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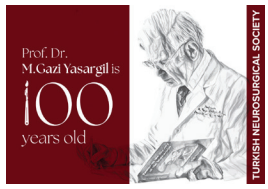

Evaluation of Prognostic Factors in Primary Central Nervous System Lymphomas: A Single-Center Study

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ABSTRACT

AIM: To evaluate the relationship between the most commonly used scoring systems, some disease parameters and prognosis in a patient group diagnosed with primary Central Nervous System Lymphoma (PCNSL).

MATERIAL and METHODS: Clinical information was collected from patients diagnosed with PCNSL between 2013 and 2024. In addition to previously defined and validated scoring systems (the International Extranodal Lymphoma Study Group (IELSG), the Nottingham/Barcelona (NB), and the Memorial Sloan-Kettering Cancer Center models (MSKCC), we have also evaluated some newly defined parameters. The predictive significance of all assessments for overall survival was investigated.

RESULTS: A total of 37 patients received the diagnosis of PCNSL. We could not use the IELSG model due to missing data. The MSKCC groups were not associated with mortality. According to Kaplan-Meier test, age, Karnofsky performance status (KPS) scores and NB scores had a significant effect on survival (logrank test: p=0.002, <0.001, and 0.006; respectively). The cut-off value for KPS score was determined as 85 points according to ROC analysis. The cut-off value for age was determined as 59 years. KPS<85 and age ≥60 years were determined as poor prognostic factors. This grouping with KPS and age variables was significant according to Kaplan-Meier survival analysis (logrank test: p=0.023). Mortality rates were significantly higher in patients fulfilling the KPS<85 and age ≥60 criteria (50.0 vs 88.9%, p=0.011, odds ratio: 8.0, CI95%: 1.4- 45.4).

CONCLUSION: This study was conducted in a single-center, under the conditions of our country's health system. As in other classification recommendations, performance score and age were the most important survival determinants. We were able to classify the risk factors of the patients according to the NB scoring system which was a significant model in the prediction of survival.

KEYWORDS: Primary central nervous system lymphoma, Prognostic factor, Survival

ABBREVIATIONS: ALB: Albumin, **β2-MG:** β2-microglobulin, **CMT:** Chemotherapy, **Cr:** Creatinine, **CSF:** Cerebrospinal fluid, **DLBCL:** Diffuse large B-cell lymphoma, **EBV:** Epstein-Barr virus, **BCL-6:** B-cell lymphoma-6, **ECOG:** Eastern Cooperative Oncology Group, **GCB:** Germinal centre B-cell-like, **Hb:** Hemoglobin, **HD-MTX:** High dose -methotrexate, **IELSG:** International Extranodal Lymphoma Study Group, **KPS:** Karnofsky performance status, **LDH:** Lactate dehydrogenase, **LYM:** Lymphocyte, **MONO:** Mononuclear cell, **MSKCC:** Memorial Sloan-Kettering Cancer Center, **MUM-1:** Multiple myeloma oncogene-1, **NB:** Nottingham/Barcelona, **NEU:** Neutrophil, **NHL:** non-Hodgkin lymphoma, **non-GCB:** Non-germinal centre B-like, **PCNSL:** Primary central nervous system lymphoma, **PLT:** Platelet, **PNI:** Prognostic nutritional index, **ROC curve:** Receiver operating characteristic curve, **SII:** Systemic immune inflammation index, **SIRI:** Systemic inflammation response index, **WBC:** White blood cell, **WHO:** World Health Organisation, **β2-MG:** β2-microglobulin

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INTRODUCTION

Hematolymphoid tumours of the central nervous system were grouped under two main headings as "lymphomas" and "histiocytic tumours" in compliance with the latest classification of the World Health Organisation (WHO) in 2021 (6). Lymphomas are also grouped under subheadings including central nervous system lymphomas and rare lymphomas of different types. Primary central nervous system lymphoma (PCNSL) is simply defined as a subtype of extranodal non-Hodgkin's lymphoma and is a very rare type among central nervous system malignancies and constitutes less than 3% of all brain tumours (6). Primary diffuse large B-cell lymphoma is defined as a lymphoma that occurs in immunocompetent individuals and is limited to the central nervous system at presentation. An acceptable and shorter nomenclature for primary diffuse large B-cell lymphoma of the central nervous system is "Primary Central Nervous System Lymphoma". The type of lymphoma seen in immunocompromised, immune-deficient individuals is defined as "immunodeficiency-associated CNS lymphomas" as a specific group within central nervous system lymphomas. The etiology of this group includes both hereditary and acquired immunodeficiency conditions such as neoplastic diseases, immunodeficiency syndromes (i.e. IgA deficiency, ataxia telangiectasia, Wiskott-Aldrich syndrome), autoimmune disorders (i.e. Sjögren's syndrome, systemic lupus erythematosus), iatrogenic immunosuppression and infectious disorders. Epstein-Barr virus (EBV) infection is a very important comorbidity associated with the majority of this group of lymphomas,

As is the case with all rarely seen diseases, and malignancies there has always been a need for the development of new and effective therapeutic agents for the treatment of central nervous system lymphomas. Some treatment modalities for central nervous system lymphomas have been reported to improve survival only in a certain proportion of patients. However, the general prognosis of these patients is poor and the recurrence potential is higher. Therefore, it is very important to optimize the prognosis. Treatment modalities include surgery, high-dose methotrexate-based polychemotherapy, consolidative whole-brain irradiation, autologous stem cell transplantation and consolidative high-dose chemotherapy (10). Since these methods are expensive and have severe side effects, especially neurotoxicity, selection of the most accurate and appropriate treatment modality for these patients carries utmost importance. Clinical status is the most important factor in determining the prognosis and treatment management of these patients. Formerly only age and performance status that were found to be clearly associated with survival were considered in determining the clinical status, (1,3,5,7,8). Subsequently, three new scoring systems which evaluated age and performance status and more recently introduced models assessing also a large number of laboratory parameters and/or their ratios to each other have been proposed (1,3,7,13,17).

The aim of this study is both to perform histopathological re-evaluation of the biopsy specimens obtained from the patients diagnosed with central nervous system lymphoma in our center, and to evaluate the prognostic value of scoring systems in comparison with literature data.

MATERIAL and METHODS

Patients

In this retrospective observational study, the archival data of the patients diagnosed with brain lymphoma between January 2013 and April 2024 at Izmir Katip Celebi University Ataturk Training and Research Hospital were derived from the hospital central data processing records. All patients with histopathologically confirmed diagnosis of non-Hodgkin's lymphoma were included in the preliminary evaluation. Patients with lymphoma involving only cranial nerves, brain, eyes, and leptomeninges, and human immunodeficiency virus seronegativity were enrolled in the study. Patients with a history of corticosteroid therapy, immunosuppression or organ transplantation, any other malignancy and/or anticancer threrapy were excluded from the study.

The present study was approved by the Ethics Committee of Izmir Katip Celebi University Ataturk Training and Research Hospital and adhered to the World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects (2022GOKAE-0139) on 4 April 2022. All patients have given their written, and signed informed consent to have this manuscript published in an academic journal.

Data Collection

Baseline information and preoperative clinical characteristics of the patients were obtained from the data processing records. Age and gender were included as basic information. Brain MRI, tumor invasion areas (including leptomeningial involvement, multifocality), blood-serum values of many laboratory parameters including preoperative hemoglobin (Hb), albumin (ALB), creatinine (Cr), β2-microglobulin (β2-MG), lactate dehydrogenase (LDHL), and C-reactive protein (CRP); peripheral blood neutrophils (NEU), lymphocytes (LYM), mononuclear cells (MONO), white blood cells (WBC), and platelets (PLT). Some proportional values were also calculated based on these blood values: the systemic inflammation response index (SIRI= NEU count x MONO count/LYM count), systemic immune inflammation index (SII= PLT count x NEU count/LYM count), neutrophil-to-lymphocyte ratio (NLR= NEU count/LYM count), derived neutrophil-to-lymphocyte ratio (dNLR= NEU count/(WBC count - NEU count)), lactate dehydrogenase / lymphocyte count (LLR= LDH/LYM count) and the prognostic nutritional index (PNI=. ALB + 5 x LYM count). Furthermore, the Nottingham/Barcelona (NB) model, International Extranodal Lymphoma Study Group (IELSG) and Memorial Sloan-Kettering Cancer Center (MSKCC) scores in the preoperative period were also estimated. In the NB model, three risk factors such as age at and above 60 years, Eastern Cooperative Oncology Group (ECOG) performance score >1, presence of multifocal lesions or meningeal involvement were assessed by assigning one point to each parameter, and we have created four risk groups (0, 1, 2, 3) according to the total score. In the IELSG model one point was assigned to each of the following parameters: age >60 years, ECOG score >1, elevated cerebrospinal fluid (CSF) protein concentration, deep brain involvement and increased serum LDH level. The patients

were allocated into 3 groups according to their estimated final scores of 0-1; 2-3 and 4-5 points. We defined three different prognostic groups according to the MSKCC model: Group 1 (age <50 years), Group 2 (age ≥50 years and KPS≥70), and Group 3 (age ≥50 years and KPS<70). Postoperative treatment management and follow-up information were also recorded. Archival preparations were re-examined for pathological diagnostic evaluations. Necessary immunohistochemical analyzes were performed to differentiate the patients into two prognostically important subgroups [(germinal center B-cell-like (GCB) and non-germinal center B-like (non-GCB)] according to the currently proposed Hans algorithm for classification of diffuse large B-cell lymphomas (9). Evaluations for CD10, BCL-6 and MUM-1 antibodies were made by considering the most intense staining areas in tumor cells, and the presence of staining intensity above 30% was considered as positive. As a result of the evaluations, diffuse large B-cell lymphomas were divided into 2 groups as germinal center B-cell-like (GCB) and non-germinal center B-cell like (non-GCB) lymphomas. All lymphoma involvement patterns (diffuse, nodular, perivascular predominant) were also evaluated.

Clinical Course

Response to treatment was evaluated according to the criteria proposed by Cheson et al; as complete response, partial response, stable disease, and progressive disease (4). The time between the initial pathological diagnosis and death from any cause was considered as overall survival.

Statistical Analysis

IBM® SPSS® Statistics 22.0 (IBM Corporation, Armonk, New York, United States) was used for statistical analysis of variables. The Kolmogorov-Smirnov test was utilized to assess the conformity of data to normal distribution, while Levene test was used to evaluate the variance homogeneity. For the comparison of two independent groups across quantitative variables, the independent samples t-test, accompanied by bootstrap results, and Mann-Whitney U test, supplemented with Monte Carlo simulation results were employed. Pearson chi-square test was utilized to compare categorical variables with each other. The impact of group variables on survival was examined with Kaplan-Meier test: Risk groups were created by determining the cut-off value of scale variables that were effective on survival using ROC analysis. Quantitative variables were expressed in the tables as mean (standard deviation) and median (1st quartile / 3rd quartile), while categorical variables were shown as numbers (n), and percentages (%). All variables were analyzed within a 95% confidence interval, with significance determined by p-values below 0.05.

RESULTS

Twenty-one male (56.8%), and 16 (43.2%) female patients diagnosed with SSSL were included in the study. The histopathological diagnoses were diffuse large B-cell lymphoma in 35 (94.6%) and T-cell lymphoma in one case (Figures 1 and 2). During a mean follow-up period of 737.6 ± 1120.5 days, 29 (78.4%) patients died. Clinicopathological, and demographic data of all patients (n=37) are summarized in Tables I and II. Beta 2-MG, CRP, PNI values could not be evaluated due to missing data. Similarly, we could not use the IELSG prognostic scoring system in our assessments due to missing data about CSF parameters in almost all of the patients. According to the NB and MSKCC prognostic models, most commonly 2 risksubgroups were determined. The tumor was multifocal in most patients (Figures 3A and 3B). Leptomeningeal involvement was present in about half of the patients (Figure 3C). All comparative data, mortality and survival analyses were evalu-

Table I: Overall Summary of Categorical Variables

		n	%
Gender	Male	21	56.8
	Female	16	43.2
Survival	Exitus	29	78.4
	Survived	8	21.6
ECOG scores	0	21	56.8
	1	7	18.9
	2	2	5.4
	3	6	16.2
	4	1	2.7
NB scores	0	2	5.4
	1	14	37.8
	2	16	43.2
	3	5	13.5
MSKCC scores	1	8	21.6
	2	21	56.8
	3	8	21.6
Focality	Solitary	11	29.7
	Multiple	26	70.3
Leptomeningeal involvement	No	18	48.6
	Yes	19	51.4
Histopathologic diagnosis	DLBCL	35	94.6
	Others	2	5.4
Invasion patterms	Diffuse	13	36.1
	Perivascular	11	30.6
	Mixed	12	33.3
Subgroups	GCB	6	16.7
	Non-GCB	30	83.3

ECOG: Eastern Cooperative Oncology Group, **NB:** Nottingham/Barcelona, **MSKCC:** Memorial Sloan-Kettering Cancer Center, **DLBCL:** Diffuse large B-cell lymphoma, **GCB:** Germinal center B cell-like, **Non-GCB:** Nongerminal center B cell-like

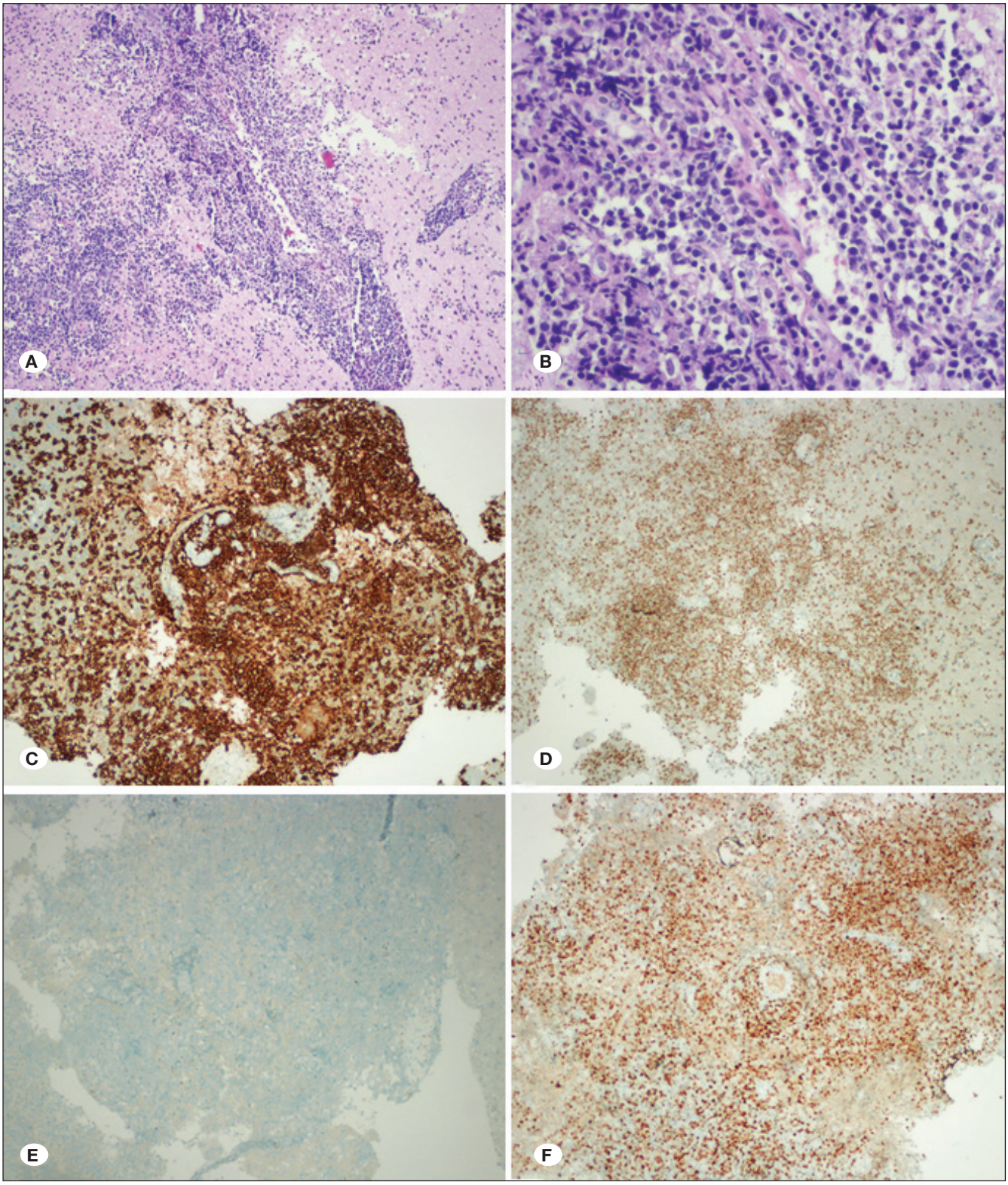

Figure 1: A) Angiocentric growth pattern of PCNSL (H&E); **B)** Higher magnification shows that the blood vessels are surrounded by neoplastic B cells; **C-F)** Immunhistochemical staining CD20 positive **(C)**, BCL6 positive **(D)**, CD10 negative **(E)**, and MUM1 positive **(F)** Original magnification: **(A)** 100x **(B)** 400x **(C, D, E, F)** 100x.

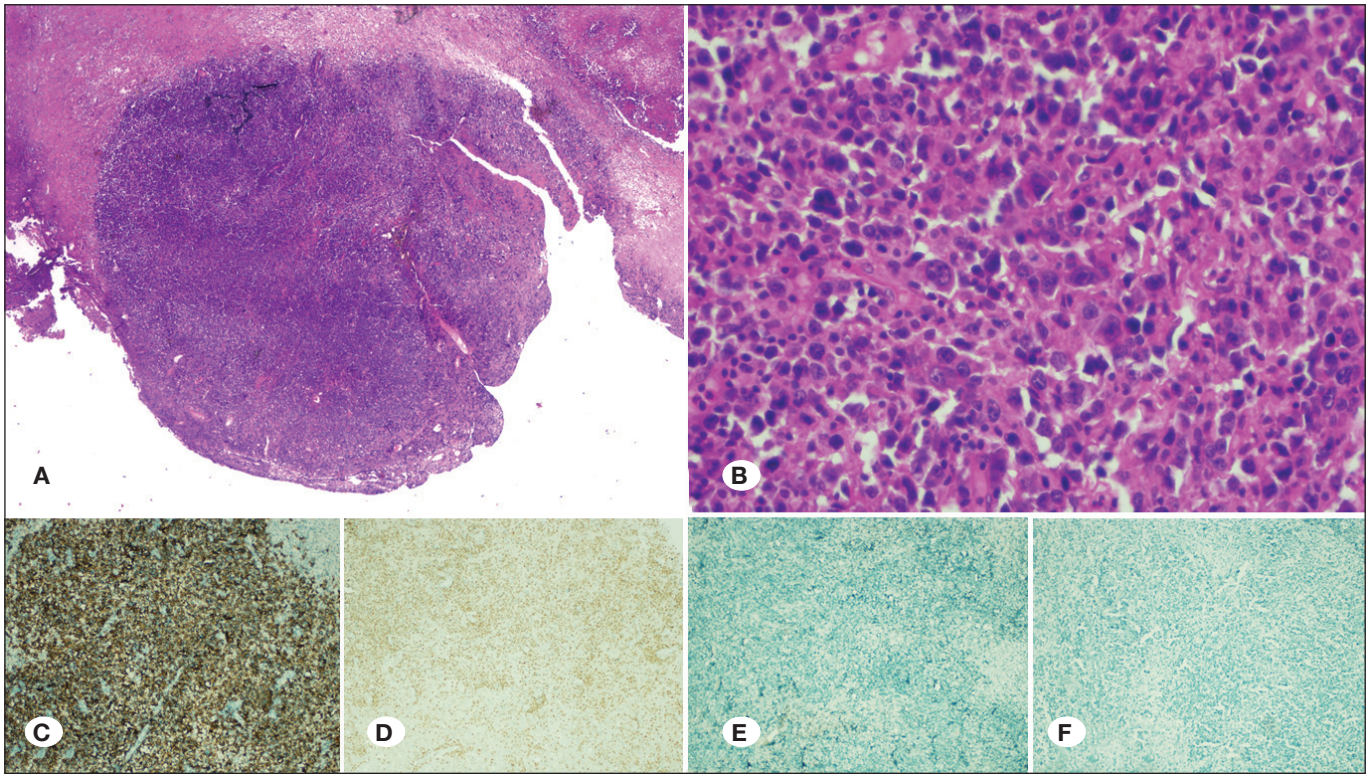

Figure 2: A) A diffuse infiltrate of mononuclear cells (H&E); **B)** Neoplastic B cells are intermediate to large and have vesicular chromatin and prominent nucleoli; **(C-F)** Immunohistochemical staining CD20 positive **(C)**, BCL6 positive **(D)**, CD10 negative **(E)** and MUM-1 negative **(F)** Original magnification: **(A)** 20x **(B)** 400x **(C-F)** 100x.

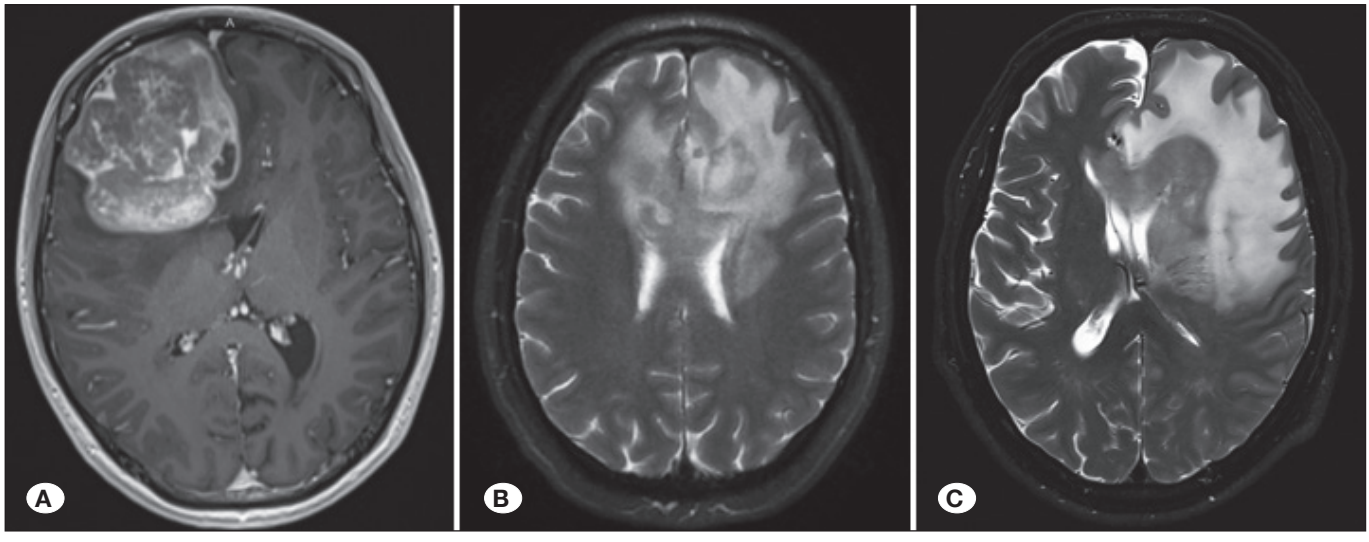

Figure 3: A) In the right frontal axial contrast-enhanced section, a solid mass with a size of 80x60 mm, containing cystic and necrotic areas, intense contrast enhancement and surrounded by vasogenic edema is observed. **B)** Contrast-enhancing mass lesions that infiltrate the corpus callosum and extend to both sides via a transcallosal route. **C)** Linear contrast enhancement showing leptomeningeal spread on the side walls of the lateral ventricle.

Table II: Overall Summary of Scale Variables

	Mean	Standard Deviation	Median	Minimum	Maximum	25th percentile	75th percentile
Age	57	15	61	20	75	51	68
ECOG score	0.9	1.2	0.0	0.0	4.0	0.0	1.0
KPS score	77.8	25.3	90.0	10.0	100.0	70.0	100.0
NB score	1.6	0.8	2.0	0.0	3.0	1.0	2.0
Total survival (days)	737.6	1120.5	324.0	6.0	4306.0	54.0	1055.0
Hemoglobin (g/L)	13.1	2.7	13.5	1.4	17.0	12.4	14.3
WBC (. 10x9/L)	10.42	5.62	9.42	2.26	30.54	6.66	12.40
PLT (. 10x9/L)	261.8	96.6	252.0	54.0	517.0	200.0	333.0
NEU (. 10x9/L)	23.58	93.65	6.80	2.09	577.00	4.63	11.00
MONO (. 10x9/L)	0.649	0.605	0.540	0.080	3.750	0.398	0.680
LYM (. 10x9/L)	1.60	0.79	1.44	0.08	3.54	1.06	2.04
ALB (g/L)	39	6	41	27	49	36	43
Cr (µmol/L)	0.81	0.22	0.77	0.36	1.63	0.68	0.89
LYM/MONO	2.97	1.29	2.85	0.53	5.41	2.21	3.72
NEU/LYM	23.93	103.25	3.72	1.19	634.07	2.93	10.39
dNEU/LYM	3.92	3.76	2.55	-7.67	12.29	1.97	5.49
SIRI	8.96	27.49	2.17	0.64	164.86	1.51	4.30
SII	4964.12	20299.41	1238.34	249.74	124910.99	738.23	2813.99
LDH (U/L)	253	98	241	124	486	183	328
LDH/ LYM	369.89	1083.90	164.19	36.72	6075.00	106.21	201.65

ECOG: *Eastern Cooperative Oncology Group,* ***KPS:*** *Karnofsky performance status,* ***NB:*** *Nottingham/Barcelona,* ***WBC:*** *White blood cell,* ***PLT:*** *Platelet,* ***NEU:*** *Peripheral blood neutrophil,* ***MONO:*** *Mononuclear cell,* ***LYM:*** *Lymphocyte,* ***ALB:*** *Albumin,* ***Cr:*** *Creatinine,* ***dNEU/LYM:*** *Derived NEU/LYM,* ***SIRI:*** *Systemic inflammation response index,* ***SII:*** *Systemic immune inflammation index,* ***LDH:*** *Lactate dehydrogenase.*

ated only in patients with diffuse large B-cell lymphoma. Age was also a prognostic factor. Indeed, patients who did not survive were considerably older than those survived (59.9 ± 14.2 vs 47.1 ± 15.0, p=0.015). In addition, mean KPS score was considerably lower in patients who passed away (75.0 ± 25.8 vs 91.4 ± 15.7). In the NB scoring system, higher points were assigned to exited patients when compared to those survived (1.8 ± 0.8:median: 2.0, Q1: 1.0 - Q3: 2) vs 1.1 ± 0.4: median: 1.0, Q1: 1.0 - Q3: 1.0) (p=0.023) (Table III). However, MSK-CC groups were not associated with mortality (Table III). In addition, other categorical variables such as gender, involvement pattern, leptomeningeal involvement were not found to be associated with mortality. Furthermore, according to Kaplan-Meier survival analysis, age, KPS score and NB score had a significant effect on survival (logrank= 0.002, <0.001, and 0.006; respectively). Blood parameters such as Hb, WBC, PLT, NEU, MONO, LYM, ALB, Cr, NEU/LYM, dNEU/LYM, LYM/MONO, SIRI, SII, LDH, LDH/LYM were not associated with mortality (Table IV). The cut-off value for KPS score, which was found to be significantly associated with mortality, was determined as 85 points (sensitivity: 0.750, specificity: 0.862, AUC: 0.780, p=0.016) according to ROC analysis. The cut-off value for age was determined as 59 years (sensitivity: 0.250, specificity: 0.483, AUC: 0.192). KPS ≥ 85 and age ≥ 60 years were determined as poor, whereas others as good prognostic parameters (Table V). This grouping based on KPS and age variables was significant according to Kaplan-Meier survival analysis (Figure 4, logrank= 0.023). In addition, mortality was significantly higher in patients fulfilling the KPS < 85 and age ≥ 60 criteria (50.0 vs 88.9%, p=0.011, odds ratio: 8.0, CI95%: 1.4- 45.4).

DISCUSSION

Among central nervous system tumors, primary central nervous system lymphomas demonstrate very peculiar characteristics at every stage of the disease, ranging from its clinical manifestions to radiological findings, from histopathological

Table III: Comparison of Categorical Variables in Terms of Survival Status in Our Study

		Survival status				p-value
		Exitus		Survived		
		n	%	n	%	
Gender	Male	18	64.3	3	42.9	0.301
	Female	10	35.7	4	57.1	
MSKCC score	1	4	14.3	3	42.9	0.24
	2	18	64.3	3	42.9	
	3	6	21.4	1	14.3	
Focality	Solitary	9	32.1	2	28.6	0.856
	Multiple	19	67.9	5	71.4	
Leptomeningeal enhancement	No	13	46.4	4	57.1	0.612
	Yes	15	53.6	3	42.9	
Invasion patterns	Diffuse	10	35.7	3	42.9	0.923
	Perivascular	8	28.6	2	28.6	
	Mixed	10	35.7	2	28.6	
Subgroups	GCB	4	14.3	1	14.3	1
	Non-GCB	24	85.7	6	85.7	

ECOG: *Eastern Cooperative Oncology Group,* ***KPS:*** *Karnofsky performance score,* ***NB:*** *Nottingham/Barcelona,* ***MSKCC:*** *Memorial Sloan-Kettering Cancer Center,* ***GCB:*** *Germinal center B cell-like,* ***Non-GCB:*** *Nongerminal center B cell-like.*

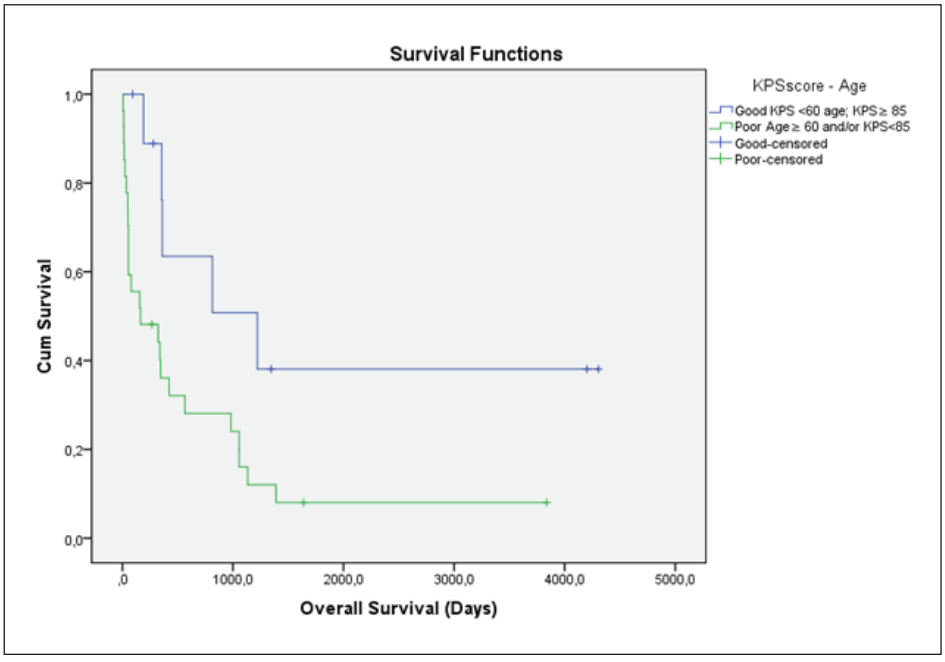

Figure 4: Comparison of Karnofsky Performance Status score - age groups for overall survival (logrank= 0.023).

Table IV: Comparison of Scale Variables in Terms of Survival Status in Our Study

	Survival						p-value
	Exitus			Survived			
	Mean	Standard Deviation	Median	Mean	Standard Deviation	Median	
Age	59.93	14.22	64.00	47.14	15.03	50.00	**0.02**
ECOG score	1.03	1.32	0.00	0.38	0.74	0.00	0.25
KPS score	75.00	25.89	90.00	91.43	15.74	100.00	**0.04**
NB score	1.8	.8	2.0	1.1	.4	1.0	**0.02**
Total survival (days)	403.04	439.21	257.00	2089.14	1966.83	1638.00	**0.01**
Hemoglobin (g/L)	13.08	1.89	13.05	12.74	5.15	14.30	0.20
WBC (. 10x9/L)	10.00	5.03	9.25	9.63	2.32	9.43	0.89
PLT (. 10x9/L)	262.00	103.76	257.50	245.29	77.32	232.00	0.67
NEU (. 10x9/L)	28.30	107.64	6.85	7.01	2.86	6.80	0.76
MONO (. 10x9/L)	0.58	0.31	0.57	0.54	0.30	0.47	0.98
LYM (. 10x9/L)	1.52	0.71	1.38	1.96	1.12	1.86	0.41
ALB (g/L)	38.22	5.56	40.00	43.75	4.57	43.50	0.20
Cr (µmol/L)	0.79	0.24	0.74	0.86	0.12	0.87	0.14
NEU/LYM	28.65	116.58	5.44	6.83	6.11	3.31	0.60
dNEU/LYM	3.80	3.75	2.66	4.33	4.04	2.27	0.73
LYM/MONO	2.87	1.21	2.77	3.33	1.57	3.61	0.38
SIRI	9.27	30.14	2.17	7.82	15.82	2.16	0.86
SII	5863.93	22920.43	1256.65	1702.29	1516.29	932.50	0.62
LDH (U/L)	270.90	100.50	249.00	211.86	95.75	192.00	0.19
LDH/ LYM	453.94	1262.00	164.19	138.74	77.08	141.30	0.48
Ki-67	81.10	16.88	90.00	86.25	8.76	90.00	0.79

ECOG: *Eastern Cooperative Oncology Group,* ***KPS:*** *Karnofsky performance status,* ***NB:*** *Nottingham/Barcelona,* ***WBC:*** *White blood cell,* ***PLT:*** *Platelets,* ***NEU:*** *Peripheral blood neutrophil,* ***MONO:*** *Mononuclear cell,* ***LYM:*** *Lymphocyte count,* ***ALB:*** *Albumin,* ***Cr:*** *Creatinine,* ***dNEU/LYM:*** *Derived NEU/LYM,* ***SIRI:*** *Systemic inflammation response index,* ***SII:*** *Systemic immune inflammation index,* ***LDH:*** *Lactic dehydrogenase.*

Table V: The Distribution of Our Cases Into Prognostic Groups as Determined by KPS Scores and Age

Prognostic groups		Survival status			
		Exitus		Survived	
		n	%	n	%
KPS-Age	Good Age - <60 years; KPS≥ 85	5	17.2	5	62.5
	Poor Age - ≥60 years; and/or KPS<85	24	82.8	3	37.5

KPS: *Karnofsky performance status.*

examination of its frozen sections to definitive pathological diagnosis. Increasing incidence rates for PCNLS have been reported especially in elderly patients. Therefore the severe side effects of the treatment methods to be applied should be taken into consideration. Accordingly, it is necessary to implement the most accurate and appropriate treatment modality. On the other hand, there is no standard treatment method for PCNLS. New treatment regimens have been proposed such as autologous molecularly targeted therapy, chimeric antigen receptor T-cell immunotherapy, autologous and hematopoietic stem cell transplantation (17). In our study, the most common treatment modality was surgery followed by HD-MTX-based CMT. Since the prognosis and treatment management of patients are determined by their clinical status, which is primarily related to age and performance status of the patient, the first studies on this issue were based on these two parameters and were found to be clearly associated with survival (1,3,5,7,8). The first treatment regimen proposed took five parameters into consideration IELSG; age, ECOG performance status, LDH, CSF protein, and deep brain involvement (ie, periventricular regions, basal ganglia, brainstem, and/or cerebellum) (7). A total of 378 patients with primary central nervous system lymphoma from 23 cancer centers in five different countries received this treatment regimen. The CSF protein level was assessed in 21, and the LDH level in only 195 patients. During implementation of this treatment regimen, complete data on CSF protein and LDH levels were not available in all patients, and thus validation studies could not always be performed using these parameters (1,9,11,15). In this group of patients, patient non-compliance (usually due to advanced age), unnecessary investigations and contraindications to lumbar puncture all cause difficulties in obtaining CSF protein results. On the other hand, CSF examination is often not preferred because of the potential risk of complications related to increased intracranial pressure. In our study, CSF protein level was analyzed in only 1 patient. LDH levels of 8 patients were not known. Therefore, IELSG classification could not be performed in our patient population and its results could not be included in the statistical evaluation. CSF protein and LDH levels cannot always be evaluated in clinical practice due to the difficulties described above. These drawbacks make it difficult to apply and validate the IELSG model in many studies. Nevertheless, it is one of the most widely used models in very large advanced centers. As far as we know, LDH levels increase in some cancer types and are associated with poor prognosis (14). Thus, LDH is reported to be a potential therapeutic target (2). As a clinical tool with utmost prognostic significance, International Prognostic Index is a validated scoring system evaluating risk factors to predict the survival rate of the patients with lymphoma (16). Therefore, we wanted to evaluate the relationship between LDH levels and prognosis of our patients with lymphoma, but we could not find a statistically significant correlation between these two parameters (p=0.19). In a study of 248 patients from six different centers, LDH levels were evaluated in 220 patients and LDH value per se was not found to be a significant prognostic parameter in this large series (18). On the other hand, lymphocyte count has recently been proposed as an independent prognostic parameter for poor prognosis in patients with NHL or DLBCL (12). Jang et al. reviewed 81 patients with primary central nervous system lymphoma and found that low lymphocyte count at diagnosis was an independent prognostic factor for decreased overall survival. Based on the same idea, we evaluated the lymphocyte counts at diagnosis in our study, but we did not perceive it as statistically significant prognostic factor (p=0.41). In a large series of 218 patients with primary DLBCL, the researchers found that LDH level and lymphocyte count alone were not prognostic factors for both disease-free survival and overall survival [(LDH; p=0.926 (DFS), p=0.470 (OS) (lymphocyte count; p=0.436 (DFS), p=0.466 (OS)] (13). We also evaluated the LDH/lymphocyte ratio in our study, but we could not reveal its prognostic significance (p=0.48). Two studies each including more than 200 patients revealed statistically significant prognostic significance of LDH/lymphocyte ratio in terms of overall survival (17,18). In our study, the LDH/lymphocyte ratio was not a significant prognostic factor for overall survival. This result may be explained by the small number of patients in our study as well as the lack of data about LDH levels of 8 patients. As in other classification recommendations, performance score and age stand out as the most important survival determinants, so much so that they are the two most common variables evaluated in other risk classification systems. In our cases, an average of 8-fold increase in mortality rates was observed in patients aged 60 years and older and those with a KPS score below 85 compared to remaining patient population

After the IELSG model was defined, the Nottingham/Barcelona (NB) model tested on 77 patients was developed and tried to be validated by researchers in Nottingham and Barcelona. This prediction scoring system takes three parameters including age, performance score, multifocality or meningeal involvement into consideration (3). Since radiological findings are already present in almost all patients diagnosed with central nervous system lymphoma, it has become an easily applicable model in routine practice. Although the older chemotherapy regimen was applied in this study that consisted of scarce number of patients, nowadays it has conceivably limited sope of application. In our study, we were able to classify lymphoma patients according to the NB model and found that it had significant predictive value in terms of survival [(1.8 ± 0.8 (median: 2.0, Q1: 1.0 - Q3: 2) points in patients who died vs 1.1 ± 0.4 (Median: 1.0, Q1: 1.0 - Q3: 1.0) points in patients who survived (p=0.023)]. Liu et al. found a poor association between the NB model and overall survival in their study of 113 patients diagnos;ed in the largest health center in Taiwan (14). In this study, only 101 patients had primary central nervous system lymphoma and histopathologically all were non-Hodgkin's lymphomas. In addition, 81 patients provided statistical support as a validation cohort. In our study, the number of patients was limited; however, all patients met the latest WHO classification of diagnostic criteria (primary diffuse large B-cell lymphoma only).

The latest prognostic scoring system is the prognostic index developed by Memorial Sloan-Kettering Cancer Center (MSKCC) researchers. In this model only two parameters, age and Karnofsky performance status are taken into consideration (6). In the original article proposing this model, the presence of

external validation was emphasized. However, the relationship between this scoring system and prognosis could not be adequately determined with subsequent new studies, and it was not very successful in this respect (11-13). In this classification, relying only on age and KPS scores for risk stratification still leads to biases. Therefore, MSKCC model is not a good predictor of PCNSL prognosis. Zuo et al. formed risk groups in their patients according to the MSKCC model. They found significant results in terms of both DFS and overall survival in moderate and high risk groups (18). In our study, MSKCC model could not yield significant prognostic information in our patients. Jar et al. successfully validated the MSKCC model in 79 patients with intracranial PCNSL. CSF examination was not feasible in their 9 patients. Probably for this reason, they did not find a prognostic relationship among parameters examined when classification was made according to the IELSG scoring model (12). SKCC and IELSG scoring models are the most commonly used models. In fact, the MSKCC model is a simpler version of the IELSG model. The IELSG model includes parameters other than age and KPS. However, such parameters cannot be applied for every patient in routine clinical practice. As a result, while the MSKCC scoring system is almost always applicable in PCNSL patients, IELSG prognostic scoring system cannot be performed in many patients. The Nottingham and Barcelona model is also recommended by some investigators. On the other hand, the effect of newer scoring systems or new parameters on patient management and prognosis has been also investigated. Accordingly, Hb, ALB, Cr, β2-MG, LDH, and CRP, as well as all peripheral blood elements and their ratios to each other have been investigated as prognostic markers. In addition, SIRI and SII indexes have been evaluated in various studies (17). In our study, we could not evaluate β2-MG and CRP values because they were not investigated in almost all patients. We also evaluated Hb, WBC, PLT, NEU, MONO, LYM, ALB, Cr, NEU/LYM, dNEU/LYM, LYM/MONO, SIRI, and SII as prognostic markers. However, we could not obtain a significant result for any of them. In their detailed study, Zuo et al. found a significant association between ALB and PLT values and DFS and OS values among continuous variables (18). A significant correlations between categorical variables of EU/LYM and SIRI. It seems that new scoring models and the use of single or multiple parameters will be proposed in studies conducted in different centers in the coming years.

Study Limitations

Some limitations of our study are primarily related to problems inherent to retrospectively designed studies. We had not a validation cohort. As a consequence, inevitably a selection bias was present. Medical information of the patients could not be collected completely using our prospective study design. Therefore, already existing infections and autoimmune problems may have been overlooked. On the other hand, our study was performed with a scarce number of patients compared to the studies conducted in large centers in the literature. However, we would like to point out that some of these studies were performed by combining the data of different centers. This study was conducted in a single center in our country conditions. In the future, we would like to combine our study data with those received from different centers in our country and contribute to the relevant literature.

CONCLUSION

PCNSL is rare and the prognosis is poor. Therefore, it is very important to optimize the prognosis. Various treatment modalities are recommended. Since these methods are expensive and have severe side effects, selection of the most accurate and appropriate treatment modality carries utmost importance. Clinical status is the most important factor in determining the prognosis and treatment management of these patients. Our study was conducted in a single-center, under the conditions of our country's health system. As in other classification recommendations, performance score and age were the most important survival determinants. We were able to classify according to the NB model and found that it was significant in terms of survival.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

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AUTHORSHIP CONTRIBUTION

Study conception and design: NOE, HSK, AK

Data collection: NOE, HSK, IES, AK

Analysis and interpretation of results: AI, NOE

Draft manuscript preparation: NOE, AI

Critical revision of the article: NOE

Other (study supervision, fundings, materials, etc...): NOE, HSK, IES, AI, AK

All authors (NOE, HSK, IES, AI, AK) reviewed the results and approved the final version of the manuscript.

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