, as a large chordoma in the upper cervical spine and sacrum cannot be excised in an ideal en bloc manner because of its proximity to vital neurovascular structures [27]. Radical resection was thought to be an ideal surgical treatment that offers the best oncological outcomes for chordoma [28]. Although all the patients in this study underwent radical resection, achieving long-term survival remains a challenge. Therefore, aside from preventing recurrence, increasing OS after surgery is an important issue that should be addressed.

In the past decade, new perspectives regarding tumor biology, microenvironment, and tumor surveillance have been widely investigated, and breakthroughs in immunotherapy in various cancers have led to renewed interest in altering the host immune system response to develop new methods of treating tumors. It is well known that early in the neoplastic process, inflammatory cells are powerful tumor promoters because they produce an attractive environment for tumor growth, facilitate genomic instability and promote angiogenesis [29,30]. Cytotoxic lymphocytes and other lymphocytes play a fundamental role in cell-mediated immunologic destruction of cancer cells [31]. Neutrophils can promote adhesion and tumoral seeding by secreting circulating growth factors [32]. Platelets can directly interact with tumor cells, synergistically activate the TGF beta/Smad and NF-kappa B pathways in cancer cells, induce an epithelial-to-mesenchymal-like transition and promote metastasis [33]. An emerging link between circulatory cytokines and an increased NLR in cancer patients may reflect increased tumor burden and aggressiveness as well as consequent systemic pro-inflammatory effects [34]. Elevated concentrations of circulating interleukin (IL)-1 receptor antagonist, IL-6, IL-7, IL-8, IL-12, monocyte chemoattractant protein-1 and platelet-derived growth factor-BB were found to be associated with a high NLR, while a highly significant association was also found between serum IL-8 and TNM stage in colorectal cancer [35]. In another study conducted by Richard A. Smith et al. [36], a clear trend towards poorly differentiated tumors presenting a greater PLR was observed. They concluded that an elevated preoperative PLR reflected an enhanced host inflammatory

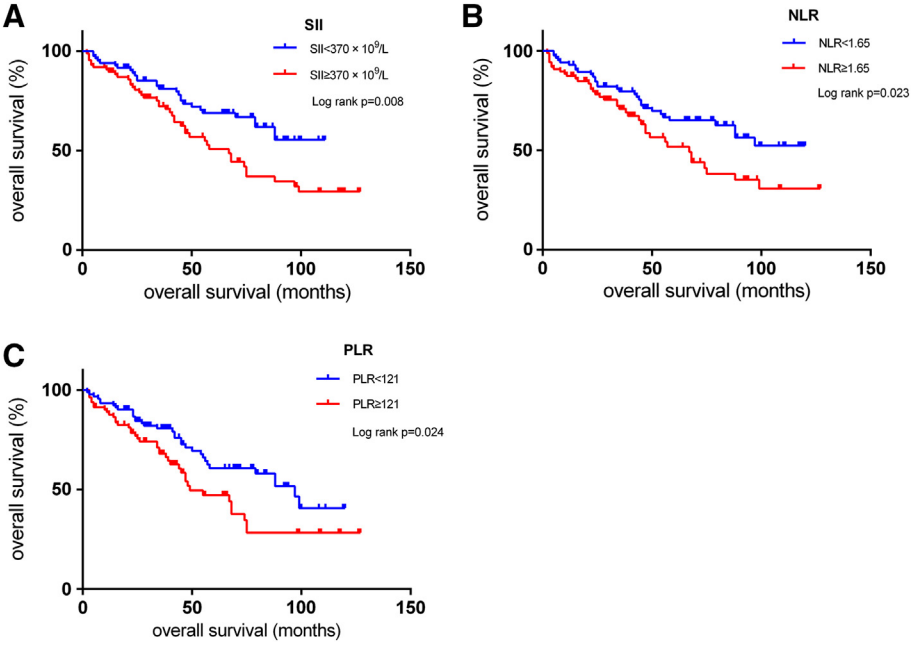

Figure 2. Kaplan-Meier survival curves for OS according to inflammation-based scores in 172 chordoma patients. (A). A total of 84 patients with an SII ≥ 370×10^9/L had a shorter median OS than 88 patients with an SII <370×10^9 (55.9 vs. 81.6 months, P = 0.008). (B). A total of 85 patients with an NLR ≥ 1.65 had a shorter median OS than 87 patients with an NLR <1.65 (56.4 vs. 82.3 months, P = 0.023). (C). A total of 89 patients with a PLR ≥ 121 had a shorter median OS than 83 patients with a PLR <121 (58.6 vs. 81.7 months, respectively; P = 0.024).

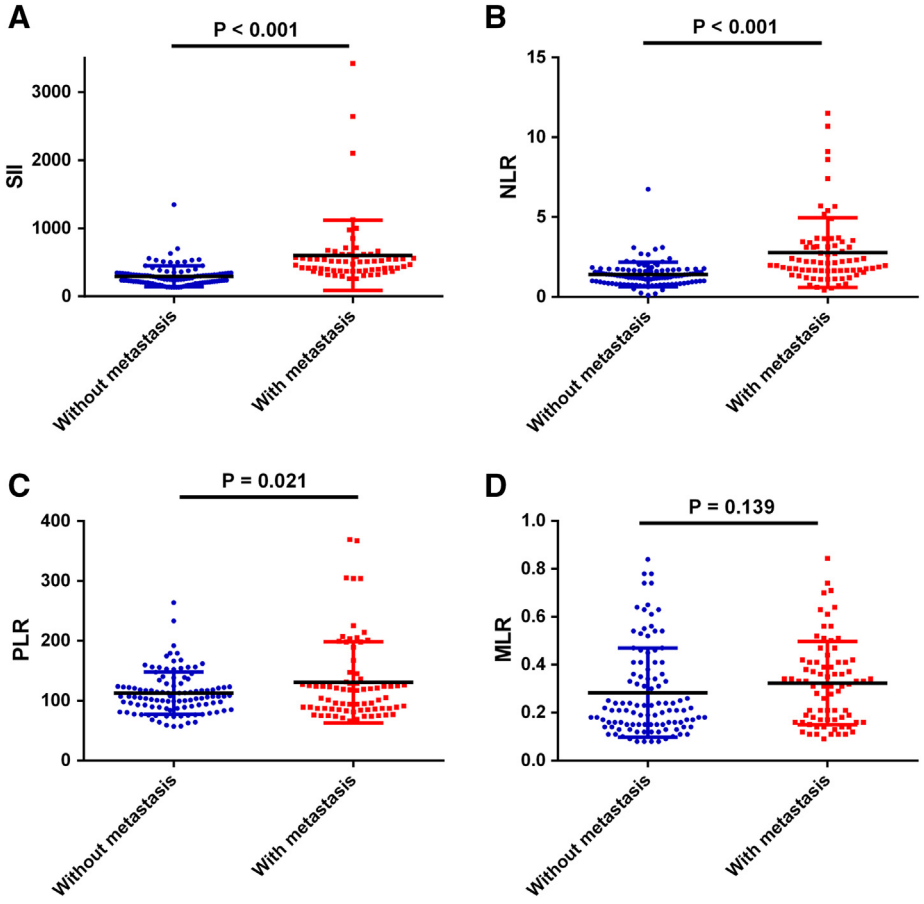

Figure 3. Association of the SII (A), NLR (B), PLR (C), and MLR (D) with tumor metastasis in 172 chordoma patients.

response to more aggressive tumor biology. SII represents a score based on the combination of the platelet count and neutrophil-lymphocyte ratio, which reflects the systemic inflammatory response [12]. An elevated SII due to high levels of neutrophils and platelets with concomitant low levels of lymphocytes, usually suggests a stronger inflammatory response and a weaker immune response in patients, and it may be associated with the invasion and metastasis of cancer cells and thus lead to poor survival [15].

In the present study, we first verified the role of these lymphocyte-related inflammatory and immune-based prognostic scores, such as NLR, PLR, and SII, prior to treatment initiation in predicting OS in patients with chordoma. We found that higher NLR, PLR, and SII indexes were associated with poor prognosis of chordoma in the Cox univariate analyses and that SII was shown to be significantly associated with the prognosis of chordoma in the multivariate Cox proportional hazard analysis. Recently, two studies conducted by Feng et al. [37] and Mathios et al. [38] reported that the programmed death 1 (PD-1) protein and its ligands PD-L1 and PD-L2 are expressed in chordoma. It is suggested that PD-1/PD-L1/PD-L2 and the cytotoxic T lymphocyte antigen 4 (CTLA4)/B7 interactions play a role in chordoma pathogenesis, which make these signaling axis as possible targets for immune checkpoint blockade therapies in chordoma patients. Another study showed that chordomas overexpress chondroitin sulfate proteoglycan 4 (CSPG4) [39], and Schoenfeld et al. [40] reported that CSPG4 expression in chordoma was correlated with an increased risk of metastasis and mortality. It is believed the CSPG4 could be a vital prognostic biomarker in the treatment of chordoma and that treatments targeting CSPG4 may be of significant value in treating chordoma. In addition, Heery et al. [41] suggested that chordoma patients have an immune response to brachyury, which may offer another option for treating chordoma patients with tumors with intact HLA class I expression. Therefore, identifying lymphocyte-related inflammatory and immune-based prognostic scores as biomarkers in patients with chordoma may be an important aspect for selecting patients for immunotherapy.

The limitations of this study include its retrospective nature and the small sample size owing to the low incidence of chordoma. However, to the best of our knowledge, our study is the largest series of chordoma to date. Another limitation is that this study could not analyze the prognostic value of CRP because it is not measured in the routine examination. Further research is needed to evaluate the predictive performance of CRP combined with these inflammation-based scores.

In conclusion, as noninvasive, low-cost, reproducible prognostic biomarkers, the NLR, PLR and SII could help predict poor prognosis in patients with chordoma after radical resection. This finding may contribute to tailoring more effective therapies in accordance with the characteristics of individual tumors.

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