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Original Article

Can peripheral blood monocyte percentage and lymphocyte monocyte ratio at diagnosis predict survival in pediatric neuroblastoma patients?

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ABSTRACT

Background. Previous studies have shown that the immune system plays a critical role in cancer pathogenesis. The lymphocyte monocyte ratio (LMR) and monocyte percentage (MP) have been found to be prognostic factors in various types of adult cancers. But studies about pediatric tumors are scarce and to our knowledge, there are no studies evaluating the immune system effect in pediatric neuroblastoma patients. The aim of this study was to assess whether LMR and MP at diagnosis may have an effect on prognosis in neuroblastoma patients.

Methods. We retrospectively analyzed MP and LMR at diagnosis in 71 pediatric neuroblastoma patients treated between 2002 and 2016.

Results. The optimal cut-off values of LMR and MP were determined using the receiver operating characteristics curves (ROC) and area under the curve (AUC). We found that a low LMR (≤3.5) and a high MP (≥7.5%) were correlated with worse overall survival and shorter event-free survival in univariate analysis. Multivariate analysis revealed that elevated LMR was an independent factor for better OS and EFS.

Conclusions. In conclusion, LMR and MP might be valuable prognostic factors for predicting OS in neuroblastoma patients. Multicenter and prospective studies are warranted to confirm this hypothesis.

Key words: neuroblastoma, lymphocyte monocyte ratio, monocyte percentage, immune system.

The immune system has an important role on the outcome of cancer patients. It can prevent tumor outgrowth or conversely immune cells can help tumor outgrowth. Recent studies have shown that advanced cancer patients had a low lymphocyte count and this was associated with poor overall survival in various cancer types.[1-4] Monocytes also have a crucial role in tumor response. Inflammatory monocytes in peripheral blood are recruited by certain chemokines into the tumor microenvironment where they differentiate into tumor associated macrophages and promote angiogenesis, metastasis, immune suppression and chemo resistance.[5] The prognostic value of lymphocyte to monocyte ratio (LMR) has been investigated in hematologic malignancies and a low LMR was reported as an unfavorable prognostic factor in patients with diffuse large B cell lymphoma and Hodgkin lymphoma.[6,7] There are also numerous studies regarding the prognostic role of LMR in solid tumors such as soft tissue sarcomas, nasopharyngeal carcinoma, and ovarian cancer but all of these studies comprise only of adult patients. To our knowledge there is no study investigating the prognostic value of LMR and peripheral blood monocyte count in any childhood cancer.

Neuroblastoma is the most common extra cranial solid tumor of childhood and the most frequently diagnosed cancer in infancy.[8,9]

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Neuroblastoma has a diverse pattern of clinical presentation; the disease course ranges from spontaneous regression to aggressive metastatic tumor.[10] It is regarded as one of the most common cancers that undergo spontaneous regression.[11-13] The induction of patients' immune response toward their own tumor cells is one of the mechanisms suggested to contribute to this phenomenon.

Age, stage, histology and genetic changes (ploidy, MYCN copy number, 11q deletion) are the well-known prognostic factors in neuroblastoma. Patients are stratified into risk groups and treated according to these prognostic factors. In this study, we aimed to analyze whether peripheral LMR and blood monocyte percentage (MP) might have an effect on survival and can be used for improving predictive ability of existing prognostic tools in neuroblastoma patients.

Material and Methods

Patients

Seventy-one neuroblastoma patients, who were diagnosed and treated between January 2002 and December 2016, were retrospectively evaluated. All patients were staged according to International Neuroblastoma Staging System (INSS).[14] Patients were treated according to national neuroblastoma protocols of Turkish Pediatric Oncology Group (TPOG); TPOG-Neuroblastoma 2003, and TPOG-Neuroblastoma 2009 protocols. The poor prognostic factors are older age at diagnosis [≥18 months for TPOG- 2009 and ≥12 months for TPOG 2003], advanced stage [stage 3-4], unfavorable histology, presence of genetic alterations (MYCN amplification, chromosome 1p, 11q and/or 17 q deletion). Being stage IV and older than 18 months for TPOG- 2009 and ≥12 months for TPOG 2003 made patients a high-risk group regardless of MYCN amplification and histology in both protocols. According to these parameters patients were stratified in to three risk groups: high, intermediate and low risk. Data including age, gender, clinical findings, stage, histopathology, genetic alterations, treatment modalities, survival of patients, peripheral blood MP and LMR were retrospectively analyzed from the files. The peripheral MP and LMR were determined from routine complete blood counts with five-part differential counts (absolute and percent of lymphocytes, monocytes, eosinophils, basophils and neutrophils) obtained at diagnosis using ADVIA 2120 Hematology System (Siemens, NY, USA). Peripheral MP was calculated by dividing the absolute monocyte count to total leukocyte count and multiplying by 100. Lymphocyte to monocyte ratio was calculated as dividing the absolute lymphocyte count to absolute monocyte count (ALC/AMC).

After obtaining the ethics approval from the local ethics committee (Akdeniz University KAEK -2020-735), the study was initiated with informed consent from the patients.

Statistical analysis

Statistical analyses were calculated by SPSS (version 20.0) software program. The choice of the best cutoff values of peripheral MP and the LMR for assessing survival was based on their utility as a marker for the clinically relevant binary outcome of death/survival using the receiver operating characteristics curves (ROC) and area under the curve (AUC). Chi-square test was used to determine relationships between categorical variables and Mann Whitney U test was used to compare the continuous variables related to two groups. Overall survival (OS) and event-free survival (EFS) were analyzed using the approach of Kaplan-Meier. Differences between survival curves were tested for statistical significance using the two-tailed log-rank test. The stepwise (backward selection) Cox proportional hazard model was used for the univariate and multivariate analyses to evaluate the variables under the prognostic factors' section to assess their impact on overall survival and event free survival. All p values are two-tailed and p values less than 0.05 were considered statistically significant.

Table I. Characteristics of patients.

Age at diagnosis (mean, months)	31.2 (1-204)
Gender	N (%)
Female	38 (53.5)
Male	33 (46.5)
Age at diagnosis	
< 12 months	17 (24.9)
≥12 months	54 (76.1)
Stage	
Stage I	5 (7)
Stage II	5 (7)
Stage III	13 (18.3)
Stage IV	40 (56.4)
Stage IVS	8 (11.3)
Histology	
Favorable	18 (25.4)
Unfavorable	42 (59.2)
NA	11 (15.5)
Chromosome 1p11q deletion	
Presence	5 (7)
Absence	5 (7)
Not determined	61 (86)
Risk group	
Low	11 (15)
Intermediate	15 (21)
High	45 (64)
MYCN amplification	
High	19 (41.3)
Normal	27 (58.7)
Not determined	25 (35.2)
Chemotherapy	
Yes	62 (87.3)
No	9 (12.7)
Surgery	
At diagnosis	19 (26.7)
Second look	29 (40.8)
No	23 (32.5)
Radiotherapy	
Yes	22 (31)
No	49 (69)
Autologous transplantation	
Yes	25 (35)
No	46 (65)
Relapsed	
Yes	22 (31)
No	49 (69)
Cellular status at diagnosis	
Mean leukocyte count /mm^3	8918 (2070-20100)
Mean absolute lymphocyte Count (ALC)/mm^3	3143 (300-12320)
Mean absolute monocyte Count (AMC)/mm^3	715 (100-2300)
Monocyte percentage (MP) %	8.2 (2-22)
Mean ALC/AMC (LMR)	5 (1-16)

Results

Clinical Characteristics

Totally 71 neuroblastoma patients were enrolled. Thirty-eight (53.5%) of the patients were female and the mean age at diagnosis was 31.2 months (range; 1–204 months). Patients were staged according to INSS; 5 patients had (7%) stage I, 5 (7%) patients had stage II, 13 (18.3%) patients had stage III, 40 (56.4%) patients had stage IV and 8 (11.3%) patients had stage IVS disease. Metastasis was detected in 48 patients (67.6%) at initial diagnosis. MYCN amplification were high in 19 (41.3%) of patients and non-amplified in 27 (58.7%) of patients. MYCN status were unknown in 25 (35.2%) patients. Eleven of them were ≥18 months (or ≥ 12 months) and had stage IV, 7 patients were ≥18 months (or ≥ 12 months) and had unfavorable histology, 7 patients had stage I –II disease. Forty-five patients (64%) were in high-risk group, 15 patients (21%) were in intermediate risk group and 11 (15%) patients were in low-risk group. Fifteen of patients with unknown MYCN status in high-risk group, while the others were in low-risk group. Clinical characteristics of patients are shown in (Table I).

At diagnosis, mean leukocyte count was 8918/mm^3 (range; 2070-20100), mean peripheral absolute lymphocyte count (ALC) was 3143/mm^3 (range; 300-12320), mean peripheral absolute monocyte count (AMC) was 715/mm^3 (range; 100-2300), mean MP was 8.2% (range; 2%-22%) and mean peripheral LMR was 5 (range; 1-16).

LMR and MP at diagnosis

Cut-off values for LMR and peripheral blood MP were determined according to ROC analysis. Peripheral MP of 7.5% or more had an AUC of 0.74 [95% confidence interval (CI), 0.63 to 0.86] with a sensitivity of 73% and specificity of 70% (Fig. 1). A LMR of 3.5 or less had an AUC of 0.75 (95% CI, 0.64 to 0.86) with a sensitivity of 80% and a specificity of 61% (Fig. 2). Area under the curve values from ROC analysis support the use of LMR of ≤3.5 and peripheral blood MP ≥7.5% as the cut-off values as markers of binary clinical outcome of survival. Patients were then assigned either to the high LMR (LMR > 3.5) group and low LMR (LMR ≤ 3.5) group. Forty patients were in high LMR group and 31 patients were in low LMR group. According to cut-off value of MP, 39 patients were in high MP (MP ≥7.5), 32 patients were in low peripheral MP (MP <7.5) group.

When the patients were classified according to peripheral MP levels, there were more patients in the high peripheral MP group with metastatic disease (p=0.005), stage 4 disease (p<0.001), unfavorable histology (p<0,001), MYCN amplification (p=0.003), high risk disease (p<0.001), and older age (≥12 months; p=0.015) compared to the low peripheral MP group. Also, in the low LMR group there were more patients with stage 4 disease (p=0.014) unfavorable histology (p=0,046) and high-risk disease (p=0.003) (Table II).

Outcome:

The median follow-up time after diagnosis was 22 months (range; 1-182 months). The 3 year OS and EFS rates were 51% ± 6.0 and 37% ± 6.1, respectively. The 3 year OS and EFS rates in low LMR group were significantly lower than that in the high LMR group (3-year OS: 38% ± 8.8 vs 62% ± 7.8 p=0.002 and 3-year EFS: 22% ± 7.7 vs 50% ± 8.5 p=0.003) (Fig. 3). The patients with high peripheral MP had significantly lower 3-year OS and EFS compared to the patients with low peripheral MP (3-year OS: 38.5% ± 7.8 vs 67.5% ± 8.5, p=0.005 and 3-year EFS: 24% ± 7.1 vs 54% ± 9.5 p=0.027) (Fig. 3).

The univariate analysis showed that stage IV disease, unfavorable histology, high risk disease, low LMR and high MP were associated with low EFS and OS (Table III). The multivariate analysis revealed that low LMR (Hazard ratio

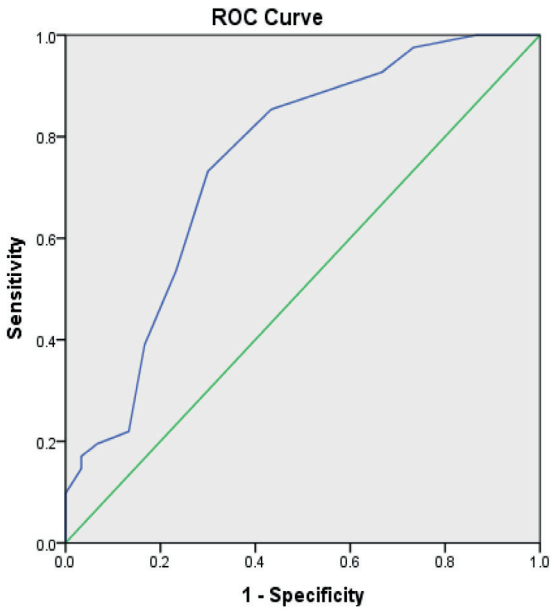

Fig. 1. Monocyte percentage of ≥7.5% had an AUC of 0.74 [95% confidence interval (CI), 0.63 to 0.86] with a sensitivity of 73% and specifity of 70%.

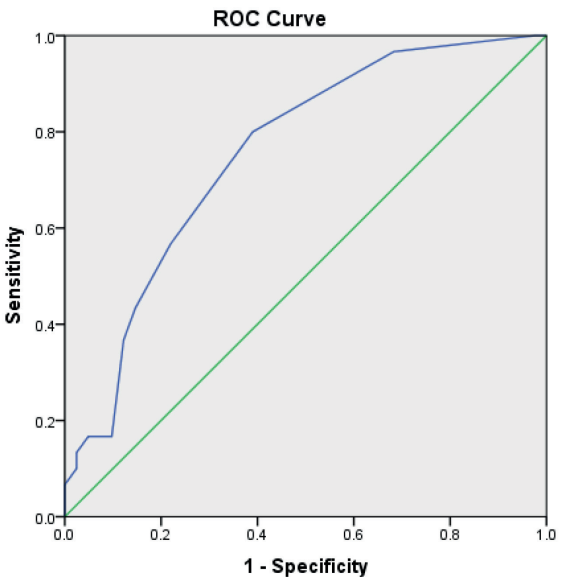

Fig. 2. Lymphocyte monocyte ratio of ≤ 3.5 had an AUC of 0.75 [95% confidence interval (CI), 0.64 to 0.86] with a sensitivity of 80% and specifity of 61%.

Table II. Characteristics of patients according to LMR and MP.

Variables	LMR		p-value	MP		p-value
	High (>3.5) (n=40)	Low (≤3.5) (n=31)		High (≥7.5%) (n=39)	Low (<7.5%) (n=32)	
Age at diagnosis						
<12 months	13 (32.5)	4 (12.9)	0.055	5 (12.8)	12 (37.5)	0.015
≥12 months	27 (67.5)	27 (87.1)		34 (87.2)	20 (62.5)	
Gender, N (%)						
Female	20 (50)	18 (58.1)	0.499	20 (51.3)	18 (56.2)	0.676
Male	20 (50)	13 (41.9)		19 (48.7)	14 (43.8)	
Stage, N (%)						
Stage 1,2,3,4S	22 (55.0)	8 (25.8)	0.014	8 (20.5)	22 (68.8)	<0.001
Stage 4	18 (45.0)	23 (74.2)		31 (79.5)	10 (31.3)	
Metastatic Disease						
Presence	25	23	0.29	32	16	0.005
Absence	15	8		7	16	
Risk Group, N (%)						
Low-Intermediate	20 (50.0)	5 (16.1)	0.003	5 (12.8)	20 (62.5)	<0.001
High	20 (50.0)	26 (83.9)		34 (87.2)	12 (37.5)	
Histology, N (%)						
Favorable	14 (40.0)	4 (16.0)	0.046	2 (6.7)	16 (53.3)	<0.001
Unfavorable	21 (60.0)	21 (84.0)		28 (93.3)	14 (46.7)	
MYCN amplification						
High	7 (29.2)	12 (54.5)	0.081	16 (59.3)	3 (15.8)	0.003
Normal	17 (70.8)	10 (45.5)		11 (40.7)	16 (84.2)	

(HR), 2.29; 95% CI, 1.11-4.75; p=0.025) and stage IV disease (HR, 2.97; 95% CI, 1.26-7.02; p=0.013) were the factors that were significantly associated with low 3-year OS. Low LMR (HR, 2.15; 95% CI, 1,07-4.30; p=0.03) and stage IV disease (HR, 3.13; 95% CI, 1.40-7.02; p=0.006) were also defined as independent factors for decreased 3-year EFS (Table III).

Discussion

Our study has shown that a low LMR might be a poor prognostic factor in pediatric neuroblastoma patients. In addition, a high MP was also associated with low EFS and OS even though the noteworthy association between high MP and clinical outcome could not be established in the multivariate analysis. Current literature has indicated that the combination of cellular components of the systemic inflammatory response, such as monocyte count, L/M ratio, and MP represent significant markers of clinical outcome in a wide variety of cancers.[15,16] Lymphocytes are regarded as the crucial factors in immune surveillance, and the presence of an immunologic antitumor reaction is based on lymphocytic infiltration into the tumor microenvironment.[17,18] The prognostic role of LMR was first described by Porrata et al.[6] in Hodgkin Lymphoma patients in 2011. Shortly after this study, in 2012, Li et al.[7] documented that LMR was also an independent prognostic factor of survival in diffuse large B-cell lymphoma patients. The association between low LMR and poor OS was shown later on in non-hematologic solid tumors. Li et al.[19] documented that pretreatment LMR level was a significant favorable factor for prediction of the clinical outcome in nasopharyngeal carcinoma patients. The following reports were similar

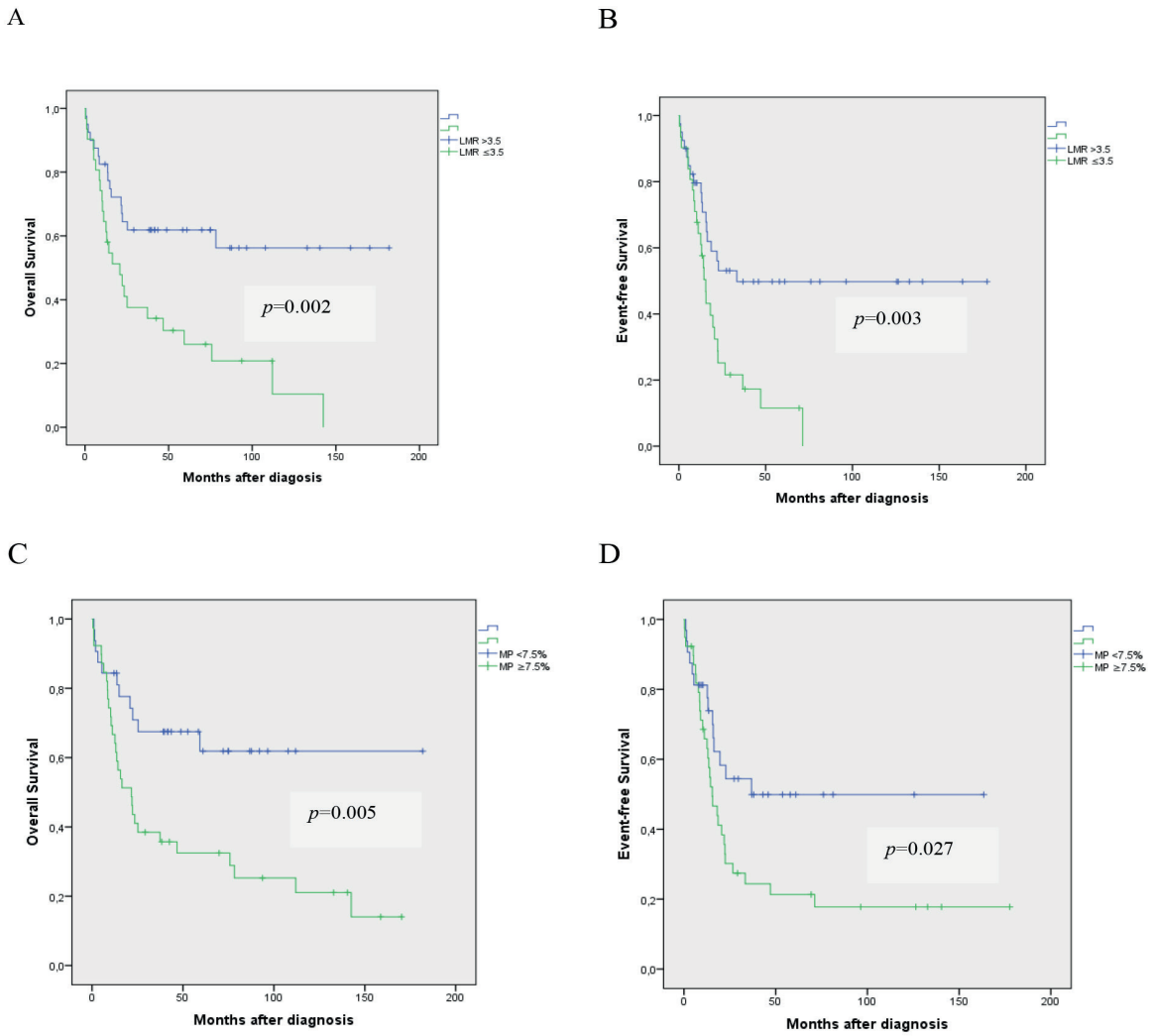

Fig. 3. Comparison of low and high LMR on OS (A), EFS (B) and low and high MP on OS (C) and EFS (D).
EFS: event-free survival, OS: overall survival, LMR: lymphocyte to monocyte ratio, MP: blood monocyte percentage

Table III. Univariate and multivariate analyses for OS and EFS.

		OS			EFS	
Covariate	HR	95% CI	p-value	HR	95% CI	p-value
Univariate analysis						
LMR ≤3.5	2.65	1.41-4.99	0.002	2.48	1.34-4.56	0.004
MP ≥7.5%	2.60	1.30-5.21	0.007	2.02	1.07-3.81	0.030
Stage 4 disease	3.13	1.49-6.57	0.003	3.13	1.54-6.35	0.002
Unfavorable histology	3.77	1.32-10.74	0.013	4.25	1.5-12.06	0.006
High risk	2.84	1.25-6.42	0.012	2.74	1.27-5.92	0.010
Multivariate analysis						
LMR ≤3.5	2.29	1.11-4.75	0.025	2.15	1.07-4.30	0.030
Stage 4 disease	2.97	1.26-7.02	0.013	3.13	1.40-7.02	0.006

LMR: lymphocyte to monocyte ratio
MR: monocyte percentage

to previously reported data; a lower LMR was associated with lymph nodes metastasis, tumor progression and poor 5-year cancer specific survival in esophageal squamous cell carcinoma patients.[20] The low LMR was related with more aggressive tumor behavior and worse long-term survival in resectable gastric adenocarcinoma patients.[21] Low LMR was significantly correlated with higher degree of tumor infiltration and poor prognosis also in other digestive system cancers such as pancreas and colorectal carcinomas.[22,23] Deng et al.[24] have retrospectively evaluated 317 newly diagnosed locally advanced rectal cancer patients and shown that the LMR was a valuable prognostic factor for predicting the OS in this group of patients. A meta-analysis showed that the patients with lower LMR had poorer OS in non-small cell lung cancer.[25] Low LMR was also associated with unfavorable survival in patients with ovarian cancer and could serve as a prognostic biomarker.[26]

The definite mechanism of the association between low LMR and poor survival of cancer patients are not totally explained. This relevance may de described through tumor infiltrating immune cells which contribute significantly in destruction or development of tumor growth. In tumor microenvironment the lymphocytes are considered as one of the most vital components of the host's cellular immunity. Therefore, a low lymphocyte count might be responsible for a fragile, inadequate reaction to tumor and thereby an exacerbated clinical outcome.[17]

Macrophage is another essential component of tumor infiltrating inflammatory cells. Tumor associated macrophages (TAM) are derived from peripheral blood monocytes and a positive correlation between TAM and peripheral blood monocyte count has been shown in previous studies.[27,28] Therefore, circulating level of monocytes may reflect formation or presence of TAMs. TAM may promote angiogenesis, metastasis, immune suppression and chemo resistance.[5,29-31] Macrophages do not only contribute to tumor growth but also impair effective anti-tumor lymphocyte response. Some clinical studies have indicated a significant correlation between elevated macrophage content and poor clinical outcome in soft tissue cancer patients.[32]

Metastatic disease at diagnosis is one of the most important prognostic factors for neuroblastoma.[10] It was shown that TAM enhance neo-angiogenesis, promote tumor cell migration and metastases.[27,30,33] The high peripheral monocyte count can reflect the presence or formation of TAM and has been reported as a poor prognostic factor in adult patients with various types of cancer.[33] Koh et al.[27] also reported that there was a positive correlation between TAM and MP in patients with Hodgkin lymphoma. We found that there were more patients with advanced stage and metastasis in the group who had high MP, unfortunately we could not evaluate tumor microenvironment. There is a unique study by Asgharzadeh et al.[34] which shows significantly greater numbers of infiltrating macrophages in tumor samples of neuroblastoma patients with metastatic (stage 4) disease. These findings support that number of peripheral monocyte count, which will convert to TAM, may have prognostic significance in neuroblastoma. However, there was a prognostic significance of high MP in neuroblastoma outcome according to univariate analysis, multivariate analysis did not reveal that high MP was an independent prognostic factor for EFS and OS in our study. Further studies including higher number of patients are needed to determine the prognostic value of peripheral monocytes count or MP in neuroblastoma patients.

The limitations of this study are the retrospective nature of the design, small number of patients, short follow up period and absence of tumor microenvironment evaluation. We evaluated LMR and MP on outcome of neuroblastoma patients. LMR was found as an independent prognostic factor for EFS and OS in this study. The peripheral blood count and cell count ratio can be determined readily and inexpensively by a standard automated complete blood count machine. LMR and MP may be new

prognostic factors for neuroblastoma and can be used for predicting survival which is a cost effective and easy-accessible biomarker. Our results should be verified by multi-centric and prospective studies which also evaluate the tumor microenvironment concomitantly.

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Author contribution

The authors confirm contribution to the paper as follows: study conception and design: KY, EG; data collection: KY, AK; analysis and interpretation of results: SB, GT, AK, EG; draft manuscript preparation: KY, GT, FTK, EG; All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

After obtaining the ethics approval from the local ethics committee (Akdeniz University KAEK -2020-735), the study was initiated with informed consent from the patients

Source of funding

We have nothing to disclose

Conflict of interest

All the authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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