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Prognostic significance of T cells and NK cells in osteosarcoma: a dual-center retrospective study

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Abstract

Background There is no study on the relationship between peripheral blood different lymphocyte subtypes and the prognosis of osteosarcoma (OS). Therefore, this study aims to investigate the predictive value of T cells and natural killer (NK) cells for the prognosis of OS patients.

Methods This study retrospectively analyzed the clinical data and preliminary laboratory indicators of patients with OS admitted from dual-center between January 2014 and January 2021. The receiver operating characteristic (ROC) curve was employed to determine optimal cutoff values for different lymphocyte subtypes, with T cells, NK cells, and B lymphocytes subsequently stratified into high- and low-proportion groups based on their respective optimal cutoff values. Kaplan–Meier curve was employed to analyze the impact of different lymphocyte on survival time and status. Univariate and multivariate Cox analyses were performed on clinical and laboratory indicators to identify independent prognostic factors influencing the prognosis of OS patients.

Results After screening 277 patients with OS, a total of 106 patients were eligible for this study. The median follow-up time was 36.00 months. At the last follow-up, patients were categorized as having a good prognosis if they survived or a poor prognosis if they died: good prognosis ($n=48$) and poor prognosis ($n=58$). Kaplan–Meier curve revealed that patients with a high proportion of T (Median overall survival: 41 months vs. 32 months, $P=0.007$) and NK (Median overall survival: 44 months vs. 32 months, $P=0.004$) cells had a better prognosis compared to those with a low proportion. Univariate analysis indicated that age, body mass index (BMI), C-reactive protein (CRP), tumor size, Enneking stage, surgical method, and the proportions of T, NK, and B cells were associated with the prognosis of OS patients ($P<0.05$). Multivariate analysis indicated that Enneking stage (II vs. I, HR = 12.543, $P=0.015$; III vs. I, HR = 29.078,

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$P = 0.001$), and the proportions of T and NK cells (HR = 0.466, $P = 0.048$; HR = 0.497, $P = 0.029$) were independent factors influencing the prognosis of OS patients ($P < 0.05$).

Conclusion The proportions of T and NK cells may serve as efficient and practical prognostic indicators for OS patients, with higher proportions often associated with a better prognosis.

Keywords Osteosarcoma, T cells, NK cells, Prognosis

Introduction

Osteosarcoma (OS) is the most common malignant bone tumor in adolescents and children, with an incidence rate of approximately 3.4 per 100,000 [1]. The current standard of treatment for OS primarily involves a combination of surgery and chemotherapy. However, due to its high malignancy and aggressiveness, patients face a poor prognosis, with a 5-year survival rate of approximately 60% [2]. Various factors influence the prognosis of OS, primarily categorized into clinical-pathological features, radiomics, and genomics. Although these factors play a crucial role in predicting the prognosis of OS, their predictive accuracy and applicability still have limitations.

Firstly, clinical-pathological features, such as tumor size, metastasis, Enneking stage, and surgical method, have been studied for prognostic evaluation in OS patients [3]. However, the clinical presentation of OS patients is complex, and no single clinical-pathological feature can accurately predict patient prognosis. In recent years, imaging indicators have also been utilized as prognostic factors for OS. Researchers have extracted imaging feature parameters from PET-CT and MRI scans of OS patients to construct prognostic models [4, 5]. Although these indicators have achieved certain effectiveness in prediction, there are still shortcomings in terms of measurement accuracy and sensitivity. In the field of genomics, especially single-cell genomics, there has been a recent emergence of novel sequencing technologies. Currently, recent advancements in sequencing technologies have led to the identification of several genes associated with the prognosis of OS. These genetic markers provided relatively accurate prognostic predictions at the molecular level [6]. However, the high cost of sequencing limits its accessibility, and the technology has not yet been widely integrated into clinical practice. Given these challenges, the need for a more accurate, practical, and easily measurable prognostic indicator remains critical.

Laboratory parameter testing is convenient, operationally simple, and cost-effective. In recent years, the prognostic value of laboratory indicators in OS has been increasingly emphasized. Early research found that a high ratio of neutrophils to lymphocytes could predict the chemotherapy response and overall prognosis in OS patients, highlighting the crucial role of lymphocytes in OS prognosis. However, the specific lymphocyte subtype responsible for this effect remains unclear [7, 8]. T cells, natural killer (NK) cells, and B cells are the primary subtypes of lymphocytes. Researchers have explored the prognostic evaluation of patients in different malignant tumors such as gastric cancer, colorectal cancer, and ovarian cancer by analyzing peripheral blood T, NK, and B lymphocytes, confirming their high predictive value [9–11]. However, there is currently no literature reporting on the relationship between different lymphocyte subtypes and prognosis in OS.

Hence, this retrospective study explores the correlation between the proportions of different lymphocyte in peripheral blood and the prognosis of OS. The objective is to identify an efficient, cost-effective, and practical predictive indicator, providing insights for the prognosis prediction of OS patients.

Materials and methods

Patients and study design

This study retrospectively analyzed patients with OS who were admitted from dual-center between January 2014 and January 2021. The criteria for inclusion were as follows: (1) Patients diagnosed with OS by histopathology; (2) Complete laboratory examination data; (3) Patients who had not undergone chemotherapy at their initial hospitalization; (4) Complete follow-up data. The criteria for exclusion were as follows: (1) Patients with immune system disorders (including systemic lupus erythematosus, rheumatoid arthritis and other autoimmune diseases); (2) Incomplete medical records; (3) Patients who had undergone chemotherapy or received immunosuppressive agents before their initial hospitalization; (4) Patients with concurrent infections, fever, or other malignant tumors; (5) Patients suffering from uremia, liver cirrhosis, liver failure, or other liver and kidney diseases affecting the immune system [12–14].

The study has received ethical support from their respective institutions (Approval number: 2024-E368-01). We confirmed that this study was conducted following the Declaration of Helsinki.

Clinical data and laboratory indicators

The clinical baseline data included the gender, age, body mass index (BMI), tumor size, Enneking stage, primary tumor site, pathological type, and treatment method. Laboratory indicators were blood samples collected from patients during their first hospitalization

before chemotherapy. Tumor staging was defined using the Enneking stage system. Based on the malignancy determined by pathological histology, patients without metastasis were classified into stage I and stage II, while those with metastasis were categorized as stage III [15]. Because metastasis is highly correlated with the Enneking stage, this variable was not included. The treatment modalities in this study comprised surgery, chemotherapy, and radiotherapy. Surgical interventions primarily included resection and amputation. For chemotherapy, both participating centers predominantly utilized the MAP regimen (high-dose methotrexate, cisplatin, and doxorubicin) administered as neoadjuvant/adjuvant therapy. In refractory or recurrent cases, the IE regimen (ifosfamide and etoposide) was employed. Radiotherapy was reserved for unresectable tumors (e.g., jaw or pelvic lesions) or margin-positive lesions, with definitive doses of 60–70 Gy (1.8–2 Gy per fraction) and palliative doses of 40–50 Gy (3–5 Gy per fraction).

Lymphocyte subtypes were detected using a flow cytometer (BD Biosciences, Franklin Lakes, NJ, USA). Recently collected blood samples were placed into tubes containing heparin and analyzed promptly after staining with monoclonal antibodies. Lymphocytes were identified based on the CD45 or side scatter dot plots. A total of 5000 lymphocytes were analyzed by flow cytometry, and dual-parameter analysis was performed on lymphocyte surface marker antigens. The differentiation antigens for T cells were defined as CD3+/CD4 + and CD3+/CD8+, NK cells were defined as CD3-/CD16+/CD56+, and B cells were defined as CD19+. The percentages of each lymphocyte subtype were calculated [16]. Additionally, other laboratory indicators included C-reactive protein (CRP) and white blood cell (WBC) count.

Follow-up

For all OS patients, telephone follow-ups were conducted every 6 months. Overall survival was defined as the time from the diagnosis of OS to death or the last follow-up. Based on the follow-up duration at the endpoint, patients were categorized as having a good prognosis if they survived or a poor prognosis if they died, reflecting their overall survival status. The other follow-up endpoints included loss to follow-up and other non-tumor outcome events (including death from cardiovascular and cerebrovascular accidents, traffic accidents, or psycho-related causes, etc.). Ultimately, complete follow-up data were obtained for 106 OS patients in this study.

Statistical analysis

This study evaluated the predictive accuracy of risk features by establishing a 10-year receiver operating characteristic (ROC) curve. The optimal cut-off values for T, NK, and B cell proportions were determined based on the ROC curve and Youden index (sensitivity + specificity − 1). These cut-off values were applied to classify patients into high and low proportion groups. Subsequently, Kaplan-Meier curves were employed to analyze the peripheral blood lymphocyte proportions and the prognosis of OS, and the statistical significance was tested by Log-rank.

Data compilation was executed through Excel 2016, and subsequent analysis was conducted using SPSS 24.0 software The measurement data following a normal distribution and a skewed distribution were respectively represented by the mean ± standard error and the median. The associations between the proportions of T, NK, and B cells, other important clinical parameters, and survival were assessed using the chi-square test and Fisher's exact test. Factors included in the analysis were tested for multicollinearity using linear regression, and the results indicated no evidence of multicollinearity among the independent variables. Cox regression models were used for both univariate and multivariate analyses to identify independent factors predicting the prognosis of OS. $P < 0.05$ was considered statistically significant.

Results

Clinical baseline data of patients

After screening 277 patients with OS according to the inclusion and exclusion criteria, this study ultimately enrolled 106 patients (Fig. 1). Final censoring date for follow-up was January 2024, and the median follow-up time was 36.00 months. At the last follow-up, 48 patients had a good prognosis, and 58 patients had a poor prognosis. The demographic information and clinical characteristics of patients are shown in Table 1.

Optimal cut-off values and Kaplan–Meier curve for lymphocyte proportions

The area under the curve (AUC) for the proportions of T, NK, and B cells was 0.702, 0.625, and 0.625, respectively. The optimal cutoff values were determined as 0.741 (sensitivity: 60.4%, specificity: 79.3%) for T cells, 0.099 (sensitivity: 58.3%, specificity: 67.2%) for NK cells, and 0.103 (sensitivity: 54.2%, specificity: 74.1%) for B cells (Fig. 2A-C). Based on the optimal cutoff values, 106 OS patients were grouped. There were 41 cases in the high T cell proportion group (≥ 0.741) and 65 cases in the low proportion group (< 0.741). Additionally, there were 47 cases in the high NK cell proportion group (≥ 0.099) and 59 cases in the low proportion group (< 0.099). Furthermore, the high B cell proportion group comprised 65 cases (≥ 0.103), while the low proportion group had 41 cases (< 0.103). (Table 1). According to the Kaplan–Meier curves, patients in the high proportion of T (Median overall survival: 41 months vs. 32 months, $P = 0.007$) and NK (Median overall survival: 44 months vs. 32 months,

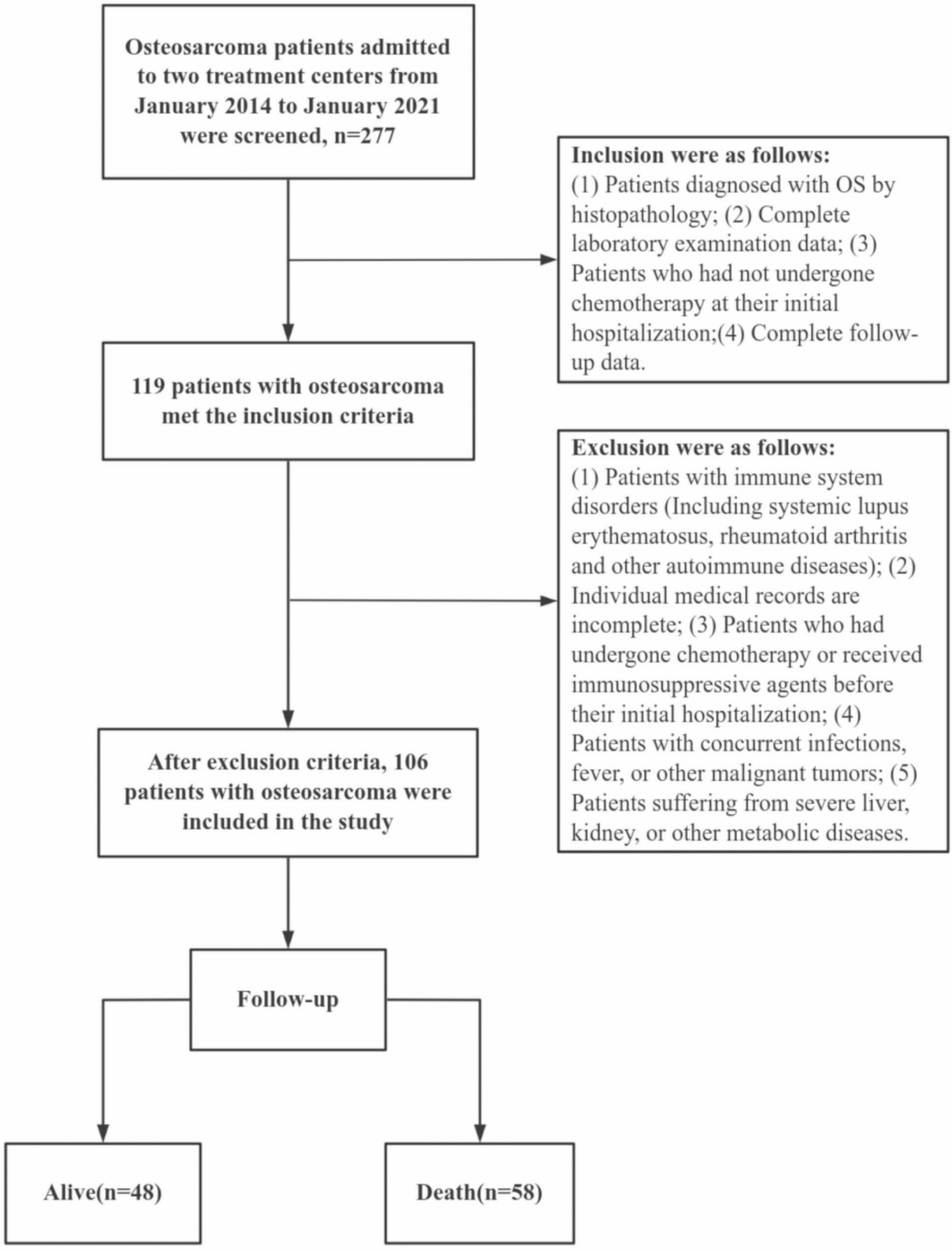

Fig. 1 The cases in this study are included in a flow chart detailing the selection process for osteosarcoma patients

Table 1 Clinical characteristics of two groups of OS patients

Clinical characteristics	*n*	Alive(*n* = 48)	Death(*n* = 58)
Gender			
Male	66	29	37
Female	40	19	21
Age (years)	18.00(13.00–29.00)	15.5(12.25-25.00)	18.5(15.00–33.00)
BMI (kg/m^2)	18.07(15.82–20.57)	17.53(15.32–20.04)	18.18(15.92–20.63)
WBC (10^9/L)	6.26(4.70–8.70)	5.81(4.06–7.77)	6.63(5.33–9.49)
CRP (mg/L)	6.97(1.70–19.10)	4.16(1.20-11.88)	9.84(3.38–26.98)
Tumor size (cm^3)			
≥ 355.96	53	18	35
< 355.96	53	30	23
Enneking stage			
I	18	17	1
II	50	26	24
III	38	5	33
Primary site			
Upper limb	9	6	3
Lower limb	85	39	46
Others	12	3	9
Pathological type			
Conventional	100	47	53
Others	6	1	5
Surgical method			
Resection	56	35	21
Amputation	26	9	17
No	24	4	20
Chemotherapy			
Yes	92	44	48
No	14	4	10
Radiotherapy			
Yes	4	3	1
No	102	45	57
T-cell proportion			
≥ 0.741	41	29	12
< 0.741	65	19	46
NK-cell proportion			
≥ 0.099	47	28	19
< 0.099	59	20	39
B-cell proportion			
≥ 0.103	65	22	43
< 0.103	41	26	15

$P = 0.004$) cell groups exhibited a significantly better prognosis compared to the low proportion groups. (Fig. 2D, E), while there was no statistically significant difference in the prognosis associated with high or low proportion of B cell ($P = 0.228$) (Fig. 2F).

Univariate and multivariate Cox analysis of clinical indicators and prognosis

To investigate the relationship between various clinical parameters and the prognosis of OS patients, we conducted univariate and multivariate Cox analyses on 106 patients to identify independent factors. In univariate Cox regression analysis, it was observed that the survival group had lower age ($P = 0.002$), BMI ($P = 0.045$), and CRP ($P = 0.040$) compared to the deceased group. Conversely, small tumor volume ($P = 0.008$), low Enneking stage ($P < 0.001$), and resection($P < 0.001$) indicated better prognosis. Regarding peripheral blood lymphocytes, this study found that a T cell proportion greater than or equal to 0.741 ($P = 0.002$), NK cell proportion greater than or equal to 0.099 ($P < 0.001$), and B cell proportion less than 0.103 ($P = 0.023$) were indicative of a favorable prognosis for patients. There were no significant differences in the prognosis of patients with gender, WBC, primary site, pathological type of chemotherapy and radiotherapy ($P > 0.05$). (Table 2). Finally, in the multivariate Cox analysis, age, BMI, CRP, tumor size, Enneking stage, surgical method, T cell proportion, NK cell proportion, and B cell proportion were included in the multivariate analysis. The results revealed that Enneking stage (II vs. I, $P = 0.015$; III vs. I, $P = 0.001$), T cell proportion ($P = 0.048$), and NK cell proportion ($P = 0.029$) were independent factors affecting the prognosis of OS patients. Specifically, T cell proportion ≥ 0.741 and NK cell proportion ≥ 0.099 were identified as protective factors influencing the prognosis of OS patients (HR 0.466, 95% CI 0.219–0.992, $p = 0.048$; HR 0.497, 95% CI 0.266–0.930, $p = 0.029$) (Table 3).

Discussion

OS is a solid tumor originating from mesenchymal tissue, characterized by its strong invasiveness and extremely poor prognosis, which make it imperative to search for novel prognostic indicators associated with OS prognosis. A total of 106 OS patients were enrolled in our study. Kaplan-Meier curves, along with univariate and multivariate Cox regression, revealed that a T cell proportion greater than or equal to 0.741, NK cell proportion greater than or equal to 0.099, and lower Enneking stage were associated with a better prognosis for patients. These factors are independent prognostic predictors in OS patients.

In this study, the T cell proportion emerged as an independent factor influencing the prognosis of OS. The anti-tumor function of T cells is primarily mediated through the T-cell receptor (TCR). Upon stimulation by tumor antigens, TCR interacts with major histocompatibility complex presented antigen complexes, generating effector T lymphocytes capable of traversing tissues and eliminating tumor cells [17]. In a retrospective analysis

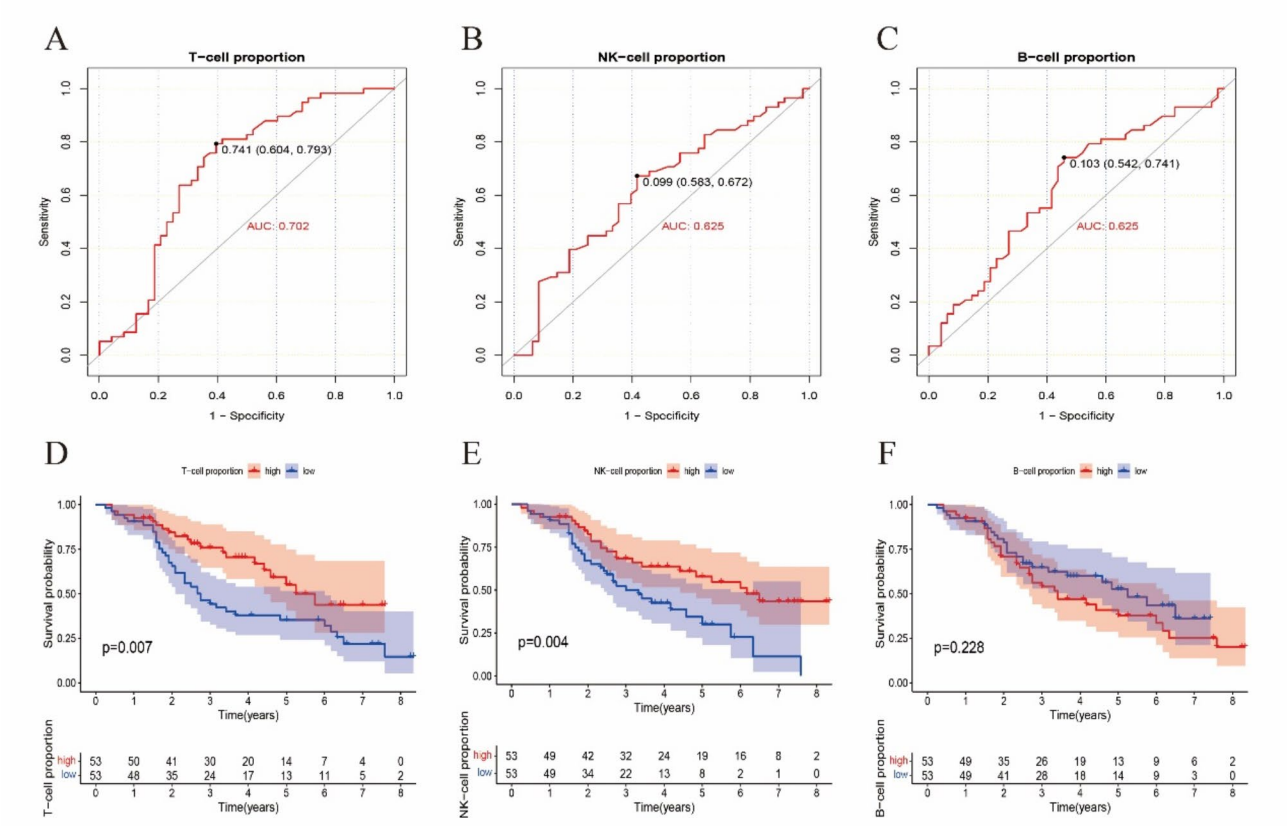

Fig. 2 Optimal cut-off values and Kaplan–Meier curve for different lymphocyte proportions of T, NK, and B cells

of 447 colorectal cancer patients, Tang et al. [10] similarly identified the T cell proportion as an independent factor affecting patient prognosis, with higher preoperative T cell proportion associated with better prognosis. This finding is consistent with our study, which revealed that individuals with a higher T cell proportion exhibited a 0.466 times lower risk of mortality compared to those in the lower T cell proportion group. Furthermore, Lu et al. [18] focused on the follicular helper T cells (Tfh) subtype within T lymphocytes. By using flow cytometry to assess Tfh expression in the peripheral blood of 148 OS patients, they discovered that OS patients had higher Tfh levels compared to benign tumor and normal groups, and those with high Tfh expression had a poorer outcome. Studies suggested that Tfh in OS can downregulate the expression of IL-21, affecting the activation of cytotoxic T cells and impeding their cytotoxic effects on OS [19, 20]. Despite the negative correlation between Tfh proportion and OS prognosis, considering the minimal proportion of Tfh within T lymphocytes and the primary role of effector T cells in tumor killing, we believe that peripheral blood T cells are a crucial factor influencing prognosis. An increased T cell proportion in peripheral blood enhances their cytotoxic activity against circulating tumor cells and promotes immune infiltration at the tumor site.

NK cells are also considered to be closely associated with the prognosis of OS patients. Unlike other immune cells, NK cells can non-specifically target and kill both tumor cells and virus-infected cells without requiring antigen stimulation. They achieve this by releasing cytotoxic substances, such as perforin and granzymes, which directly damage the tumor cell membrane, leading to tumor cell lysis and apoptosis [21]. A high proportion of NK cells has been shown to indicate better prognosis in various malignancies, including gastric cancer [9], colorectal cancer [10], and acute myeloid leukemia [22]. Similarly, in this study, patients with an NK cell proportion greater than or equal to 0.099 exhibited significantly better prognosis compared to those in the low NK cell proportion group. A higher proportion of NK cells can promote their non-specific killing of OS cells, making it a protective factor influencing the prognosis of OS patients. However, there is still some controversy regarding the relationship between B cells and tumor immunity. A study involving 72 cases of recurrent ovarian cancer found that individuals with a higher proportion of B cells experienced a better prognosis than those with a lower proportion, suggesting a positive correlation between

Table 2 Association between OS patient data and prognosis in univariate analysis

Variable	HR (95%)	*P*-value
Gender (Female vs. Male)	0.893(0.522–1.528)	0.680
Age (years)	1.026(1.010–1.043)	**0.002**
BMI (kg/m^2)	1.081(1.002–1.166)	**0.045**
WBC (10^9/L)	1.033(0.996–1.071)	0.081
CRP (mg/L)	1.007(1.000-1.013)	**0.040**
Tumor size (≥ 355.96 cm^3 vs. <355.96 cm^3)	2.058(1.212–3.494)	**0.008**
Enneking stage		**< 0.001**
I	1	
II	14.753(1.988-109.478)	**0.008**
III	49.848(6.693-371.236)	**< 0.001**
Primary site		0.140
Others	1	
Upper limb	0.288(0.077–1.077)	0.064
Lower limb	0.579(0.282–1.188)	0.136
Pathological type		
(Conventional vs. Others)	0.498(0.197–1.258)	0.140
Surgical method		**< 0.001**
No	1	
Amputation	0.536(0.278–1.033)	0.062
Resection	0.270(0.145–0.502)	**< 0.001**
Chemotherapy		0.071
Yes	1	
No	1.885(0.948–3.749)	
Radiotherapy		0.530
Yes	1	
No	1.885(0.260-13.658)	
T-cell proportion (≥ 0.741 vs. <0.741)	0.364(0.192–0.688)	**0.002**
NK-cell proportion (≥ 0.099 vs. <0.099)	0.366(0.208–0.644)	**< 0.001**
B -cell proportion (≥ 0.103 vs. <0.103)	1.984(1.099–3.580)	**0.023**

Table 3 Association between OS patient data and prognosis in multivariate analysis

Variable	HR (95%)	*P*-value
Age (years)	1.022(0.999–1.046)	0.062
BMI (kg/m^2)	1.004(0.907–1.112)	0.931
CRP (mg/L)	1.000(0.992–1.007)	0.901
Tumor size (≥ 355.96 cm^3 vs. <355.96 cm^3)	1.462(0.761–2.811)	0.254
Enneking stage		**0.001**
I	1	
II	12.543(1.638–96.053)	**0.015**
III	29.078(3.774-224.056)	**0.001**
Surgical method		0.303
No	1	
Amputation	0.638(0.304–1.340)	0.235
Resection	0.574(0.269–1.225)	0.151
T-cell proportion (≥ 0.741 vs. <0.741)	0.466(0.219–0.992)	**0.048**
NK-cell proportion (≥ 0.099 vs. <0.099)	0.497(0.266–0.930)	**0.029**
B -cell proportion (≥ 0.103 vs. <0.103)	0.963(0.484–1.915)	0.914

the proportion of B cells and patient prognosis [11]. In contrary, other studies have shown that B cell infiltration is associated with poor prognosis in malignant tumors such as renal clear cell carcinoma and pancreatic cancer [23]. Additionally, research indicated that B cells can suppress the anti-tumor response of T cells by secreting inflammatory mediators such as IL-10, IL-35, and TGF-β, indicating that B cells may promote tumor progression [24, 25]. In our study, we observed a negative correlation between B cell proportion and the prognosis of OS patients. However, in multivariate analysis, there was no statistical difference, suggesting that the B cell proportion may be influenced by other factors and may not be an independent influencing factor for the prognosis of OS patients. Notably, comparing lymphocyte subtype proportion before and after chemotherapy as dynamic indicators could have significant potential value. Studies have shown that chemotherapeutic agents can affect the function and number of peripheral blood lymphocytes [26, 27]. When the total number of lymphocytes decreases, various lymphocyte subtypes undergo distinct changes. In contrast, the proportion of lymphocyte subtype prior to chemotherapy more accurately reflects the patient's initial lymphocyte composition. However, the dynamic changes in lymphocyte proportion remain an important direction for future research.

Furthermore, our study found that the Enneking stage was also an independent factor affecting the prognosis of OS patients. The Enneking stage, as an important indicator of OS progression, is closely related to the tumor characteristics and disease development in patients. Specifically, patients in Enneking stage III, due to the presence of distant metastasis, usually have a poorer prognosis. Stages I and II are determined based on pathological findings, with stage II patients exhibiting higher tumor cell atypia and greater malignancy. As a result, compared to stage I patients, those in stage II experience faster tumor progression and worse prognosis. For this reason, the Enneking staging system was widely recognized in clinical prognostic evaluation [2, 28]. However, Enneking stage primarily relies on pathological and imaging examinations, and the limitations of biopsy samples and sampling errors may lead to staging discrepancies, which pose challenges for accurate staging, particularly in early-stage patients. While age, BMI, CRP, surgical method, and tumor size are not independent risk factors, the univariate analysis in this study revealed that they also impact the prognosis of OS patients. In the systematic meta-analysis of OS by Yi [29] and Song et al. [30], patients with high preoperative CRP levels were found

to have a poorer prognosis. Similarly, our study also observed that OS patients with elevated CRP levels tend to have a worse prognosis. Previous studies have demonstrated that the tumor size significantly impacts both prognosis and chemotherapy response in osteosarcoma patients [7, 8], and our study also found that patients with larger tumor size have a worse prognosis. Meanwhile, Weng et al. [31], in a study of 3106 colorectal cancer patients undergoing surgical treatment, investigated the preoperative white WBC. They found that patients in the high preoperative WBC group had lower overall survival rates ($P = 0.002$) and disease-free survival rates ($P = 0.003$) compared to the low WBC group. Nevertheless, our study found no statistically significant difference in the prognosis of patients with varying WBC levels, which could be attributed to the relatively small sample size. With advancements in chemotherapy and radiotherapy, resection has become a preferred option for more OS patients, maximizing the preservation of limb functionality. Multiple studies have demonstrated that the survival rate of OS patients undergoing resection is not lower than those undergoing amputation [32–34]. In our study, OS patients who underwent resection demonstrated a better prognosis compared to those who underwent amputation or received no surgical treatment. For OS patients with nerve and vascular invasion, amputation was typically the treatment of choice. In contrast, patients undergoing resection generally have a better overall condition and are usually free from nerve and vascular invasion, which may introduce some bias.

This study still has several limitations. Firstly, the sample size and the number of research centers included were relatively small. The study was a retrospective analysis and there may be potential bias. In addition, the laboratory indicators selected in this study were all single indicators before chemotherapy, and there was no dynamic comparison of laboratory indicators during treatment. Therefore, dynamic comparison with larger samples and multi-center prospective studies are needed to further validate these finding.

Conclusion

This study highlights that the proportions of peripheral blood T and NK lymphocytes are highly practical and efficient prognostic indicators for OS. Therefore, for OS patients, assessing peripheral blood lymphocyte proportions prior to chemotherapy provides valuable prognostic insights. When the T cell proportion is ≥ 0.741 and the NK cell proportion is ≥ 0.099, it suggests a better prognosis for the patients.

Abbreviations

OS	Osteosarcoma
ROC	Receiver operating characteristic
BMI	Body mass index
CRP	C-reactive protein
WBC	White blood cell
AUC	Area under the curve
TCR	T-cell receptor
Tfh	Follicular helper T cells

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Author contributions

Dehuai Liu, Juliang He and Yun Liu were responsible for conception, design, quality control of this study, reviewed, and edited the manuscript. Kai Luo, Haijun Tang, Weijie Yan and Shanhang Li was responsible for conception, design, quality control of this study, statistical analyses, and manuscript writed. Xiaoting Luo, Mingxiu Yang and Feicui Li were responsible for data collection, Jiming Liang and Shijie Liao were responsible for proofreading and patient's follow-up. All authors have approved the final version of the manuscript and all aspects of the work.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study is in accordance with the Declaration of Helsinki and has been approved by the Institutional Review Board (IRB) of the First Affiliated Hospital of Guangxi Medical University and Affiliated Tumor Hospital of Guangxi Medical University. The study was conducted in strict accordance with all relevant guidelines and regulations. As a retrospective cohort study, it involved only the collection of clinical data from patients, without any intervention in their treatment plans or exposure to additional physiological risks.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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