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Research Article

Beyond conventional staging: prognostic significance of systemic inflammatory indices at diagnosis in malignant peripheral nerve sheath tumors

Geleneksel evrelemenin ötesinde: malign periferik sinir kılıfı tümörlerinde tanı anındaki sistemik enflamatuar indekslerin prognostik önemi

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Abstract

Aim: Malignant Peripheral Nerve Sheath Tumors (MPNSTs) are rare soft tissue sarcomas characterized by aggressive behavior and high recurrence rates. Conventional TNM staging may sometimes be insufficient to predict survival differences among patients with a similar tumor burden. The aim of this study was to investigate the prognostic value of systemic inflammatory indices at diagnosis in patients with MPNST and to determine whether these indices represent prognostic biomarkers independent of classical prognostic factors.

Material and Methods: A total of 43 patients with histopathologically confirmed MPNST were retrospectively analyzed. Demographic characteristics, tumor-related features, and inflammatory indices derived from pretreatment complete blood count parameters were recorded. Factors affecting overall survival (OS) were evaluated using Kaplan–Meier survival analysis and Cox proportional hazards regression models.

Results: At the end of the median follow-up period, the median OS for the entire cohort was 25.7 months. In univariate analyses, the presence of metastasis ($p = 0.005$), a high platelet-to-lymphocyte ratio (PLR) ($p < 0.001$), and a high systemic immune-inflammation index (SII) ($p = 0.012$) were significantly associated with poor survival, whereas tumor size–based T stage (T1–T2 vs. T3–T4) did not show a significant impact on survival ($p = 0.446$). In multivariate Cox regression analysis, even after adjustment for metastatic status and T stage, high PLR (hazard ratio [HR]: 3.61, 95% confidence interval [CI]: 1.53–8.50, $p = 0.003$) and high SII (HR: 2.95, 95% CI: 1.35–6.44, $p = 0.006$) remained independent and strong risk factors for OS.

Conclusion: PLR and SII at diagnosis are simple, readily available, and powerful prognostic biomarkers in patients with MPNST, independent of tumor burden as reflected by T stage. These indices may assist clinicians in identifying high-risk patients beyond conventional staging systems and may contribute to the personalization of treatment strategies.

Keywords: malignant peripheral nerve sheath tumor. platelet-to-lymphocyte ratio. systemic immune-inflammation index. prognosis

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Öz

Amaç: Malign Periferik Sinir Kılıfı Tümörleri (MPNST), agresif seyirli ve yüksek nüks oranına sahip nadir yumuşak doku sarkomlarıdır. Klasik TNM evrelemesi, benzer tümör yüküne sahip hastalardaki sağkalım farklılıklarını öngörmede bazen yetersiz kalmaktadır. Bu çalışmanın amacı, tanıdaki sistemik inflamatuvar indekslerin MPNST hastalarındaki prognostik değerini araştırmak ve klasik prognostik faktörlerden bağımsız birer belirteç olup olmadıklarını ortaya koymaktır.

Gereç ve Yöntemler: Histopatolojik olarak MPNST tanısı alan 43 hasta retrospektif olarak incelendi. Hastaların demografik verileri, tümör özellikleri ve tedavi öncesi hemogram parametrelerinden türetilen inflamatuvar indeksler kaydedildi. Genel sağkalımı (OS) etkileyen faktörler Kaplan-Meier ve Cox regresyon analizleri ile değerlendirildi.

Bulgular: Medyan takip süresi sonunda tüm kohort için medyan sağkalım 25,7 aydı. Tek değişkenli analizlerde metastaz varlığı (p = 0,005), yüksek platelet/lenfosit oranı (PLR) (p < 0,001) ve yüksek sistemik inflamatuvar indeks (SII) (p = 0,012) kötü sağkalım ile ilişkili bulunurken; tümör boyutuna dayalı T evresinin (T1-T2 vs T3-T4) sağkalım üzerinde anlamlı bir etkisi izlenmedi (p = 0,446). Çok değişkenli Cox regresyon analizinde; metastaz durumu ve T evresi için düzeltme yapıldığında dahi, yüksek PLR (HR: 3,61, %95 CI: 1,53-8,50, p = 0,003) ve yüksek SII (HR: 2,95, %95 CI: 1,35-6,44, p = 0,006) genel sağkalım için bağımsız ve güçlü birer risk faktörü olarak saptandı.

Sonuçlar: Tanıdaki PLR ve SII, MPNST hastalarında tümör yükünden (T evresi) bağımsız, kolay uygulanabilir ve güçlü prognostik biyobelirteçlerdir. Bu indeksler, klasik evreleme sistemlerinin ötesinde yüksek riskli hastaların belirlenmesinde ve tedavi stratejilerinin kişiselleştirilmesinde klinisyenlere rehberlik edebilir.

Anahtar Kelimeler: malign periferik sinir kılıfı tümörü, trombosit-lenfosit oranı, sistemik immün-enflamasyon indeksi, prognoz

Introduction

Malignant Peripheral Nerve Sheath Tumors (MPNSTs) are rare and aggressive malignancies arising from Schwann cells or their precursors within peripheral nerves, accounting for approximately 5-10% of all soft tissue sarcomas [1,2]. Nearly half of cases develop in the setting of Neurofibromatosis Type 1 (NF1), while the remaining cases occur sporadically or, less frequently, following radiotherapy [3,4]. These tumors typically present as deeply located soft tissue masses and are most commonly observed along the sciatic nerve in the lower extremities, the trunk, or the brachial plexus region [5].

The cornerstone of treatment for malignant peripheral nerve sheath tumors is wide surgical resection with negative margins; however, despite aggressive surgery and multimodal treatment approaches including radiotherapy and chemotherapy prognosis remains poor [6,7]. Due to high rates of local recurrence and distant metastasis, reported 5-year OS rates range between 20% and 50% [8,9]. Traditional clinicopathological prognostic factors such as tumor size, anatomical location, surgical margin status, and the presence of NF1 have been shown to have prognostic significance in multiple studies [10,11]. Nevertheless, the marked variability in survival outcomes even among patients with similar TNM stage and clinical characteristics has highlighted the need for novel, easily accessible prognostic biomarkers that more accurately reflect tumor biology and host response [12].

The interaction between the tumor microenvironment and the systemic inflammatory response plays a critical role in cancer progression [13]. Neutrophils and platelets promote tumor cell proliferation, angiogenesis, and metastasis through the secretion of growth factors such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) as well as pro-inflammatory cytokines, whereas lymphocytes represent a fundamental component of antitumor immune surveillance and tumor control [14]. Inflammatory indices such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), which can be readily calculated from a simple peripheral blood count, are considered robust indicators reflecting the balance between systemic inflammation and immune status of the host [15,16]. In the literature, elevated NLR and PLR levels have been shown to be associated with reduced response to chemotherapy and immunotherapy in non-small cell lung cancer, while high SII scores have been directly correlated with greater depth of tumor invasion and lymph node metastasis in gastric and colorectal cancers, as demonstrated in large-scale meta-analyses [17]. Despite the well-established prognostic relevance of these indices in many solid tumors, studies evaluating their role specifically in patients with MPNST remain extremely limited.

Although the prognostic significance of systemic inflammatory indices has been demonstrated across a wide range of solid tumors particularly lung, gastric, and colorectal cancers data regarding their prognostic role in MPNST, are scarce [2,15]. Therefore, the aim of the present study was to investigate the prognostic value of systemic inflammatory indices at diagnosis including SII, PLR, NLR, PIV (pan-immune-inflammation value), SIRI (systemic inflammation response index), MLR (monocyte-to-lymphocyte ratio) and HRR (hemoglobin to red cell distribution width ratio) on OS in patients with histopathologically confirmed MPNST, and to determine whether these indices represent prognostic biomarkers independent of classical clinicopathological risk factors.

Material and Methods

Patients diagnosed and treated between January 2009 and October 2021 were included in the study cohort. Patients' demographic characteristics (age and sex) and tumor anatomical localization (trunk, extremity, head and neck) were retrospectively obtained from hospital medical records. Inclusion criteria were: (1) age ≥18 years, (2) histopathological confirmation of MPNST, (3) availability of complete clinical records, and (4) availability of pretreatment complete blood count (CBC) data obtained within one week prior to biopsy or surgery. Exclusion criteria were: (1) presence of active infection or inflammatory disease at the time of blood sampling, (2) concomitant hematological malignancy, (3) chronic steroid or immunosuppressive drug use, and (4) missing or incomplete laboratory or follow-up data. In histopathological evaluation, tumor size was recorded as the largest macroscopic diameter (in centimeters) of the resection specimen, and tumors were classified according to the American Joint Committee on Cancer (AJCC) 8th Edition TNM staging system (T1-T4) [18]. In patients with metastatic disease who did not undergo surgery, primary tumor size was determined using imaging modalities, including computed tomography (CT), positron emission tomography–computed tomography (PET-CT), and magnetic resonance imaging (MRI). For patients who underwent surgical treatment, surgical margin status was categorized as R0 (negative microscopic margins), R1 (microscopically positive margins), or R2 (macroscopic residual disease). Regarding systemic treatment data, neoadjuvant and adjuvant treatment status, chemotherapy lines administered during the metastatic course (first-line, second-line, and subsequent lines), and specific chemotherapy regimens or targeted therapies used (anthracycline/ifosfamide, gemcitabine/docetaxel, pazopanib, etc.) were recorded in detail.

In all patients, complete blood count (CBC) results obtained from venous blood samples collected within one week prior to surgery or biopsy were used for analysis. Absolute neutrophil, lymphocyte, monocyte, and platelet counts were recorded. Using these parameters, systemic inflammatory indices were calculated according to the following formulas: Neutrophil-to-Lymphocyte Ratio (NLR): Absolute neutrophil count / Absolute lymphocyte count, Platelet-to-Lymphocyte Ratio (PLR): Absolute platelet count / Absolute lymphocyte count, Systemic Immune-Inflammation Index (SII): (Absolute platelet count × Absolute neutrophil count) / Absolute lymphocyte count, Systemic Inflammation Response Index (SIRI): (Absolute neutrophil count × Absolute monocyte count) / Absolute lymphocyte count, Pan-Immune-Inflammation Value (PIV): (Absolute neutrophil count × Absolute platelet count × Absolute monocyte count) / Absolute lymphocyte count, Monocyte-to-Lymphocyte Ratio (MLR): Absolute monocyte count / Absolute lymphocyte count, Hemoglobin-to-Red Cell Distribution Width Ratio (HRR): Hemoglobin / Red Cell Distribution Width.

This study was conducted under the institutional research committee's ethical standards and with the 1964 Helsinki Declaration. This study was approved by the clinical research ethics committee of the Bursa Uludag University Faculty of Medicine (Decision No: 2022-5/26, dated March 2, 2022).

Statistical Analysis

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences), version 25.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Continuous variables were presented as mean ± standard deviation or median (minimum–maximum), while categorical variables were expressed as numbers (n) and percentages (%). OS was defined as the time from the date of diagnosis to the date of death or last follow-up, disease-free survival (DFS) was defined as the time from surgical treatment to recurrence or progression, and progression-free survival (PFS) was defined as the time from diagnosis to tumor progression or death for patients with metastatic diseas. Survival analyses were performed using the Kaplan–Meier method, and differences between groups were compared using the log-rank test. Univariate and multivariate Cox proportional hazards regression analyses were conducted to identify independent prognostic factors affecting survival. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the prognostic performance of inflammatory indices for mortality. To minimize statistical bias and overfitting, optimal cut-off values for both SII and PLR were determined using the Youden Index. A p-value < 0.05 was considered statistically significant.

Results

A total of 43 patients were included in the study. The median age was 42.4 years (range: 19.0–80.4), and 27 patients (62.8%) were male. Tumor localization was most commonly observed in the trunk (22 patients, 51.2%) and the lower extremities (10 patients, 23.3%). Neurofibromatosis type 1 was present in 9 patients (20.9%). At the time of diagnosis, 32 patients (74.4%) had non-metastatic (localized) disease, while 11 patients (25.6%) presented with metastatic disease. Histopathological evaluation revealed a median tumor size of 10 cm (range: 1.7–78.0 cm). Among the 40 patients who underwent surgical treatment, negative surgical margins (R0) were achieved in 25 patients (62.5%), while microscopic positive margins (R1) were observed in 10 patients (25.0%) and macroscopic residual disease (R2) in 5 patients (12.5%) (Table 1).

Table 1. Demographic and clinical characteristics of patients.

Characteristic	n	%
Age (median, min-max)	42.4 (19.0 - 80.4)	
Sex		
Male	27	62.8
Female	16	37.2
Tumor localization		
Trunk	22	51.2
Lower extremity	10	23.2
Upper extremity	5	11.6
Head and Neck	6	14.0
Tumor size, cm (median, min-max)	10 (1.7 – 78.0)	
NF1 status		
Sporadic	34	79.1
NF1 associated	9	20.9
Metastatic disease at diagnosis		
Non-Metastatic	32	74.4
Metastatic	11	25.6
Surgical Status		
Operated	40	93.0
Non-operated	3	7.0
Surgical Margin		
R0	25	62.5
R1	10	25.0
R2	5	12.5
T stage		
T1	7	16.3
T2	7	16.3
T3	12	27.9
T4	17	39.5
Chemotherapy		
Neoadjuvant	7	16.3
Adjuvant	20	46.5
Recurrent/Metastatic	28	65.1

Abbrev.: NF1: Neurofibromatosis type 1; R0: negative surgical margin; R1: microscopically positive margin; R2: macroscopic residual disease; T: tumor (TNM staging).

Pretreatment hematological parameters and the distribution of systemic inflammatory indices derived from these parameters are summarized in Table 2. Accordingly, the median values were determined as 2.99 for NLR, 153.3 for PLR, 686.6 for SII, 384.5 for PIV, 1.66 for SIRI, 0.36 for MLR, and 0.91 for HRR.

At the end of the follow-up period, 30 patients (69.8%) died. The median OS for the entire cohort was 25.7 months. When clinical subgroups were evaluated, the median DFS and median OS were 22.2 months and 31.1 months, respectively, in the non-metastatic group, whereas the metastatic group demonstrated a median PFS of 7.7 months and a median OS of 17.4 months. Kaplan-Meier survival analysis revealed that patients with metastatic disease at diagnosis had significantly shorter overall survival (OS) compared to non-metastatic patients (p=0.005, Figure 1A). In contrast, T-stage based on tumor size (T1-T2 vs. T3-T4) did not show a statistically significant difference in OS (p=0.446, Figure 1B). Regarding inflammatory indices, the optimal cut-off values were determined using the Youden Index. Patients with elevated PLR (>153.3) demonstrated significantly poor prognosis (p=0.001, Figure 1C). Similarly, high SII levels (>677.4) were significantly associated with worse survival outcomes compared to the low SII group (p=0.013, Figure 1D). Receiver Operating Characteristic (ROC) curve analysis was performed to determine the optimal cut-off values for inflammatory indices in predicting mortality (Figure 2). The PLR demonstrated a strong predictive value with an Area Under the Curve (AUC) of 0.710. The optimal cut-off value determined by the Youden Index was 153.3, yielding a sensitivity of 78.9% and a specificity of 75.0%. The SII showed an AUC of 0.654, with an optimal cut-off value of 677.4 (sensitivity: 63.3%, specificity: 69.2%).

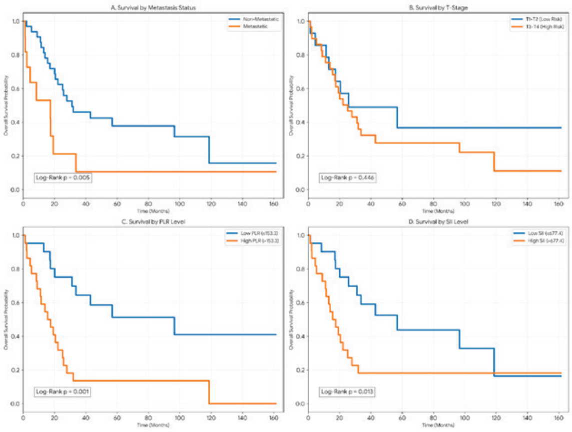

Figure 1. Kaplan-Meier survival estimates for overall survival (OS) in MPNST patients. (A) Stratification by metastatic status (Blue: Non-Metastatic, Orange: Metastatic; p=0.005). (B) Stratification by T-Stage (Blue: T1-T2 / Low Risk, Orange: T3-T4 / High Risk; p=0.446). (C) Stratification by PLR levels with an optimal cut-off of 153.3 (Blue: Low PLR ≤153.3, Orange: High PLR >153.3; p=0.001). (D) Stratification by SII levels with an optimal cut-off of 677.4 (Blue: Low SII ≤677.4, Orange: High SII >677.4; p=0.013). P-values were calculated using the Log-Rank test.

The results of univariate and multivariate Cox proportional hazards regression analyses evaluating factors affecting OS are summarized in Table 3. In univariate analyses, no statistically significant association was observed between OS and NLR, MLR, SIRI, HRR or PIV levels ($p > 0.05$). While adjuvant therapy showed a marginal association with survival (p=0.043), other factors such as surgical margin (p=0.314), NF1 status (p=0.316), and neoadjuvant therapy (p=0.217) did not reach statistical significance. However, PLR and SII were identified as significant prognostic factors. The presence of metastasis (hazard ratio [HR]: 3.05, p = 0.008), absence of surgical treatment (HR: 0.28, p = 0.044), high PLR (HR: 3.71, p = 0.001), and high SII (HR: 2.54, p = 0.016) were significantly associated with OS. Even after adjustment for T stage and metastatic status in multivariate models (Model 1 and Model 2), high PLR (HR: 3.61, 95% confidence interval [CI]: 1.53–8.50, p = 0.003) and high SII (HR: 2.95, 95% CI: 1.35–6.44, p = 0.006) remained independent and strong prognostic factors for poor OS.

The distribution of chemotherapy regimens administered according to treatment lines is detailed in Table 4. In the neoadjuvant (7 patients, 16.3%) and adjuvant (20 patients, 46.5%) settings, the most frequently used regimen was the standard sarcoma protocol consisting of ifosfamide, mesna and doxorubicin (AIM). In patients treated for metastatic or recurrent disease, gemcitabine-based or anthracycline-based regimens were most commonly used as first-line therapy. In the second-line setting, the use of the tyrosine kinase inhibitor pazopanib was particularly prominent, administered in 11 patients (64.7%).

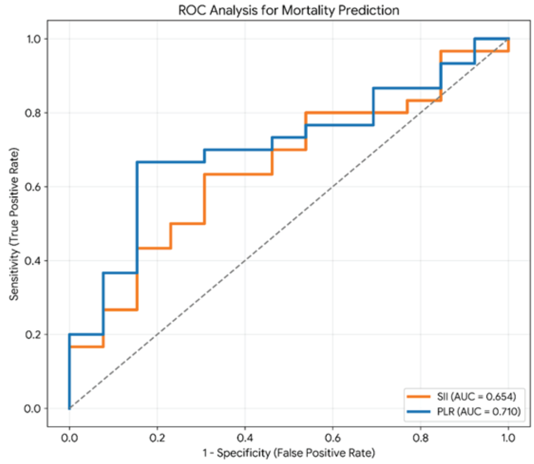

Figure 2. Receiver Operating Characteristic (ROC) curve analysis evaluating the predictive performance of inflammatory indices for overall survival. The optimal cut-off values were determined using the Youden Index. The PLR (blue line) showed an AUC of 0.710 with a cut-off of 153.3, while the SII (orange line) showed an AUC of 0.654 with a cut-off of 677.4.

Table 2. Hematological parameters and systemic inflammatory indices at diagnosis.

Parameter / Index	Median (Min - Max)
Hematological parameters	
Neutrophils (103/μL)	5.64 (0.10 - 15.70)
Lymphocytes (103/μL)	1.75 (0.10 - 20.90)
Monocytes (103/μL)	0.58 (0.10 - 10.30)
Thrombocytes (103/μL)	245.0 (70.0 - 564.0)
Hemoglobin (g/dL)	13.00 (6.60 - 15.90)
RDW (%)	15.10 (10.50 - 24.90)
Inflammatory indices	
NLR	2.99 (0.24 - 138.0)
PLR	153.3 (11.4 - 3910.0)
SII	686.6 (16.7 - 53958.0)
PIV	384.5 (2.2 - 9791.8)
SIRI	1.66 (0.03 - 24.7)
MLR	0.36 (0.03 - 3.00)
HRR	0.91 (0.28 - 1.35)

Abbrev.: HRR: hemoglobin-to-RDW ratio; MLR: monocyte-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; PIV: pan-immune-inflammation value; PLR: platelet-to-lymphocyte ratio; RDW: red cell distribution width; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index; μL: microliter.

Table 3. Univariate and Multivariate Cox Regression Analysis of factors affecting overall survival in patients with MPNST.			
Variable	**HR**	**%95 (CI)**	**p**
Age	1.02	1.00 - 1.05	0.096
Sex	0.73	0.35 - 1.51	0.391
NF1 status	0.61	0.23 - 1.60	0.316
Surgery (operated)	0.28	0.08 - 0.97	**0.044**
Surgical margin	1.48	0.69 – 3.16	0.314
Metastasis (present)	3.05	1.34 - 6.93	**0.008**
T stage (T3-T4)	1.37	0.61 - 3.11	0.448
Neoadjuvant treatment	1.78	0.71 – 4.43	0.217
Adjuvant treatment	0.45	0.21 – 0.97	**0.043**
PLR	3.71	1.69 - 8.16	**0.001**
SII	2.54	1.19 - 5.44	**0.016**
Multivariate Model 1			
T stage (T3-T4)	0.74	0.30 - 1.82	0.509
Metastasis (present)	2.51	1.07 - 5.89	**0.035**
PLR (high)	3.61	1.53 - 8.50	**0.003**
Multivariate Model 2			
T stage (T3-T4)	1.09	0.47 - 2.53	0.850
Metastasis (present)	3.63	1.52 - 8.70	**0.004**
SII (high)	2.95	1.35 - 6.44	**0.006**

Abbrev.: CI: confidence interval; HR: hazard ratio; MPNST: malign peripheral nerve sheet tumor; NF1: Neurofibromatosis type 1; PLR: platelet-to-lymphocyte ratio; SII: systemic immune-inflammation index; T: tumor.

Total number of patients: 43, Total number of events (deaths): 30

Table 4. Distribution of systemic treatment regimens according to treatment lines.		
Treatment period / line	**Regimen**	**n**
Curative-intent treatments		
Neoadjuvant Therapy	Total	7
	AIM	5
	Gemcitabine + Docetaxel	1
	Doxorubicin Monotherapy	1
Adjuvant Therapy	Total	20
	AIM	15
	Doxorubicin Monotherapy	2
	Epirubicin Monotherapy	1
	Cisplatin + Epirubicin	1
	Cisplatin + Doxorubicin	1
Metastatic / recurrent setting		
First-line therapy	Total	28
	Gemcitabine-based	11
	AIM	10
	Other	7
Second-line therapy	Total	17
	Pazopanib	11
	Gemcitabine-based	4
	Other	2
Third-line therapy	Total	4
	Gemcitabine-based	2
	Pazopanib	1
	Oral Etoposide	1
Fourth-line therapy	Gemcitabine-based	1

Abbrev.: AIM: ifosfamide–mesna–doxorubicin; n: number of patients.

Discussion

In this study, we investigated the prognostic value of inflammatory indices at the time of diagnosis in patients with MPNST, a rare and aggressive subtype of soft tissue sarcoma. The most significant finding of our analysis was that elevated PLR and SII levels remained independent and negative prognostic factors of OS even after adjustment for powerful conventional prognostic factors such as tumor burden–related T stage and the presence of metastatic disease. These findings suggest that, in MPNST, not only anatomical tumor characteristics but also the host's systemic inflammatory response play a critical role in determining disease outcomes.

The demographic and clinical characteristics of our patient cohort were largely consistent with previously published data. The observed NF1 association rate of 20.9% aligns with the 20–50% range reported by Stucky et al., Ducatman et al., and Kolberg et al. [3,8,9]. Similarly, the median OS of 25.7 months in our series parallels the outcomes reported by Evans et al., while appearing slightly more favorable than those observed in NF1-associated cohorts reported by Valeyrie-Allanore et al.; this difference may be attributed to the relatively higher proportion of sporadic cases in our study population [4,10].

The role of systemic inflammation in cancer prognosis is mediated through complex interactions between the tumor microenvironment and the host immune system. In the present study, PLR emerged as the strongest independent prognostic factor (HR: 3.61), a finding that may be explained by the pivotal role of platelets in MPNST pathogenesis. Platelets are not merely passive components of hemostasis but active biological modulators that promote tumor progression. Activated platelets within the tumor microenvironment secrete potent cytokines and growth factors, including transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF), thereby enhancing tumor cell proliferation and neoangiogenesis [2,7]. Given the frequent expression of platelet-derived growth factor receptor (PDGFR) and c-Kit in MPNST cells, elevated platelet counts may serve as a biological "fuel" sustaining autocrine and paracrine signaling loops that facilitate tumor growth. Moreover, circulating tumor cells can be shielded by platelets from natural killer cell–mediated immune destruction, thereby promoting metastatic dissemination and facilitating adhesion at distant sites [12]. While previous studies have emphasized the importance of the tumor microenvironment and immune evasion mechanisms in MPNST biology, our findings provide clinical evidence that PLR a surrogate marker reflecting these biological processes represents a powerful prognostic biomarker in this tumor entity. [12]. Conversely, lymphocytes, which constitute the denominator of the PLR formula, represent key effector cells of antitumor immunity, including $CD4^{+}$ helper T cells and $CD8^{+}$ cytotoxic T lymphocytes. Lymphopenia reflects an impaired host immune response against tumor cells and may indicate the activation of tumor-driven immune escape mechanisms. Therefore, elevated PLR and SII values do not merely signify heightened inflammation but rather reflect a state of biological imbalance characterized by increased tumor-promoting factors (platelets and neutrophils) alongside a collapse of antitumor immune defense (lymphocytes). This imbalance may explain the strong association between these indices and poor survival outcomes observed in our cohort.

The SII, which integrates neutrophil, platelet, and lymphocyte counts into a single composite score, has been proposed as a more comprehensive marker reflecting the balance between tumor burden and host immune competence [16]. Our study is among the limited number of investigations validating the prognostic relevance of SII specifically in the MPNST population. Notably, the persistence of SII as a significant prognostic factor in multivariate models in which T stage lost statistical significance ($p = 0.006$) supports the hypothesis that the biological aggressiveness of the tumor, as reflected by systemic inflammatory markers, may outweigh physical tumor size in determining clinical outcomes.

Most previous studies in the literature have primarily focused on the diagnostic utility of inflammatory indices. For instance, Mısırlıoğlu et al. highlighted the potential role of NLR and PLR in distinguishing MPNST from benign peripheral nerve sheath tumors [15], whereas Krawczyk et al. reported limited discriminatory power of PLR in a pediatric MPNST cohort [19]. In contrast, our study demonstrates that PLR serves as a robust prognostic indicator in an adult-predominant population, outperforming conventional T stage–based risk stratification. To the best of our knowledge, this study is among the first to demonstrate that PLR and SII possess superior and independent prognostic value compared to classical TNM staging parameters in patients with MPNST. These findings underscore the clinical relevance of systemic inflammatory indices as robust biomarkers for risk stratification and outcome prediction. Prior studies have explored the systemic immune-inflammation index (SII) as a prognostic biomarker in various cancers. Specifically, Hou et al. demonstrated that an elevated preoperative SII was independently associated with worse overall survival in soft tissue sarcoma patients following radical surgery [20]. Other systematic assessments have reaffirmed the potential of SII as a prognostic marker across solid tumors, including sarcoma subgroups [21]. However, evidence specific to MPNST remains limited, highlighting the need for further disease-specific studies.

An evaluation of treatment patterns in our cohort revealed that the use of anthracycline–ifosfamide–based regimens in the neoadjuvant and adjuvant settings, as well as gemcitabine-based regimens in metastatic disease, was consistent with current sarcoma treatment guidelines. The prominent use of pazopanib in the second-line setting (64.7%) reflects real-world clinical practice and aligns with previous reports emphasizing the potential efficacy of angiogenesis inhibition in advanced MPNST [14]. Given the established link between platelets and VEGF signaling, the observed association between elevated PLR and poor prognosis indirectly supports the biological rationale for antiangiogenic therapies, such as pazopanib, in high-risk patient subgroups.

Limitations of the Study

This study has several limitations inherent to its retrospective and single-center design. First, the rarity of MPNST resulted in a relatively small sample size (n=43), which may limit the statistical power and the generalizability of our findings to broader populations. Second, although we utilized the Youden Index to determine optimal cut-off values for inflammatory indices, these thresholds are specific to our study cohort and lack external validation. Consequently, population-specific biases cannot be ruled out, and large-scale validation studies are required to establish standardized cut-off values. Third, inflammatory indices were assessed at a single time point at diagnosis; therefore, the potential prognostic value of dynamic changes in these markers during treatment could not be evaluated. Fourth, despite our careful review, potential confounding factors such as subclinical infections, concomitant inflammatory conditions, or medication use that might transiently influence hematological parameters could not be fully excluded. Finally, the heterogeneity of treatment modalities across neoadjuvant, adjuvant, and metastatic settings may have influenced survival outcomes, although we attempted to adjust for these factors in our analysis.

In conclusion, elevated PLR and SII levels at diagnosis represent strong, independent, and easily accessible prognostic biomarkers for OS in patients with MPNST, independent of established risk factors such as T stage and metastatic status. In addition to PLR and SII, our study provides preliminary evidence regarding the potential prognostic relevance of emerging inflammatory indices such as PIV and HRR in MPNST. To the best of our knowledge, these markers have not been previously evaluated in MPNST-focused cohorts and warrant further validation in larger, prospective studies. These simple hematological parameters may assist clinicians in the early identification of patients with aggressive disease behavior and could potentially inform decisions regarding intensified multimodal treatment strategies or closer surveillance protocols.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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Ethics approval

This study was approved by the clinical research ethics committee of the Bursa Uludag University Faculty of Medicine (Decision No: 2022-5/26, dated March 2, 2022).

Authors' contributions

Concept and design: S.O.O., B.O., B.C. Data collection and processing: B.O., S.S., B.C., F.B.D., A.B.Ş. Analysis and interpretation: S.O.O., A.D., E.Ç., T.E. Literature search: B.O., S.S., F.B.D., E.Ç., T.E. Manuscript writing: S.O.O., B.O., S.S., B.C., Critical revision: All authors.

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