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Potential prognostic parameters and real-world data in patients with primary central nervous system lymphoma: a new brick on the old ones

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ABSTRACT

Objectives: We aimed to evaluate the potential prognostic factors of patients with primary central nervous system lymphoma (PCNSL).

Methods: Thirty-two patients with PCNSL were retrospectively analyzed.

Results: All the patients received high doses of methotrexate-based chemotherapy as the first-line treatment. Overall survival was 30.0 ± 7.2 months. Those with partial response and without response had a higher risk of mortality. The increased leukocyte and neutrophil levels were associated with high mortality. Besides, the SIIL as a product of the systemic immune inflammation (SII) and lactate dehydrogenase (LDH); the SIRIL as a product of systemic immune response index (SIRI) and LDH; and the NLL as a product of neutrophil-lymphocyte ratio and LDH were taken into consideration for the first time for the purposes of the present study. Elevated NLL, SIIL, and SIRIL indexes were associated with mortality. Elevated SIIL level, radiotherapy, and partial and no response were the independent predictors of mortality on the basis of the multivariable regression model including the risk factors associated with mortality.

Conclusions: SIIL, SIRIL and NLL are prognostic factors in PCNSL. Determining the prognostic factors and risk profile may predict the requirement for more intensive treatment, especially in young patients at high risk.

Keywords: Primary central nervous system lymphoma, prognostic score and parameters

Primary central nervous system lymphoma (PCNSL) accounts for approximately 3% of brain tumors and 4-6% of all the extranodal lymphomas. PCNSL is an aggressive form of non-Hodgkin lymphoma (NHL), which occurs in the brain, spinal cord, eye, or leptomeninx without systemic involvement. Its annual incidence is 0.47/100.000 [1]. High dose methotrexate-based regimens are used in treatment. Although scores such as International Extranodal Lymphoma Study Group (IELSG), The Nottingham / Barcelona (NB) score and Memorial Sloan-Kettering Cancer Center (MSKCC) score are used to predict prognosis, challenges are still encountered. [2-4]. Therefore, biomarkers that can better predict prognosis need to be developed to achieve more appropriate treatment.

It is known that inflammation increases tumor risk and has an effect on all stages. Many inflammatory

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markers such as C-reactive protein (CRP), neutrophil count-lymphocyte ratio (NLR) and platelet count-lymphocyte ratio (PLR) have been associated with poor prognosis in many malignancies [5-7]. However, systemic immune inflammation index (SII), which is formed by using absolute neutrophil, platelet and lymphocyte counts in peripheral blood, and systemic immune response index (SIRI), which is formed by using neutrophilia, monocyte and lymphocyte counts, have started to be used as inflammatory biomarkers in many cancers in recent years [8-11]. Prognocytic nutritional index (PNI) is a measurement calculated by using serum albumin and absolute lymphocyte value and reflects the inflammatory, nutritional and immune status of patients with cancer. There have been studies showing the prognostic importance of PNI in many cancer types [12-14].

In our study, we analyzed the prognostic impact of inflammatory markers and SIIL, SIRIL and NLL measurements obtained by multiplying SII, SIRI and NLR by serum LDH value in PCNSL patients.

METHODS

Patient Recruitment

The demographic and clinicopathological data of 32 patients with PCNSL followed-up at Bursa Uludag University Hematology Department between 2010 and 2021 were retrospectively reviewed. The criteria for inclusion included pathologically confirmed PCNSL diagnosis and age over 18 years.

Data Collection

Clinical data included gender, age, symptoms at diagnosis, examination findings, KPS, localization and number of lesions, biopsy type, pathological subtype, Ki-67(%), Memorial Sloan-Kettering Cancer Center (MSKCC) score, lactate dehydrogenase (LDH), β2 microglobulin (B2M), sedimentation (Sed), CRP, albumin, globulin, total bilirubin, ferritin level, complete blood count, NLR, PLR, platelet count × neutrophil count/ lymphocyte count (SII), neutrophil count × monocytes count/lymphocytes count (SIRI), lymphocyte count-to-monocyte ratio (LMR), albumin-globulin ratio (AGR), serum albumin (g/L) + 5 × lymphocytes count (×109/L) [prognostic nutritional index (PNI), LDH-lymphocyte ratio (LLR), WBC-lymphocyte ratio (WLR), Ferritin-LDH ratio (FLR), CRP-albumin ratio (CAR), PLR × LDH (PLL), SII × LDH (SIIL), SIRI × LDH (SIRIL), NLR × LDH (NLL) indexes and treatment regimens and responses. The results of routine blood tests performed within one week prior to the onset of the treatment, were retrospectively retrieved from medical records. The location, number, and size of the lesions in all the patients were evaluated by means of magnetic resonance imaging (MRI).

MSKCC Score

The MSKCC model is comprised of two variables, including age and KPS, and defines three prognostic classes: Class 1 (age < 50), Class 2 (age ≥ 50 and KPS ≥ 70) and Class 3 (age ≥ 50 and KPS < 70).

Response Evaluation

Responses were evaluated according to international working group recommendations as defined by Abrey *et al*. [15].

Statistical Analysis

IBM Statistical Package for the Social Sciences (SPSS) v.20 software (IBM Corp., Armonk, NY, USA) was used for the purposes of analyses in the scope of the study. The distribution of normality hypothesis was tested using the Kolmogorov-Smirnov test. Numerical variables with and without normal distribution were expressed as mean ± standard deviation and median (min-max), respectively. The categorical variables were expressed as numbers and percentages. Univariable Cox Regression analysis was used to identify the potential risk factors associated with mortality, and the statistically significant factors were included in the multivariable regression model. ANOVA test (post hoc: Bonferroni test) and Kruskal-Wallis H test (post hoc: Dunn's test) were used to compare the numerical variables by class groups depending upon the normality of distribution. Fisher's Exact and Chi-square tests were used to compare categorical variables. A p value of < 0.05 was considered statistically significant.

RESULTS

The Entire Population and Mortality Relation

The study population was comprised of 32 patients,

Table 1. Demographic and clinical characteristics of patients

Variables	Data (n = 32)
Gender, n (%)	
Female	18 (56.3)
Male	14 (43.8)
Age (years)	54.1 ± 14.3
Female	61.1 ± 8.1
Male	45.1 ± 15.6
Number of involvements, n (%)	
Solitary	18 (56.2)
Multiple	14 (43.8)
Involvement area, n (%)	
Cerebral hemisphere	15 (46.9)
Cerebellum	3 (9.4)
Periventricular	6 (18.8)
Hemisphere	1 (3.1)
Thalamus	5 (15.6)
Corpus callosum	1 (3.1)
Eye	1 (3.1)
Involvement of deeper brain structures, n (%)	
None	18 (53.3)
Yes	14 (43.8)
Pathology/cytology, n (%)	
DLBCL	29 (90.6)
Others	3 (9.4)
Biopsy, n (%)	
SBX	19 (59.4)
EBX	13 (40.6)
Ki-67(%)	80 (20-98)
Treatment, n (%)	
MATRIX	7 (21.9)
HD-MTX	2 (6.3)
HD-MTX+RTX	1 (3.1)
HD-MTX+RTX+VINC	8 (25.0)
HD-MTX+VINC	14 (43.8)
Radiotherapy, n (%)	
None	13 (40.6)
Yes	19 (59.4)
Radiotherapy duration (days)	25 (8-45)
Response, n (%)	
Complete response	13 (40.6)
Partial response	6 (18.8)
No response	2 (6.3)
Could not be assessed	11 (34.4)
ASCT, n (%)	
None	29 (90.6)
Yes	3 (9.4)
Follow-up duration (days)	7.2 (0.2-93.8)

DLBCL = diffuse large B cell lymphoma, SBX = stereotactic biopsy, EBX = excisional biopsy, Ki-67 = proliferation index, MATRIX = high dose methotrexate+cytosine arabinoside + thiotepa + rituximab, HD-MTX = high dose methotrexate, RTX = rituximab, VINC = vincristine, ASCT = autologous stem cell transplantation

including 18 female and 14 male patients (mean age: 54.1 ± 14.3 years). The patients most frequently complained about dysphasia (n = 7; 21.9%), headache (n = 6; 18.8%), and impaired balance (n = 6; 18.8%). Paresthesia was the most prevalent manifestation during the neurological examinations (31.3%). Eighteen patients had solitary and 14 had multiple lesions. The cerebral hemisphere was the most frequently affected area (n = 15; 46.9%). Twenty-nine (90.6%) cases involved diffuse large B-cell lymphoma (DLBCL) subtype 68.8% (n = 22) of the patients died. There was no association between the demographic characteristics and mortality. Demographic and clinical characteristics of patients are shown in Table 1. Relationship between clinical findings and mortality were included in detail in.The patients with partial or no response had a higher risk of mortality compared to those with complete response (HR: 12.93, p = 0,003; HR: 10.64, p = 0.025, respectively). There was no association with other clinical findings and mortality.

Distribution of laboratory findings and their relationship with mortality included in detail in Table 2. Elevated hemoglobin level (HR: 1.42; p = 0.017), elevated leukocyte level (HR: 1.14; p = 0.050), elevated neutrophil level (HR: 1.17; p = 0.023), elevated SIIL (HR: 1.02; p = 0.008), elevated SIRIL (HR: 1.04; p = 0.021), and elevated NLL index (HR: 1.28; p = 0.037) were associated with mortality. There was no relation between other laboratory findings and mortality.

Elevated SIIL level (HR: 1.03; p = 0.019) and partial and no response (HR: 17.6, p = 0.009; HR:11.6, p = 0.004, respectively) were the independent predictors of mortality on the basis of the multivariable regression model including the potential risk factors associated with mortality. Independent predictors of mortality are included in detail in Table 3.

The median neutrophil level and SII score were lower in Class 1 patients than in the others ($p < 0.05$). Those with Class III had a higher median SII score, median PLR, median NLR, median CRP, and lower median creatinine than others. Other laboratory findings did not differ significantly between the groups. Distribution of laboratory findings by prognostic score are included in detail in Table 4.

The predictive value of the SIIL index in prediction of mortality was > 377.4 × 103 with a sensitivity of 59.1% and specificity of 100% (AUC ± SE = 0.73 ± 0.08; 95% CI = 0.546-0.872; p = 0.008) (Fig. 1A).

Table 2. Distribution of laboratory findings and their relationship with mortality

Variables	Survival			Univariable Cox regression		
	Total (n = 32)	Alive (n = 10)	Dead (n = 22)	HR	95% CI	*p* value
Hemoglobin (g/dL)	12.9 ± 1.6	11.4 ± 1.5	13.5 ± 1.0	1.42	1.06-1.90	**0.017***
Leukocyte ($\times10^3/\mu L$)	10.2 (5.1-18.8)	8.1 (6.3-13.4)	10.3 (5.1-18.8)	1.14	1.01-1.31	**0.050***
Neutrophils ($\times10^3/\mu L$)	8.7 (3.0-16.8)	6.7 (3.0-10.8)	9.0 (3.4-16.8)	1.17	1.02-1.35	**0.023***
SII	1255.3 (252.6-6283.6)	1219.3 (252.6-1585.8)	1760 (330-6283.6)	1.00	0.99-1.02	0.094
SIIL	365.8 (59.1-1994.7)	238.3 (59.1-377.4)	475.5 (90.1-1994.7)	1.02	1.01-1.03	**0.008***
SIRIL	7.1 (1.3-53.7)	4.7 (1.3-15.1)	8.9 (1.9-53.7)	1.04	1.01-1.07	**0.021***
NLL	1.8 (0.3-6.0)	1.2 (0.02-3.4)	2.2 (0.4-6.0)	1.28	1.02-1.062	**0.037***
PLL	51.5 (18.2-175.0)	25.5 (19.7-68.0)	57.1 (18.2-174.9)	1.01	0.98-1.02	0.060

Categorical variables were expressed as numbers (%). Numerical variables with and without normal distribution were expressed as mean ± SD and median (min-max), respectively. SII = systemic immune inflammation index, SIIL = SII × LDH, SIRIL = SIRI × LDH, NLL = Neutrophil/Lymphocyte × LDH, PLL = Platelet/Lymphocyte × LDH, HR = Hazard ratio, CI = Confidence interval

SII × LDH levels are divided by 1000. SIRI × LDH levels are divided by 100.

*$p < 0.05$ is considered statistically significant.

The risk of mortality was 5.9 times higher in patients with a SIIL index of > 377.4 × 103 compared to patients with a SIIL index of ≤ 377.4 x103 (HR: 5.9; $p < 0.001$) (Fig. 1B).

MSKCC Prognostic Scoring Relationship

There was a lower rate of male patients as MSKCC prognostic score increased ($p = 0.031$). There was no relation between other demographic character-

Table 3. Independent predictors of mortality

Variables	Multivariable Cox regression		
	HR	95% CI	*p* value
SIIL	1.03	1.01-1.05	**0.019***
Radiotherapy			
None	ref		
Yes	0.15	0.02-0.34	**< 0.001***
Response			
Complete response	ref		
Partial response	12.8	1.6-103.8	**0.017***
No response	12.2	1.9-75.7	**0.007***
Could not be assessed	40.6	0.1-728.3	0.893

SIIL = SII × LDH, HR = Hazard ratio, CI = Confidence interval.

2 Log Likelihood: 82.2; $p < 0.001$

*$p < 0.05$ is considered statistically significant.

Table 4. Distribution of laboratory findings by prognostic score

Variables	MSKCC Class			*p* value
	1 (n = 7)	2 (n = 14)	3 (n = 11)	
Leukocyte (×10^3/µL)	7.6 (5.1-14.6)	10.2 (6.3-18.8)	11.5 (6.8-18.0)	0.061
Neutrophils (×10^3/µL)	4.9 (3.6-9.7)	8.7 (3-16.8)	9.3 (5.9-16.4)	**0.029***
CRP	0.3 (0-0.4)	0.3 (0.3-5.8)	0.9 (0.1-42)	**0.030***
SII	619.3 (330-1503.5)	1255.3 (252.6-6283.6)	1857.4 (946,7-4199.4)	**0.007***
PLR	117.1 (66.5-227.1)	133.2 (84.2-667.8)	191.5 (106.4-368.4)	**0.048***
NLR	3.3 (2-7.9)	5.6 (1.2-30.7)	11.2 (2.9-20.8)	**0.019***
LLR, %	3.9 (2.3-6.9)	2.4 (1.4-10.5)	2 (1.2-4.5)	0.064
WLR	0.5 (0.3-0.9)	0.7 (0.2-3.4)	1.2 (0.4-2.3)	**0.024***
CAR	0.1 (0-0.1)	0.1 (0.1-1.5)	0.3 (0-11.7)	**0.050***
LNR	0.7 (0.6-0.9)	0.7 (0.5-0.9)	0.9 (0.7-0.9)	**0.029***
SIIL	209.5 (90.1-401.5)	316.1 (59.1-1237.8)	780.1 (148.3-1994.7)	0.062
NLL	1.7 (0.5-2)	1.6 (0.3-6)	3.4 (0.4-5.5)	0.094

Categorical variables were expressed as numbers (%). Numerical variables with and without normal distribution were expressed as mean ± SD and median (min-max), respectively.

MSKCC = Memorial Sloan-Kettering Cancer Center score, SII = systemic immune inflammation index, SIRI = systemic immune response index, PLR = platelet-lymphocyte ratio, NLR = neutrophil-lymphocyte ratio, LLR = LDH/lymphocyte ratio, WLR = WBC/lymphocyte ratio, CAR = CRP/albumin ratio, LNR = Lymphocyte/neutrophil ratio, SIIL = SII × LDH, SIRIL = SIRI × LDH, NLL = Neutrophil/Lymphocyte × LDH, HR = Hazard ratio, CI = Confidence interval

*$p < 0.05$ is considered statistically significant.

istics and clinical findings and prognostic score. Patients classified under MSKCC class 1, had lower median neutrophil and median SII scores compared to the others ($p < 0.05$). Patients classified under Class 3 had higher median CRP level, median SII score, median PLR level, median NLR level, median WLR level, median CAR level, and median LNR level and lower median creatinine compared to others. There was no significant difference by other laboratory findings between the groups.

DISCUSSION

There is growing evidence that cancer-related inflammation (CRI) may promote malignant cell proliferation, invasion, and metastasis [16, 17]. Tumor-related macrophages play a leading role in CRI, the prognostic value of which has been demonstrated as regards a number of lymphoproliferative malignancies [18]. The prognostic value of other systemic inflammation response indicators represented by NLR and LMR has also been verified in several cancers [19-22]. Neutrophils as a part of the innate immune system may promote oncogenesis and suppress the function of lymphocytes that work for antitumor immunity [23]. Monocytes, which can be recruited by large B-cell lymphoma cells through CCL5 that adhere leukocytes, may promote the survival and proliferation of tumor cells [24].

In a study on 60 patients with PCNSL, the LMR (HR 6.195, $p = 0.093$), SII (HR 5.144, $p = 0.012$), and total bilirubin level (HR: 3.892, $p = 0.009$) were suggested as the independent risk factors for OS [25]. Nevertheless, NLR and LMR were not associated with mortality in the present study. Yet, elevated NLL index (HR: 1.28; $p = 0.037$), a product of NLR value and LDH, was associated with mortality.

In an in vitro experiment, platelets activated tumor cell invasion by increasing the secretion of metalloproteinase-9 (MMP-9) [26]. However, there was no correlation in the present study between platelet counts

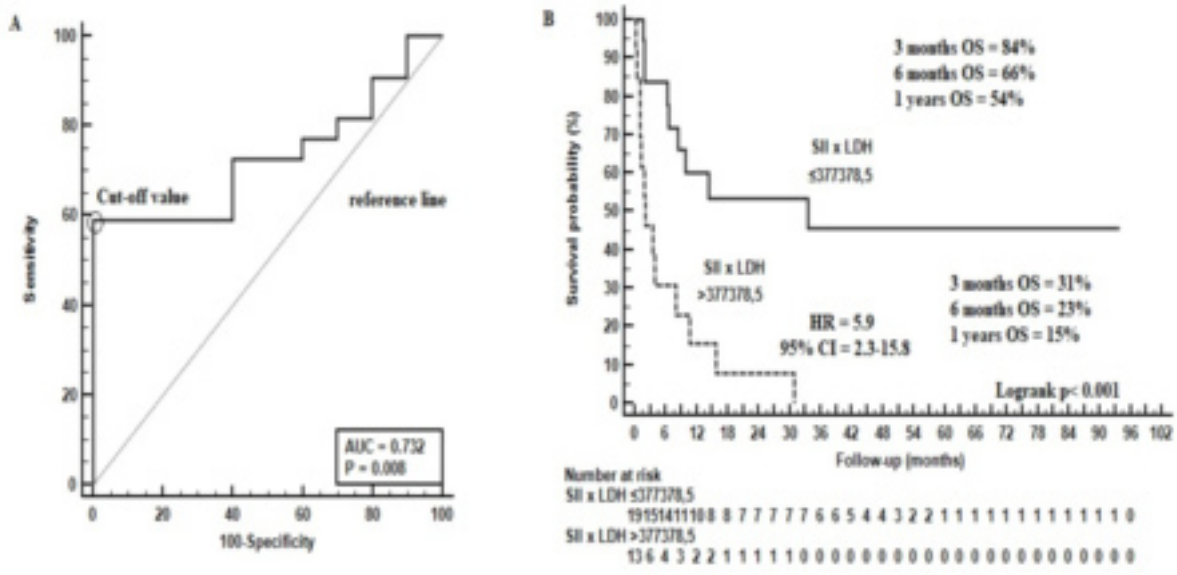

Fig. 1. **(A) SIIL diagnostic performance assessment and (B) survival risk based on the predictive value. SIIL = SII × LDH**

and PLR, and mortality.

In a study, which retrospectively investigated 73 patients with PCNSL, both age and MSKCC scores were correlated with lower progression-free survival (PFS) and OS ($p < 0.05$) rates and that elevated NLR, PLR, SII, and SIRI levels were suggested as significant predictors of shorter PFS and OS rates ($p < 0.05$) [27]. It was shown that upon the combination of neutrophil, lymphocyte, and platelet counts, the prognostic ability of the SII was higher compared to NLR, LMR, and PLR in lung cancer [28] and classic Hodgkin lymphoma [29]. Nevertheless, SII was not prognostic upon the single-variable analysis for the purposes of the present study. On the other hand, elevated SIIL (HR: 1.03; $p = 0.019$) was identified as an independent risk factor for mortality according to the multivariable regression model. The predictive value of the SIIL index in prediction of mortality was > 377.4 x 103 with a sensitivity of 59.1% and specificity of 100%. Patients with a SIIL level of > 377.4 × 103 were at 5.9 times higher mortality risk compared to patients with a SIIL level of ≤ 377.4 × 103.

PNI is an indicator of systemic inflammation and nutritional status, nevertheless, there was no association between PNI and survival in the present study.

Although the IELSG model was derived from a relatively large group of patients from multiple centers, there was no data on LDH level or the CSF protein in two-thirds of the samples. Information about the LDH level or CSF protein was not always available in clinical practice, which made IELSG difficult to apply and verify in many previous studies [4, 30-32].

In addition, CSF protein concentration among those parameters is not easily applicable. Routine lumbar puncture cannot be performed due to the high intracranial pressure in patients [2, 4, 30-32]. The Nottingham/Barcelona (NB) model was derived form a relatively smaller patient population, where the patients received legacy chemotherapy regimens. Therefore, its application for the PCNSL populations of the day is limited. A few recent studies suggested that there was no adequate correlation between the MSKCC score and survival [30, 33]. This raises doubts with regard to the reliability of the said two-parameter model.

The rather wide survival range in patients with PCNSL indicates the need to develop a reliable prognostic model that is able to predict disease outcomes and facilitate decision-making for further treatments. In addition, given the low incidence of PCNSL, there is a comparatively limited number of large randomized phase III studies with regard to optimal standard therapy, and thus consensus is mainly based on the comparative analysis of retrospective and phase II studies [34-36]. A number of studies in the relevant literature have investigated the prognostic factors for PCNSL. Age and performance status (PS) are the two factors

that are reported to have consistently associated with disease survival [2-4, 37, 38]. In the present study age limits of > 50, < 50 and of > 60, < 60 years were not associated with mortality. There was no association between the patients' KPS scores of > 70 and < 70 and mortality.

A recent study of 167 patients with PCNSL reported a median OS rate of 7 months (95% CI, 25-49) with a follow-up period of 25 months (1-152). The post-operative residual tumor, HD-MTX-free chemotherapy, and palliative therapy were identified as independent prognostic markers. Furthermore, the ECOG > 3, multifocal lesions, and palliative therapy were reported as negative independent prognostic markers for PFS [39].

While the role of MSKCC score is still controversial, it was not associated with mortality in patients treated with standard HD-MTX based therapy in the present study.

In PCNSL, there are various options for induction chemotherapy and consolidation therapy. Therefore, a better disease risk classification score can help with clinical decision-making and develop treatments tailored to the risk assessment. In PCNSL, the effect of surgical excision on survival has not been conclusively confirmed [40, 41]. In the present study, the rates of patients, who underwent excisional biopsy and stereotactic biopsy were 40.6% and 59.4%, respectively, where the was no difference in the two methods by survival.

The addition of rituximab as another important treatment for PCNSL is controversial [42, 43] and there was no significant difference in the present study. A previous study suggested that ASCT was better at consolidation treatment compared to WBRT [44], yet this was not confirmed in the present study, since probably only three patients were treated with ASCT, and one died of pneumonia subsequent to ASCT.

Therefore, there is a requirement for further studies to determine the better therapeutic options in PCNSL. However, the present study had several limitations. Firstly, the selection bias and information bias could not be avoided in the present study due to its retrospective and single-centered design. Secondly, the study population was relatively small. Despite these limitations, SIIL, SIRIL, NLL, PLL, FLR, CAR, and AGR prognostic factors were investigated for the first time in patients with PCNSL, who initially received standard HD-MTX-based chemotherapy.

PCNSL treatment has significantly improved in the last 20 years and long-term survival has been observed in approximately 15-20% of patients upon HD-MTX-based chemotherapy with or without radiotherapy. However, relapse is prevalent, and long-term survival rate is still not good enough. Although clinical prognostic scoring, including MSKCC and IELSG, is available in predicting prognosis and survival, it is still not adequate for today and there is a requirement for further prognostic parameters. Many studies [25, 27, 42] reported an association between alterations in laboratory parameters and outcomes in patients with PCNSL.

CONCLUSION

In brief, the likelihood of survival was higher in patients with PCNSL, who received RT, compared to RT-naive patients in this 6-year retrospective and single-centered study, which investigated the demographic and clinicopathological characteristics and possible prognostic factors. The risk of mortality was higher in patients with partial and no response compared patients with complete response. Elevated hemoglobin levels, elevated leukocyte levels, elevated neutrophil levels, elevated SIIL index, elevated SIRIL index, and elevated NLL index were associated with mortality. SIIL, SIRIL, and NLL indexes were investigated for the first time in the literature. Elevated SIIL index level and partial and no response were the independent predictors of mortality on the basis of the multivariable regression model including the potential risk factors associated with mortality. Other parameters (ALC, AMC, RDW, total bilirubin) and their respective ratios (LMR, PLR, NLR, PLL, FLR, AGR, WLR, CAR) were also not associated with OS. The serum LDH level was not associated with OS and there was a paradoxical association with anemia in the present study. The fact that a single-variable analysis was conducted, and the number of cases may account for the above. Elevated neutrophil levels, elevated leukocyte levels, and elevated SIIL, SIRIL, and NLL index levels are effective and promising blood markers as prognostic factors. Further studies and research are required for verification of these results and for the prognostic role of hematologic parameters in PCNSL.

Authors' Contribution

Study Conception: TE, FÖ; Study Design: TE; Supervision: TE, FÖ; Funding: TE; Materials: İEP, BO, CY, ÖC, RA; Data Collection and/or Processing: TGK, SÇ, TE; Statistical Analysis and/or Data Interpretation: TE; Literature Review: TE; Manuscript Preparation: TE, FÖ, VÖ and Critical Review: FÖ, VÖ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Ethics Committee Approval

Clinical Research Ethics Committee, Faculty of Medicine, Bursa Uludag University, 2021-8/3

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