

Potential of Inflammatory and Nutritional Markers and Clinicopathological Factors for Prognostic Prediction in Osteosarcoma

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Abstract

Background/Aim: Prognostic factors for osteosarcoma remain insufficiently defined. This study evaluated the prognostic significance of the neutrophil-to-lymphocyte ratio (NLR), systemic inflammatory response index (SIRI), and prognostic nutritional index (PNI), and examined their associations with clinicopathological factors.

Patients and Methods: Eighteen patients with osteosarcoma treated at our institution were retrospectively analyzed. NLR, SIRI, and PNI were calculated from pretreatment blood tests. Associations between each index and clinical factors – including stage, lung metastasis, distant metastasis, and local recurrence – were assessed using the Kaplan–Meier method and Cox proportional hazards regression.

Results: The median follow-up was 79 months. Eight patients (44.4%) died of disease. In univariate analysis, stage was the only significant prognostic factor (HR=1.681, $p=0.0308$). Lung metastasis showed borderline significance (HR=3.593, $p=0.0817$). PNI demonstrated borderline significance in Kaplan–Meier analysis ($p=0.0880$) and was lower in patients who died (50.03 vs. 54.93). In multivariate analysis, the PNI-adjusted model showed the highest concordance index (0.704). NLR and SIRI were not independent prognostic factors but tended to be elevated in advanced-stage disease and in patients with lung metastasis.

Conclusion: Although PNI was not an independent prognostic factor, it demonstrated clinical relevance as an indicator of nutritional and immune status. NLR and SIRI may reflect tumor progression. An integrated risk assessment combining stage, lung metastasis, and PNI may improve prognostic prediction in osteosarcoma.

Keywords: Neutrophil-to-lymphocyte ratio, systemic inflammatory response index, prognostic nutritional index, osteosarcoma, prognosis, clinical factors, pathology.

Introduction

Osteosarcoma is the most common primary malignant bone tumor, characterized by malignant mesenchymal cells that directly produce bone matrix or osteoid (1).

Epidemiologically, osteosarcoma exhibits a bimodal age distribution, with the first peak occurring during adolescence and periods of rapid growth, followed by a second peak in individuals older than 60 years (1, 2). It most frequently arises near the epiphyses of long bones, such as



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Received March 3, 2026 | Revised March 23, 2026 | Accepted March 30, 2026

the distal femur, proximal tibia, and proximal humerus, and is often associated with rapid tumor progression.

Periosteal reactions and bone destruction observed on plain radiographs serve as important initial diagnostic findings (3). Magnetic resonance imaging is used to evaluate the extent of soft tissue involvement, while chest computed tomography is performed to screen for pulmonary metastases (4). Histopathological examination using needle or incisional biopsy is essential for definitive diagnosis and for identifying diverse histological subtypes, including osteoblastic, chondroblastic, and fibroblastic variants (5).

Since the 1970s, osteosarcoma treatment has undergone a dramatic shift with the introduction of combined surgical resection and chemotherapy (6). The current standard of care consists of preoperative and postoperative chemotherapy (MAP therapy) using high-dose methotrexate, adriamycin, and cisplatin, along with wide surgical resection to achieve negative margins (7). This multimodal approach has enabled limb preservation in more than 90% of cases, including many that previously required amputation (8). However, significant challenges remain regarding prognosis. While the 5-year survival rate for patients with localized disease reaches 60%-70%, outcomes for those presenting with pulmonary metastases at diagnosis or with recurrent disease remain extremely poor (approximately 20%), with little improvement over the past 30 years (9). The degree of tumor necrosis following preoperative chemotherapy is a major prognostic factor; however, establishing effective treatment strategies for poor responders remains an ongoing challenge (10). Novel therapeutic approaches, including molecularly targeted agents and immunotherapies, as well as the identification of precise biomarkers and more accurate prognostic indicators, are needed to further improve clinical outcomes.

Hematological markers reflecting systemic inflammatory responses and host nutritional status have gained attention as prognostic indicators in various malignancies. The neutrophil-to-lymphocyte ratio (NLR) reflects the balance between systemic inflammation and

immune status and has been associated with prognosis in many cancer types (11). The systemic inflammatory response index (SIRI), which incorporates neutrophils, monocytes, and lymphocytes, may provide a more comprehensive assessment of inflammatory status (12). The prognostic nutritional index (PNI), calculated from serum albumin levels and lymphocyte counts, has been proposed as an indicator of nutritional and immune function (13). However, the predictive value of these indices in osteosarcoma has not been sufficiently investigated. This study aimed to comprehensively evaluate NLR, SIRI, and PNI as prognostic predictors in patients with osteosarcoma, including their associations with clinical and pathological factors such as stage, pulmonary metastasis, and local recurrence.

Patients and Methods

Patients. This study included 18 patients who were diagnosed with osteosarcoma and treated at our hospital. Their ages ranged from 8 to 74 years (median: 26 years), and the follow-up period ranged from 5 to 225 months (median: 79 months) (Table I). The study was approved by the Ethics Committee of the Kindai University Faculty of Medicine (Approval No. 31-187). Comprehensive consent for publication was obtained from all patients.

Staging was performed according to the Enneking classification (14), revealing one case of Stage IA, six of Stage IIA, six of Stage IIB, one of Stage III, three of Stage IVA, and one of Stage IVB. Pulmonary metastasis was observed in three cases (16.7%), and distant metastasis, including mediastinal lymph node involvement, was present in two cases (11.1%). Local recurrence occurred in four patients (22.2%). Histopathologically, the conventional subtype was the most common (nine cases, 50.0%), followed by fibroblastic (three cases), chondroblastic (three cases), low-grade (two cases), and osteoblastic (one case). During the observation period, eight patients (44.4%) died of disease (DOD), whereas ten patients (55.6%) remained continuously disease-free (CDF), alive with disease (AWD), or had no evidence of disease (NED).

Calculation of inflammation and nutritional indicators.

Indices were calculated from blood test data obtained before treatment initiation; in principle, blood samples collected within one week prior to treatment were used. The NLR was calculated as neutrophil count ($/\mu\text{l}$) \div lymphocyte count ($/\mu\text{l}$). SIRI was calculated as [neutrophil count ($/\mu\text{l}$) \times monocyte count ($/\mu\text{l}$)] \div lymphocyte count ($/\mu\text{l}$). PNI was calculated as serum albumin level (g/dl) \times 10 + lymphocyte count ($/\mu\text{l}$) \times 0.005. All indices were simple measures derived from standard peripheral blood and biochemical tests.

Clinicopathological factors. Clinicopathological factors were extracted and evaluated for their association with prognosis, including age (continuous), stage (ordinal; IA: 1, IIA: 2, IIB: 3, III: 4, IVA: 5, and IVB: 6), stage classification (binary; Stages I-II vs. Stages III-IV), lung metastasis (binary), distant metastasis outside the lung or mediastinal lymph node (binary), local recurrence (binary), and histopathological subtype (categorical).

Statistical analysis. Descriptive statistics for the distribution of each indicator and clinical factor were summarized using mean \pm standard deviation, median, and range. Intergroup comparisons were performed between the DOD group and the survival group (CDF/AWD/NED). The distribution of each indicator was compared using the Mann–Whitney *U*-test. In addition, each indicator was compared according to clinical factors, including the presence of lung metastasis and stage classification.

Survival time was defined as the period from treatment initiation to the last follow-up or death, with disease-related death considered an event. Survival curves were generated using the Kaplan–Meier method, and intergroup comparisons were conducted using the log-rank test. Each inflammation or nutritional indicator was dichotomized into high and low groups using the median value as the cutoff.

Univariate Cox proportional hazards regression analysis was performed to individually assess the association between each clinical factor, indicator, and

Table I. Patient demographics and clinical characteristics (n=18).

| Characteristic | Value |
|---|------------|
| Age at diagnosis (y); median (range) | 28 (8-74) |
| Sex | |
| Male | 10 |
| Female | 8 |
| Histological subtype | |
| Conventional | 8 (44.4%) |
| Fibroblastic | 3 (16.7%) |
| Chondroblastic | 3 (16.7%) |
| Low grade | 2 (11.1%) |
| High grade | 1 (5.6%) |
| Osteoblastic | 1 (5.6%) |
| Tumor stage | |
| IA | 1 (5.6%) |
| IIA | 6 (33.3%) |
| IIB | 6 (33.3%) |
| III | 1 (5.6%) |
| IVA | 3 (16.7%) |
| IVB | 1 (5.6%) |
| Lung metastasis at presentation | |
| Present | 4 (22.2%) |
| Absent | 14 (77.8%) |
| Distant metastasis at presentation | |
| Present | 5 (27.8%) |
| Absent | 13 (72.2%) |
| Local recurrence | |
| Yes | 4 (22.2%) |
| No | 14 (77.8%) |
| Clinical outcome | |
| DOD | 8 (44.4%) |
| CDF | 9 (50.0%) |
| NED | 1 (5.6%) |
| Follow-up period (months); median (range) | 79 (5-225) |

DOD: Died of disease; CDF: continuously disease-free; NED: no evidence of disease.

prognosis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Multivariate Cox proportional hazards regression analysis was then conducted after adjusting for factors deemed significant or clinically relevant (lung metastasis and stage). Separate models were constructed for each indicator, and adjusted HRs were calculated. Predictive accuracy was evaluated using the Concordance Index (C-index), with 0.5 indicating random prediction and 1.0 indicating perfect prediction.

Statistical analyses were performed using Python 3.12 (pandas, scipy, lifelines, and matplotlib). A two-sided significance level of 5% was applied, and *p*-values between 0.05 and 0.10 were considered borderline significant.

Table II. Patient background and clinicopathological factors.

| Age | Lung metastasis | Distant metastasis | Pathology | Local recurrence | Stage | Outcome | Follow-up | WBC count | Neutrophil count | Monocyte count | Lymphocyte count | Albumin |
|-----|-----------------|--------------------|-------------------|------------------|-------|---------|-----------|-----------|------------------|----------------|------------------|---------|
| 17 | + | - | Conventional | + | IVB | DOD | 43 | 5,600 | 2,917.6 | 308 | 2,016 | 4.5 |
| 8 | - | + | Fibroblastic | | III | CDF | 89 | 7,160 | 3,451.12 | 622.92 | 2,720.8 | 4.3 |
| 52 | - | - | High grade | + | IIB | DOD | 38 | 2,100 | 617.4 | 273 | 924 | 2.7 |
| 14 | - | - | Conventional | | IIA | CDF | 84 | 4,700 | 2,115 | 333.7 | 2,115 | 5 |
| 13 | - | - | Conventional | | IIB | CDF | 125 | 5,900 | 2,891 | 312.7 | 2,596 | 4.3 |
| 15 | - | - | Osteoblastic | | IIA | CDF | 144 | 4,900 | 2,401 | 245 | 1,911 | 4.5 |
| 36 | - | - | Chondroblastic | | IIA | CDF | 100 | 7,500 | 4,125 | 450 | 2,550 | 3.2 |
| 51 | - | - | Low grade | | IA | CDF | 104 | 8,700 | 5,655 | 539.4 | 2,262 | 4.4 |
| 74 | - | - | Fibroblastic | | IIB | CDF | 74 | 5,060 | 2,580.6 | 506 | 1,771 | 4.2 |
| 16 | - | - | Conventional | | IIB | CDF | 99 | 4,500 | 1,755 | 225 | 2,340 | 4.7 |
| 36 | - | - | Conventional | + | IIA | NED | 114 | 7,000 | 4,550 | 343 | 1,820 | 4.7 |
| 24 | - | - | Low grade central | | IIA | CDF | 225 | 7,100 | 3,621 | 553.8 | 2,769 | 4.2 |
| 28 | + | + | Chondroblastic | | IVA | DOD | 6 | 7,500 | 4,275 | 480 | 2,550 | 4.4 |
| 32 | + | - | Conventional | | IVA | DOD | 64 | 5,300 | 3,710 | 355.1 | 1,113 | 4.5 |
| 28 | - | - | Chondroblastic | | IVA | DOD | 10 | 4,320 | 2,635.2 | 181.44 | 1,425.6 | 4.3 |
| 63 | - | - | Fibroblastic | | IIB | DOD | 14 | 3,200 | 1,440 | 278.4 | 1,376 | 4 |
| 19 | - | - | Conventional | + | IIB | DOD | 24 | 5,770 | 3,346.6 | 548.15 | 1,731 | 5 |
| 13 | - | - | Conventional | | IIA | DOD | 5 | 4,550 | 2,866.5 | 182 | 1,319.5 | 4.4 |

WBC: White blood cell; CDF: continuously disease-free; NED: no evidence of disease; DOD: died of disease.

Results

Patient background and clinicopathological factors. The 18 cases had a median age of 28 years (range=8-74 years) and a median observation period of 79 months (range=5-225 months). Thirteen cases (72.2%) were classified as Stages I-II, and five cases (27.8%) were classified as Stages III-IV. Pulmonary metastasis was observed in three patients (16.7%), while other distant metastasis (mediastinal lymph node metastasis) was observed in one patient (5.6%). Local recurrence occurred in four cases (22.2%) (Table II).

Distribution of inflammation and nutritional indicators. The mean NLR was 1.61 ± 0.69 , with a median of 1.45 (range=0.67-3.33). The mean SIRI was 613.47 ± 352.72 , with a median of 584.97 (range=168.75-1,348.50). The mean PNI was 52.75 ± 6.75 , with a median of 55.20 (range=31.62-0.58) (Table III).

Inflammation and nutritional indicators by clinical factor. In the DOD group, the NLR was 1.77, the SIRI was 587.30,

and the PNI was 50.03. In the survival group, the NLR was 1.48, the SIRI was 634.41, and the PNI was 54.93. Among patients with lung metastases, the NLR was 2.15, the SIRI was 811.37, and the PNI was 54.13. In cases classified as Stages III-IV, the NLR was 1.91, the SIRI was 711.93, and the PNI was 53.83 (Table IV).

Univariate Cox regression analysis. In the univariate Cox regression analysis, the HR for stage (treated as an ordinal variable) was 1.681 (95%CI=1.049-2.693, $p=0.0308$); the HR for lung metastasis was 3.593 (95%CI=0.851-15.159, $p=0.0817$), that for distant metastasis was 1.540, and that for local recurrence was 2.189. The HRs for NLR, SIRI, and PNI were 1.372, 1.000, and 0.944, respectively (Table V).

Kaplan–Meier survival analysis. Each inflammatory and nutritional marker was dichotomized at the median value, and survival curves for the high- and low-value groups were constructed using the Kaplan–Meier method (Figure 1). PNI demonstrated borderline significance (log-rank $p=0.0880$), whereas NLR ($p=0.2813$) and SIRI ($p=0.3207$) showed no statistically significant differences.

Table III. Descriptive statistics for inflammation and nutritional indicators.

| Indicators | Average±SD | Mean | Minimum | Maximum |
|------------|---------------|--------|---------|----------|
| NLR | 1.61±0.69 | 1.45 | 0.67 | 3.33 |
| SIRI | 613.47±352.72 | 584.97 | 168.75 | 1,348.50 |
| PNI | 52.75±6.75 | 55.20 | 31.62 | 60.58 |

SD: Standard deviation; NLR: neutrophil-to-lymphocyte ratio; SIRI: systemic inflammatory response index; PNI: prognostic nutritional index.

Table IV. Comparison of inflammation and nutritional indicators by clinical factor.

| Clinical factors | Number of cases | NLR | SIRI | PNI |
|------------------|-----------------|-----------|---------------|------------|
| Outcome | | | | |
| DOD Group | 8 | 1.77±0.73 | 587.30±340.17 | 50.03±7.86 |
| Survival | 10 | 1.48±0.64 | 634.41±372.99 | 54.93±4.79 |
| Metastasis | | | | |
| + | 3 | 2.15±0.83 | 811.37±420.48 | 54.13±3.43 |
| - | 15 | 1.50±0.61 | 573.89±330.43 | 52.48±7.15 |
| Stage | | | | |
| I-II | 13 | 1.49±0.59 | 575.60±335.07 | 52.34±6.18 |
| III-IV | 5 | 1.91±0.87 | 711.93±418.05 | 53.83±8.53 |

NLR: Neutrophil-to-lymphocyte ratio; SIRI: systemic inflammation response index; PNI: prognostic nutritional index.

Pulmonary metastasis ($p=0.0629$) and Stages I-II versus III-IV ($p=0.0797$) were also borderline significant. A steep decline in survival was observed, particularly among patients with lung metastasis.

The box-and-whisker plots (Figure 2) visually confirmed that the DOD group tended to exhibit higher NLR and lower PNI values, and that NLR and SIRI were elevated in patients with lung metastasis or Stage III-IV disease. The results of the intergroup comparisons using the log-rank test are summarized in Table VI.

Multivariate Cox regression analysis. Cox proportional hazards regression analysis was performed, adjusting for lung metastasis and stage (I-II vs. III-IV) as confounding factors. Separate models were constructed for each inflammatory and nutritional marker, and the adjusted HRs and C-indices were evaluated (Table VII). After adjustment,

NLR (HR=0.968, $p=0.942$), SIRI (HR=0.999, $p=0.419$), and PNI (HR=0.939, $p=0.151$) were not statistically significant.

The PNI-adjusted model (C-index=0.704) demonstrated the highest predictive accuracy, followed by the SIRI-adjusted model (0.676) and the NLR-adjusted model (0.639). The C-index of the PNI-adjusted model exceeded the threshold for random prediction (0.5), indicating moderate-to-high predictive performance. In the multivariate analysis, the HRs for lung metastasis and Stages III-IV remained elevated at 1.8-2.1, although they did not reach statistical significance.

Discussion

This study comprehensively evaluated the prognostic significance of the NLR, SIRI, and PNI in 18 patients with osteosarcoma, including their associations with clinical and pathological factors. The 5-year survival rate for osteosarcoma is 60%-70% (1, 2), with prognosis worsening as disease stage advances; the 5-year survival rate for Stage IV osteosarcoma is approximately 20% (15, 16). In this cohort, univariate Cox regression analysis identified stage as the only statistically significant prognostic factor (HR=1.681, $p=0.0308$), indicating that each increase in stage was associated with a 1.68-fold higher risk of death. Kaplan–Meier analysis also demonstrated a borderline significant difference in survival between Stages I-II and III-IV ($p=0.0797$).

The impact of lung metastasis on osteosarcoma prognosis has been consistently reported in previous studies (17, 18). In this study, the hazard ratio for lung metastasis in the univariate analysis was 3.593 ($p=0.0817$), which was borderline significant; Kaplan–Meier analysis similarly showed borderline significance ($p=0.0629$). Although only three cases had lung metastases, these patients exhibited a steep decline in survival, confirming their extremely poor prognosis and reinforcing lung metastasis as a critical indicator of unfavorable outcomes (1, 2, 19).

The PNI is calculated from serum albumin levels and lymphocyte counts, enabling simultaneous assessment

Table V. Univariate Cox regression analysis results.

| Variable | Hazard ratio | 95%CI | p-Value | Significance |
|---|--------------|--------------|---------|--------------|
| Clinical factors | | | | |
| Age | 1.004 | 0.969-1.041 | 0.8104 | n.s. |
| Stage | 1.681 | 1.049-2.693 | 0.0308 | * |
| Lung metastasis | 3.593 | 0.851-15.159 | 0.0817 | BL |
| Distant metastasis | 1.540 | 0.188-12.604 | 0.6872 | n.s. |
| Local recurrence | 2.189 | 0.511-9.378 | 0.2910 | n.s. |
| Inflammation and nutritional indicators | | | | |
| NLR | 1.372 | 0.569-3.305 | 0.4813 | n.s. |
| SIRI | 1.000 | 0.998-1.002 | 0.6713 | n.s. |
| PNI | 0.944 | 0.871-1.023 | 0.1607 | n.s. |

* $p < 0.05$ (significant); BL: borderline ($0.05 < p < 0.10$); n.s.: not significant. NLR: Neutrophil-to-lymphocyte ratio; SIRI: systemic inflammation response index; PNI: prognostic nutritional index.

of nutritional and immune status (19, 20). In cancer patients, malnutrition is known to reduce treatment tolerance, impair immune function, delay wound healing, and worsen prognosis (21, 22). Previous reports have suggested that the PNI correlates with osteosarcoma prognosis (19). In this study, univariate Cox regression analysis showed that PNI was not statistically significant ($p = 0.1607$), but Kaplan–Meier analysis demonstrated borderline significance (log-rank $p = 0.0880$). Furthermore, the DOD group had lower PNI values than the survival group (50.03 vs. 54.93), and the PNI-adjusted model exhibited the highest C-index (0.704) in multivariate analysis. These findings suggest that although PNI alone was not significant, its combination with clinical factors improved prognostic model accuracy. The lower PNI values observed in the DOD group also imply that poor nutritional and immune status may influence overall survival. Preoperative nutritional assessment and intervention may therefore improve outcomes, and future clinical applications are anticipated.

The NLR and SIRI are established markers of systemic inflammation and have been reported as prognostic indicators in osteosarcoma. Although neither NLR nor SIRI served as independent prognostic factors in this study, both were associated with tumor progression. Higher NLR and SIRI values in patients with lung metastasis or Stage III-IV disease suggest that systemic inflammatory responses may reflect tumor burden. While the NLR is

an independent prognostic factor in many malignancies, the small sample size in this study may have limited the ability to detect significant associations. Larger studies may clarify the prognostic utility of NLR and SIRI in osteosarcoma.

These findings have several clinical implications. First, the importance of stage-based stratification was reaffirmed; patients with Stage III-IV disease require more aggressive treatment strategies and closer follow-up. Second, the potential utility of PNI-based nutritional assessment was suggested, indicating that preoperative nutritional intervention for patients with low PNI may improve prognosis. Third, the importance of early detection of lung metastasis was further emphasized; regular chest imaging and early therapeutic intervention may contribute to improved outcomes. An integrated risk assessment incorporating stage, PNI, and lung metastasis status may enable more accurate prognostic prediction and support personalized treatment strategies.

This study has several strengths, including the inclusion of osteosarcoma cases with long follow-up periods. However, limitations remain. The small sample size (18 cases) and limited number of events (eight) reduced statistical power; in particular, the presence of only three cases with lung metastasis hindered evaluation of this key prognostic factor. This was also a single-center retrospective study, raising the possibility of selection bias. Additionally, treatment-related factors such as

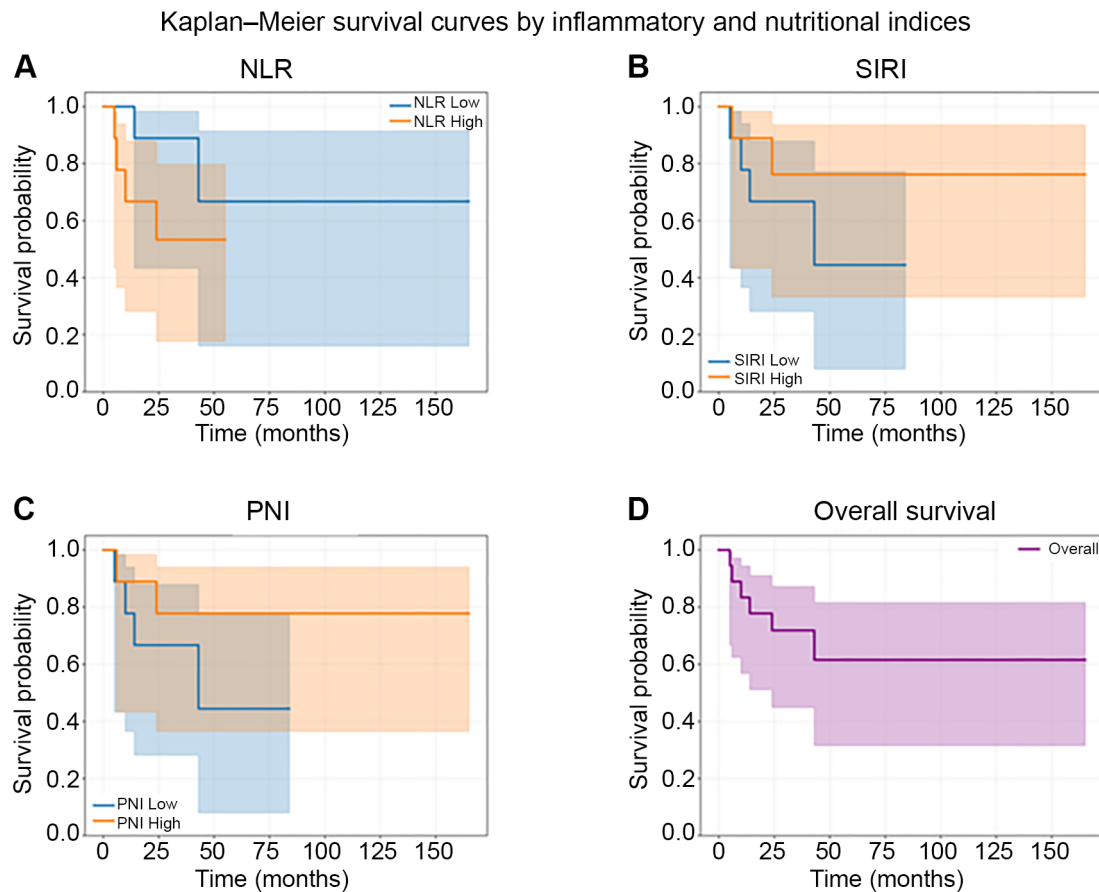


Figure 1. Kaplan–Meier survival analyses based on inflammatory and nutritional markers and clinical factors. (A) Overall survival stratified by low vs. high neutrophil-to-lymphocyte ratio (NLR) (cutoff: median 1.45). (B) Overall survival stratified by low vs. high systemic inflammatory response index (SIRI) (cutoff: median 584.97). (C) Overall survival stratified by low vs. high prognostic nutritional index (PNI) (cutoff: median 55.20). (D) Overall survival curve for all 18 patients. Data are presented as survival proportions over time. *p*-values were calculated using the log-rank test.

chemotherapy regimens, response rates, and surgical margins were not included, although these factors may significantly influence prognosis. Cutoff values for inflammatory and nutritional markers were set at median values, and optimal thresholds based on receiver operating characteristic analysis were not determined. Finally, the observation period varied widely among cases (5–225 months), and follow-up may have been insufficient in some patients.

Validation through larger multicenter collaborative studies is essential; a target sample size of at least 100 cases (with ≥ 50 events) would be required. A

comprehensive prognostic model incorporating chemotherapy response and surgical factors is also needed. Prospective studies evaluating the efficacy of preoperative nutritional interventions based on PNI are warranted, as improving nutritional status may enhance treatment tolerance and prognosis. The development of an integrated prognostic prediction system combining inflammatory and nutritional indicators with molecular markers is an important future direction. Additionally, longitudinal studies assessing the relationship between prognosis and temporal changes in inflammatory and nutritional markers may provide further insight.

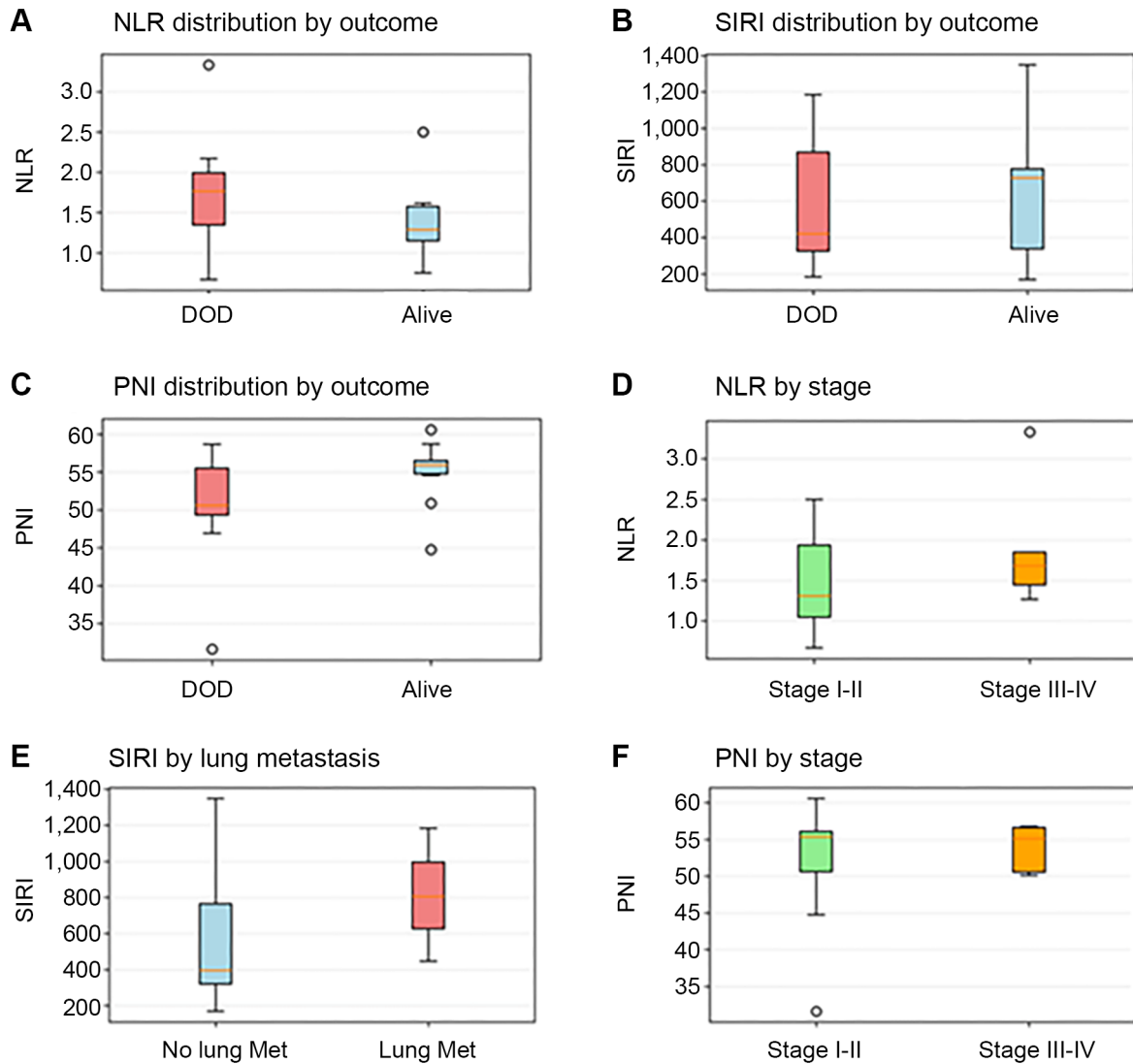


Figure 2. Distribution of inflammatory and nutritional markers by survival status, stage, and metastasis. (A-C) Comparison of neutrophil-to-lymphocyte ratio (NLR), systemic inflammatory response index (SIRI), and prognostic nutritional index (PNI) between patients who died of disease (DOD) and survivors. (D) NLR in Stages I-II vs. III-IV. (E) SIRI in patients with and without lung metastasis. (F) PNI in Stages I-II vs. III-IV. Box-and-whisker plots show medians, interquartile ranges, and ranges.

Recent studies have highlighted the prognostic value of inflammation-based markers across sarcoma types. Lee *et al.* reported that both preoperative and postoperative platelet-to-lymphocyte ratios were associated with survival in soft-tissue sarcoma (23). Similarly, Araki *et al.* demonstrated that pretreatment neutrophil counts and platelet-to-lymphocyte ratios predicted metastasis in

osteosarcoma (24). These findings support the relevance of systemic inflammatory markers in sarcoma biology and align with our observation that NLR and SIRI tended to be elevated in advanced disease, although they did not reach statistical significance in our cohort.

In addition, treatment-related prognostic factors have been emphasized in recent osteosarcoma literature.

Table VI. Log-rank test in Kaplan–Meier analysis.

| Factors/Indicators | Cut-off value | Log-rank p-Value | Significance |
|---|---------------|------------------|--------------|
| Inflammation and nutritional indicators | | | |
| PNI | 55.20 | 0.0880 | BL |
| NLR | 1.45 | 0.2813 | n.s. |
| SIRI | 584.97 | 0.3207 | n.s. |
| Clinical factors | | | |
| Lung metastasis | – | 0.0629 | BL |
| Stage (I-II vs. III-IV) | – | 0.0797 | BL |

BL: Borderline ($0.05 < p < 0.10$); n.s.: not significant. NLR: Neutrophil-to-lymphocyte ratio; SIRI: systemic inflammation response index; PNI: prognostic nutritional index.

Table VII. Multivariate Cox regression analysis results (lung metastasis, stage-adjusted).

| Model | Variable | Hazard ratio | 95%CI | p-Value |
|---|-----------------|--------------|--------------|---------|
| Model 1 | | | | |
| NLR + Lung metastasis + Stage (C-index=0.639) | NLR | 0.968 | 0.399-2.348 | 0.942 |
| | Lung metastasis | 1.987 | 0.283-13.941 | 0.490 |
| | Stages III-IV | 1.846 | 0.331-10.293 | 0.484 |
| Model 2 | | | | |
| SIRI + Lung metastasis + Stage (C-index=0.676) | SIRI | 0.999 | 0.997-1.001 | 0.419 |
| | Lung metastasis | 2.145 | 0.337-13.653 | 0.419 |
| | Stages III-IV | 2.006 | 0.352-11.418 | 0.433 |
| Model 3 | | | | |
| PNI + Lung metastasis + Stage (C-index=0.704) | PNI | 0.939 | 0.861-1.023 | 0.151 |
| | Lung metastasis | 1.841 | 0.287-11.804 | 0.520 |
| | Stages III-IV | 2.134 | 0.360-12.634 | 0.404 |

CI: Confidence interval; NLR: neutrophil-to-lymphocyte ratio; SIRI: systemic inflammatory response index; PNI: prognostic nutritional index.

Kyriazoglou *et al.* reported that $\geq 90\%$ tumor necrosis after chemotherapy strongly correlated with disease-free survival (25), underscoring the importance of treatment response. Furthermore, Restrepo *et al.* identified several clinical factors associated with survival in upper-limb osteosarcoma (26), suggesting that anatomical and biological heterogeneity may influence outcomes. These reports highlight the need for multifactorial prognostic models, supporting our conclusion that integrating stage, metastasis status, and nutritional indicators such as PNI may enhance prognostic accuracy.

Conclusion

In this study of 18 osteosarcoma cases, tumor stage emerged as the most important prognostic factor,

and lung metastasis was also identified as a strong indicator of poor prognosis. Although PNI alone was not a statistically significant prognostic factor, Kaplan–Meier analysis demonstrated a borderline significant difference, with lower values observed in the DOD group. The PNI-adjusted model showed the highest predictive accuracy (C-index=0.704), suggesting its clinical utility as an indicator of nutritional status. Although NLR and SIRI were not significant prognostic factors, both tended to be elevated in advanced-stage disease and in patients with lung metastases, suggesting an association with tumor progression. An integrated risk assessment combining stage, lung metastasis, and PNI may be useful for prognostic prediction and personalized treatment strategies in osteosarcoma, although further validation through large-scale prospective studies is required.

Conflicts of Interest

There are no conflicts of interest to disclose regarding this study.

Authors' Contributions

Conceptualization, K.H., S.N., and K.G.; methodology, K.H. and S.N.; software, K.H., and K.G.; validation, S.N. and K.G.; formal analysis, K.H., S.N., and K.G.; investigation, K.H., S.N., and K.G.; data curation, K.H., S.N., and K.G.; writing – original draft preparation, K.H., S.N., and K.G.; writing – review and editing, K.H., S.N., and K.G. All Authors have read and agreed to the published version of the manuscript.

Acknowledgements

The Authors express our deepest gratitude to the patients who participated in this study and their families.

Funding

No funding was received for conducting this study.

Artificial Intelligence (AI) disclosure

Portions of this document were created with the assistance of AI tools for the purpose of improving textual expression. AI was not used for medical judgment or clinical decision-making, and the author has taken responsibility for verifying the accuracy and validity of the content described.

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