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Pre-operative prognostic nutritional index was associated with recurrence after surgery in giant cell tumor of bone patients

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ABSTRACT

Objectives: Giant cell tumors of bone (GCT) are benign with a local recurrence rate of approximately 20–50%. Growing evidence suggests that inflammation plays an important role in tumor formation and progression. Inflammatory biomarkers, including prognostic nutritional index (PNI), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have little data in predicting postoperative recurrence of GCT.

Methods: We retrospectively investigated 105 patients with surgery for GCT between March 2010 and June 2019 at our hospital. Through the analysis of receiver operating characteristics (ROC), the optimal cutoff values of PNI, NLR and PLR were determined. Clinical features between PNI, NLR and PLR were tested with the χ^2 test. Univariate and multivariate analyses were applied to identify the prognostic factors.

Results: The optimal cut-off points of PNI, NLR and PLR were 48.6, 2.4 and 136.9, respectively. In univariate analysis, PNI, NLR, PLR, tumor size, Campanacci stage were significantly associated with recurrence-free survival (RFS). Cox multivariate regression analysis revealed that the PNI ($p = 0.003$) and Campanacci stage ($p = 0.001$) were independent prognostic factors for GCT.

Conclusions: PNI can be regarded as a novel independent prognostic factor for predicting postoperative recurrence in GCT.

1. Introduction

Giant cell tumor (GCT) is predominantly regarded as a benign but locally invasive and recurrent potential tumor, accounting for approximately 5% of all primary bone tumors in the Western population [1] and 20% in the Chinese population [2]. Conventional surgical procedures for GCT include lesion curettage and segmental resection. However, local recurrence varies from 20% to 50% according to WHO statistics [3] after surgical treatment. Treatment of GCT often is complicated by local recurrence. Although it is known that various classical factors such as tumor size, surgical approach and tumor stage are predictive for relapse [4], the clinical course of GCT may not always be predicted. Thus, a new parameter to more accurately predict the recurrence of GCT patients after operation is urgently needed.

Increasing evidence indicates that systemic inflammation plays a vital role in tumor occurrence, development and metastasis [5]. Many cytokines, such as interleukins (ILs), vascular endothelial growth factor (VEGF), and tumor necrosis alpha (TNF-α), stimulate the production of granulocytes and platelets during tumor growth [6]. Serum albumin and lymphocytes were also found to have anti-tumoral effects by enhancing the immune response to the tumor [7,8]. Accordingly, the degree of inflammatory response consists of platelets, neutrophils, lymphocytes and albumin, have been investigated in various tumors and found to predict prognosis and therapeutic response [9]. In addition, a series of combinations considering the above factors, such as prognostic nutrition index (PNI), neutrophil-to-lymphocytic ratio (NLR), and platelet-to-lymphocytic ratio (PLR), have been used to assess the prognosis of a variety of tumor types, including gastric cancer [10], colorectal cancer [11], melanoma [12] and hepatocellular carcinoma [13].

Inflammatory pathways have been recommended as a pivotal target to better improve the efficacy of therapy [14]. However, no previous study has assessed the prognostic value of PNI in GCT. Because GCT is usually considered to be benign disease with extremely low mortality, and the clinical adverse events are mostly caused by local recurrence. Therefore, we selected recurrence-free survival (RFS) rather than the overall survival (OS), as the research index in our study. According, we investigated the clinical significance of PNI, NLR and PLR, and to identify the independent prognostic factors using multivariate models.

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2. Patients and methods

2.1. Patient section

From March 2010 to June 2019, a retrospective analysis was conducted in a consecutive set of 105 GCT patients who underwent surgery at The Second Hospital of Tangshan, China. Clinicopathological features were collected from the patient medical records. The inclusion criteria comprised the following: (a) GCT confirmed by histopathology, (b) without previous anti-tumor therapy, (c) with detailed medical data and laboratory results, (d)patients had not taken anti-inflammatory medicines or received immunosuppressive therapy, and (e) no blood disease, infection, or fever.

2.2. Data collection and definition

We collected the clinical parameters of these patients from medical records, including age, gender, tumor size, surgical approach, tumor stage, local recurrence and laboratory data. Neutrophils, platelets and lymphocytes were counted by blood routine examination, and the serum albumin concentration was obtained by fasting liver function test. The PNI, NLR and PLR were calculated according to the following formula: PNI = albumin (g/L) + 5 × total lymphocyte counts per liter, NLR = neutrophil/lymphocyte counts, PLR = platelet/lymphocyte counts.

2.3. Follow-up

The patient's follow-up was initiated after the operation through a combination of outpatient visits and phone calls. Patients were required to perform physical and local radiography examinations at 3, 6 and 12 months after surgery, every 6 months for the second year and once a year thereafter. In addition to the above routine examinations, CT or MRI should be performed if necessary. Follow-up was closed by January 2020. Since GCT is a low-invasive tumor with extremely low mortality rate, and most of the adverse events lead to local recurrence. Therefore, we selected RFS as the research index for the prognosis of giant cell tumor.

2.4. Statistical analyses

The optimal cut-off values of inflammatory predictors were determined by receiver operating characteristic (ROC) analysis, using the highest Youden's index. The relationship between clinical parameters and inflammatory biomarkers were analyzed using Chi-square (χ^2) test. Survival curves were performed using Kaplan-Meier method and analyzed using log rank test. The prognostic values of PNI, NLR and PLR were evaluated by univariate and multivariate hazard ratios via Cox proportional hazard model. Every confidence interval (CI) was stated at the 95% confidence level. All statistical analyses were analyzed using SPSS software package (Version 20.0, Chicago, USA), and a two-sided *P* value < 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

Our study enrolled 105 participants totally according to the inclusion criteria (Table 1). The series consists of 65 females and 40 males, with an average age of 33 (range 15–73) years. According to the Campanacci grading criteria, 71 patients (67.6%) were in stages I and II, and 77 patients (32.4%) were in stage III. The median tumor size was 5 cm. Among all the patients, 56 (53.3%) underwent intralesional curettage while 49 patients (46.7%) underwent extensive resection. Recurrence was detected in 22 patients after initial surgery.

3.2. The optimal cut-off values of PNI, NLR and PLR

In our study, the median values of PNI, NLR, and PLR were 48.6, 2.4 and 136.9 respectively. Using the recurrence outcome of patients with GCT as an endpoint, the areas under the curve (AUC) for the PNI, NLR and PLR (Fig. 1a–c) were 0.737 ($p < 0.001$), 0.701 ($p < 0.001$) and 0.667 ($p = 0.003$), respectively. When PNI, NLR, and PLR were 46.5, 2.2 and 121.6, respectively, the Youden index calculated as sensitivity - (1-specificity) was maximal.

Therefore, according to the optimal cut-off values, the patients were divided into two groups for further analysis: low-PNI (< 46.5, n = 47) and high-PNI (≥ 46.5, n = 58) groups; low-NLR (< 2.2, n = 60) and high-NLR (≥ 2.2, n = 45) groups; and low-PLR (< 121.6, n = 49) and high-PLR (≥ 121.6, n = 56) groups.

3.3. Relationship between inflammation-based biomarkers and clinicopathological characteristics

The relationship between inflammation-based biomarkers and clinicopathological characteristics was shown in Table 1. To elucidate the prognostic significance, we investigated the association between patient clinicopathologic features and PNI, NLR, PLR levels. High NLR was significantly associated with larger tumor size ($p = 0.016$), advanced tumor stage ($p < 0.001$), wide resection ($p = 0.048$) and more local recurrence ($p = 0.027$) of patients when compared with low NLR. Furthermore, the stage III tumors ($p = 0.014$) and the local recurrence rate ($p = 0.040$) of patients in high PLR group were significantly higher than those in low PLR group.

In addition, we observed significant differences in tumor size ($p = 0.037$), Campanacci stage ($p = 0.045$), and local recurrence ($p = 0.013$) between low-PNI and high-PNI groups.

Although low PNI levels were present in both recurrent and non-recurrent groups, the percentage of low PNI in GCT with recurrence (15/47, 31.9%) was significantly higher than in the samples without recurrence (7/58, 12.1%; $p = 0.001$, Table 1). The results indicated that PNI-low levels were more frequent in GCT patients with recurrence. Whereas, no significant relationships were observed between the two groups in terms of age, sex and surgical method.

3.4. Univariate and multivariate survival analyses

By the end of the last follow-up, recurrence was recorded in 22 patients. The median follow-up time was 48 (range 6–118) months for all cases. Further analyses of the patient samples indicated that the recurrence-free rates at 1-, 2- and 5-year were 87.6%, 74.0% and 63.5%, respectively.

In the univariate Cox regression analysis, we found that PNI ($p = 0.001$), NLR ($p = 0.028$), PLR ($p = 0.041$), tumor size ($p = 0.040$) and Campanacci stage ($p < 0.001$) were the significant predictors correlated with RFS (Table 2). Patients in the high PNI group had a lower recurrence of tumors compared to those in the low PNI group ($\chi^2 = 13.091$, $p = 0.001$; Fig. 2a). The high NLR group got a significantly worse RFS than that of low NLR group ($\chi^2 = 5.054$, $p = 0.028$; Fig. 2b). Similarly, the high PLR group was observed with a markedly worse RFS than that of low PLR group ($\chi^2 = 4.321$, $p = 0.041$; Fig. 2c).

When the above demonstrated factors were analyzed in a multivariate analysis, Campanacci stage ($p = 0.001$) and PNI ($p = 0.003$) were remained the most significant and independent factors that influenced the recurrence rate of tumors (Table 2). Specifically, an advanced clinical stage was a risk factor for recurrence of GCT (HR = 2.996, 95% CI: 1.582–5.672), and a low PNI (HR = 2.461, 95% CI: 1.345–4.504) was a risk factor for the recurrence of GCT after surgery. These data indicated that PNI may be a significant and novel biomarker for evaluating the recurrence of GCT patients.

Table1
Baseline patient characteristics based on PNI, NLR, and PLR.

Variables	Cases	PNI			NLR			PLR		
		Low	High	p	Low	High	p	Low	High	p
Age (years)	35.06 + 14.42	34.40 + 16.28	35.59 + 12.84	0.678	32.85 + 12.32	38.00 + 16.51	0.070	36.06 + 14.37	34.18 + 14.54	0.507
Gender										
Male	40	18	22	0.969	27	13	0.093	18	22	0.788
Female	65	29	36		33	32		31	34	
Tumor size										
< 5	63	23	48	0.037	42	21	0.016	32	31	0.299
≥5	42	24	18		18	24		17	25	
Campanacci stage										
I–II stage	71	27	44	0.045	49	22	< 0.001	39	32	0.014
III stage	34	20	14		11	23		10	24	
Surgical method										
Intralesional curettage	56	23	33	0.416	37	19	0.048	25	31	0.657
Wide resection	49	24	25		23	26		24	25	
Local recurrence										
NO	83	32	51	0.013	52	31	0.027	43	40	0.040
YES	22	15	7		8	14		6	16	

PNI: prognostic nutritional index; NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio.

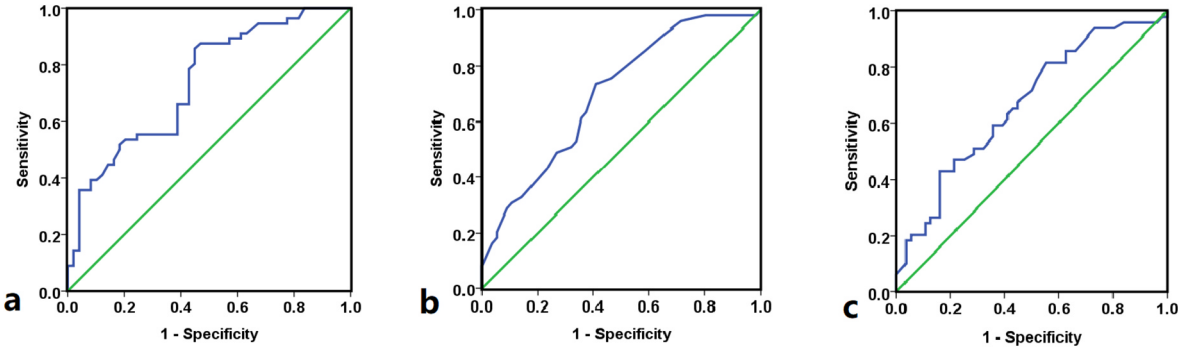

Fig. 1. Receiver operating characteristic curves for pretreatment (a) PNI, (b) NLR and (c) PLR based on RFS. The optimal cut-off values of PNI, NLR, and PLR were 46.5, 2.2 and 121.6, respectively. *PNI: prognostic nutritional index; NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio; RFS: recurrence-free survival.*

4. Discussion

The clinical behavior of GCT ranges from latent, nonactive tumors to locally aggressive tumors with destruction of the cortex and soft tissue extension. Clinical management of GCT is often complicated by local recurrence: 27%–65% after isolated curettage and 0%–12% after en bloc resection [15]. The clinical challenge in GCT treatment is to improve local control and broaden indications for intralesional surgery, providing optimal functional and oncological results. Since local recurrence is not always predictable, it is important for the clinician to detect prognostic or predictive factors.

Our study evaluated the clinical and prognostic roles of preoperative inflammatory biomarkers including PNI, NLR and PLR in GCT. The results showed that PNI was an independent prognostic factor in both univariate and multivariate survival analyses for RFS, while NLR and PLR were only significant in univariate analyses. This finding is consistent with the results of Chan et al. [16]. In their study, the authors revealed that PNI can predict tumor recurrence after surgical resection in very early/early hepatocellular carcinoma.

It is suggested that systemic inflammation and immune response are correlated with the development of tumor progression. Our study revealed that low PNI, high NLR and PLR were related with larger tumor size, advanced Campanacci stage, and more local recurrence. Most of all, we suggested that preoperative low PNI, rather than NLR and PLR, was independent prognostic factor for recurrence in GCT patients.

The immune and nutritional status could certainly influence patient prognoses, and various related markers have been established [17]. Among these markers, PNI is a new prognostic score which is calculated as albumin and lymphocyte counts and reflecting both inflammatory and nutritional status of patient [18]. Serum albumin was confirmed as being associated with systemic inflammation through high levels of proinflammatory cytokines and growth factors. Proinflammatory cytokines such as IL-1, IL-6 and TNF-α are involved in tumor formation, progression, and metastasis [19]. Preoperative serum albumin has been shown to be a good indicator of long-term outcomes [20], patients with malnutrition might delay surgery or adjuvant therapy. Lymphocytes, the other component of PNI, plays a pivotal role in cellular immunity by inhibiting the proliferation, invasion and migration of tumor cells [21,22]. Cytotoxic T cells induce tumor apoptosis and inhibit tumor growth by secreting cytokines and antiangiogenic factors [23]. Lymphocytopenia is also associated with reduced survival, similar to hypoalbuminemia, leading to the progression of cancers [24]. The reasons mentioned above may explain why lower PNI values are associated with poorer clinical outcomes.

A major limitation of the current study is a retrospective and single-center research. However, to the best of our knowledge, no study has investigated the relationships between preoperative PNI and postoperative recurrence in GCT patients. Here, we report for the first time that PNI is associated with postoperative recurrence of GCT. The findings from our study may contribute to determining the clinical value of the preoperative PNI.

Table 2
Analysis of the factors influencing the postoperative prognosis of patients with giant cell tumor.

Variables	Cases	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)	35.06 + 14.42	1(0.955–1.036)	0.136	–	–
Gender					
Male	40	1	0.892	–	–
Female	65	0.892(0.507–1.572)		–	
Tumor size					
< 5	63	1	0.040	1	0.227
≥5	42	1.807(1.028–3.175)		1.477(0.785–2.779)	
Campanacci stage					
I–II stage	71	1	< 0.001	1	0.001
III stage	34	3.541(2.005–6.253)		2.996(1.582–5.672)	
Surgical method					
Intralesional curettage	56	1	0.182	–	–
Wide resection	49	1.465(0.836–2.570)		–	
PNI					
Low-PNI	47	1	0.001	1	0.003
High-PNI	58	0.357(0.200–0.640)		0.406(0.222–0.743)	
NLR					
Low-NLR	60	1	0.028	1	0.806
High-NLR	45	1.888(1.073–3.323)		1.089(0.552–2.148)	
PLR					
Low-PLR	49	1	0.041	1	0.248
High-PLR	56	1.846(1.024–3.329)		1.430(0.780–2.622)	

HR: hazard ratios; CI: confidence interval; PNI: prognostic nutritional index; NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio.

5. Conclusion

Our results revealed that preoperative PNI might be potentially effective inflammation-based biomarkers to assess postoperative recurrence of GCT patients. Patients with this tumor with high PNI values can be given routine treatments, while those with low PNI values can be treated with more aggressive surgical methods combined with adjuvant therapy. However, the results of the current study need to be validated by future multicenter prospective studies.

Conflict of interest

None of the authors have any conflicts of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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10. Availability of data and materials

The data used in this study are available from the corresponding author on reasonable request.

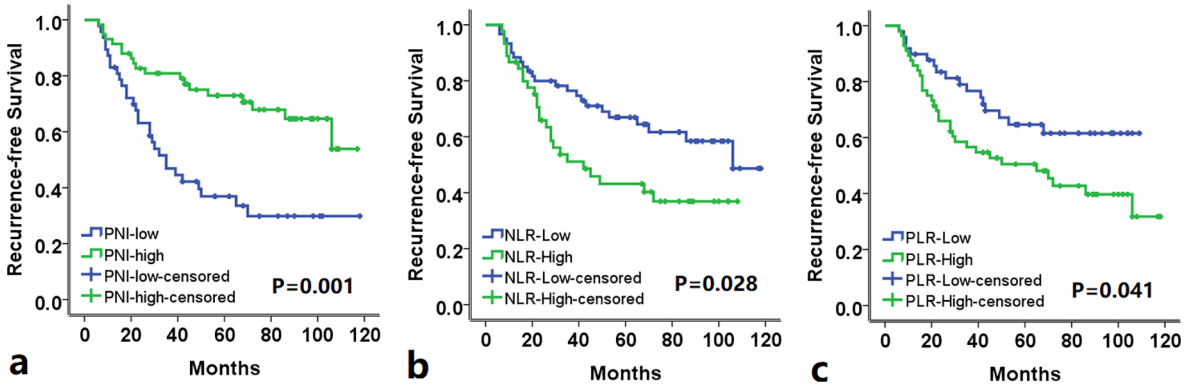

Fig. 2. Impact of (a) PNI, (b) NLR and (c) PLR based on RFS. a. The RFS rate in high PNI group significantly higher than in low PNI group ($p = 0.001$). b. The RFS rate in high NLR group significantly lower than in low NLR group ($p = 0.028$). c. The RFS rate in high PLR group significantly lower than in low PLR group ($p = 0.041$). *PNI: prognostic nutritional index; NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio; RFS: recurrence-free survival.*

CRediT authorship contribution statement

Shoulei Liang: Conceptualization, Methodology, Writing - original draft. **Yong Li:** Data curation, Software. **Hongtao Liu:** Visualization, Investigation. **Baocang Wang:** Conceptualization, Resources, Formal analysis, Project administration, Writing - review & editing.

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