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Pediatric Medulloblastoma: Prognostic Value of Preoperative Blood Cell Ratios

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ABSTRACT

Background: The prognostic significance of preoperative neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), and platelet to lymphocyte ratio (PLR) have been demonstrated in various tumors. This study aimed to evaluate the prognostic role of these ratios in pediatric medulloblastoma.

Materials and Methods: Forty-three pediatric patients with medulloblastoma were evaluated, retrospectively. Clinical, radiological, and laboratory data were extracted from the electronic medical records of the patients. Univariate and multivariate Cox proportional hazard models were used to evaluate the impact of suggested variables, including NLR, LMR, and PLR on progression-free survival (PFS) and overall survival (OS). Kaplan-Meier curves were plotted for the assessment of PFS and OS. The Log-rank test was used to assess differences between the PFS and OS in the related categories.

Results: There were 27 males (62.8%) and 16 females (37.2%) with a mean age of 7.4 ±3.3 years. The median OS and PFS were 62.8 ±17.2 and 43.3 ±15.6 months, respectively. The multivariate Cox model showed the clinical risk group, NLR, and LMR as independent predictors of the PFS and the OS ($p<0.05$). The Log-rank test revealed that OS and PFS were higher in patients with NLR <4 and those with LMR ≥ 3.48 ($p <0.05$). There were no differences between patients with PLR>200 and PLR< 200 based on OS and PFS.

Conclusion: Our results suggest an elevated preoperative NLR and a lowered preoperative LMR as simple predictors of survival in pediatric medulloblastoma. These cost-effective and easily available ratios, along with previously established variables, could be valuable to predict survival in pediatrics with medulloblastoma.

Keywords: Pediatric medulloblastoma; Progression-free survival; Neutrophil to lymphocyte ratio; Lymphocyte to monocyte ratio

INTRODUCTION

Brain tumors are the most common solid neoplasms in children[1]. Medulloblastoma is one of the most common central nervous system (CNS) neoplasms occurring in pediatrics[1, 2]. The incidence in pediatrics has been reported between 4.0 to 4.9 per 1,000,000 persons per year[3].

Maximal safe surgical resection followed by chemotherapy and/or radiotherapy is the standard treatment for medulloblastoma[4]. However, the five-year survival rate is below 50 percent for the high-risk patients[1,5]

The significance of the host immune response against the neoplasms in the survival of patients with various cancers has been demonstrated[6,7]. Neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), and platelet to lymphocyte ratio (PLR) are novel ratios that reflect systemic

inflammatory response against various stimuli. The prognostic role of these ratios has been demonstrated in several cancers[8-10]. However, the prognostic role of preoperative NLR, LMR, and PLR in the pediatric medulloblastoma has not been widely assessed. The present study aimed to evaluate the predictive role of NLR, LMR, and PLR for the survival of pediatric patients with medulloblastoma.

MATERIALS AND METHODS

All pediatric patients (aged< 18) with medulloblastoma that managed in our center between May 2009 and May 2018 were enrolled in the present study. All children underwent a maximal surgical safe resection followed by chemotherapy and/or radiotherapy. We followed all of them till death or till the last follow-up visit on April 2019.

The inclusion criteria for this study were as follows: 1- age less than 18 years at diagnosis 2- diagnosis of medulloblastoma based on histopathology according to 2007 criteria from the World Health Organization[11]. Patients with a history of preoperative sign of infection and those received preoperative steroids were excluded.

We reviewed the clinical, radiological, and laboratory data of all patients.

Blood sampling was done during a week before surgery.

NLR and PLR were calculated by dividing the absolute neutrophil or platelet count by lymphocyte count. Likewise, LMR was measured by dividing the absolute lymphocyte count by monocyte count.

Overall survival (OS) was calculated from the *date* of surgery to the date of death or the last follow-up in April 2019. The progression-free survival (PFS) was defined as the date of the first surgery until the diagnosis of progression based on imaging.

According to age, the extent of resection, and Chang's metastasis staging, patients were divided into the average-risk group and the high-risk group. Children older than three years with less than 1.5 cm of residual tumor and no metastatic disease were stratified as the average-risk group and those not fulfilling these criteria were considered as the high-risk group[12]. The study was approved by the institutional review board and Ethics Committees.

Statistical analysis

Continuous and categorical variables were expressed as mean ± standard deviation, and frequency or percentages, respectively. Univariate and multivariate Cox proportional hazards model were used for analyses of the effects of suggested variables on patients' survival time. $P < 0.05$ was considered statistically significant.

Kaplan-Meire curves for OS and PFS were plotted stratified by LMR, NLR, PLR categories. The Log-rank test applied to assess differences among the survival of patients in the related category. Crude and adjusted Hazard ratios with 95% confidence intervals were reported for each predictor.

All statistical analyses were performed using SPSS 20.0 (Chicago, IL, USA).

RESULTS

Forty-three pediatric patients with medulloblastoma were evaluated. Most patients (62.8%) were male, and the mean age was 7.4 ±3.3 years. The median OS and PFS and follow-up time were 62.8 ±17.2 months, 43.3 ±15.6 months, and 78.4 ±18.1, respectively. Twenty-five patients (58.1%) had classic medulloblastoma (Figure 1), 11 cases (25.6%) had desmoplastic/nodular type (Figure2), 5 ones (11.6%) had large-cell/anaplastic type and 2 cases (4.6%) had other different types (Table 1).

There were 16 (37.2%) patients in the high-risk group and 27cases (62.8%) in the average-risk group. Cerebrospinal fluid (CSF) shunting was done in 58.1% of patients. In our study, 88.4% and 86% of patients received radiotherapy and chemotherapy, respectively. Univariate Cox analysis showed the pathologic subtype, the clinical risk group, metastatic stage, tumor size, NLR, and LMR as predictors of OS (Table 2). While the multivariate Cox model demonstrated a high-risk group, NLR and LMR were independent predictors of OS ($p<0.05$) (Table 2). According to the multivariate Cox model clinical risk group, NLR and LMR were the predictors of PFS ($p<0.05$) (Table 3). The mean value of NLR, LMR, and PLR were 3.9 ±0.5, 3.8 ±1.4, and 201.8 ±16.4, respectively. According to the log-rank test, OS and PFS were significantly higher in patients with NLR less

than 4 ($p<0.05$) (Figure 3). Furthermore, OS and PFS were also significantly higher in patients with LMR ≥ 3.48 ($p<0.05$) (Figure 4). The Log-rank test did not show any differences between patients with PLR>200 and those with PLR< 200 based on OS and PFS (Figure 5).

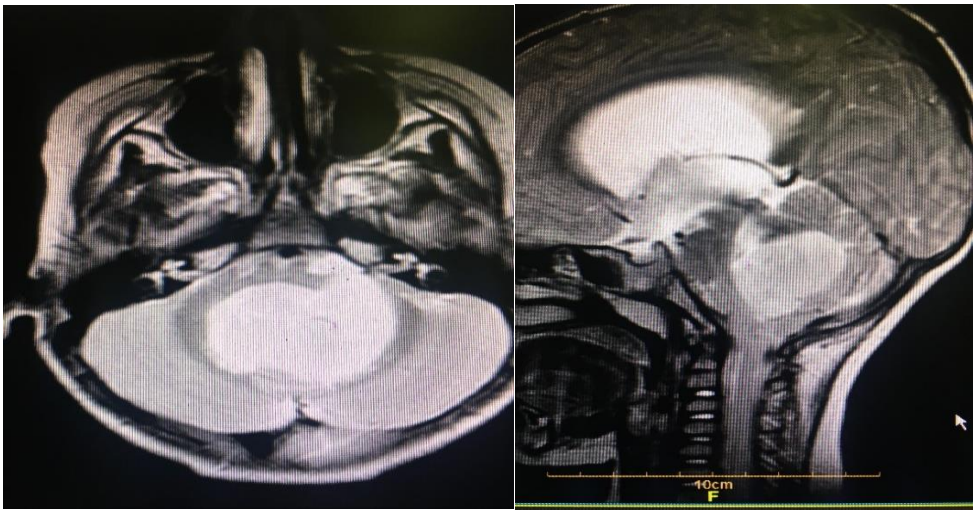

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Figure 1: A 3 y/o child with classic medulloblastoma
(A) Axial T2- weighted MRI (B) sagittal T2- weighted MRI

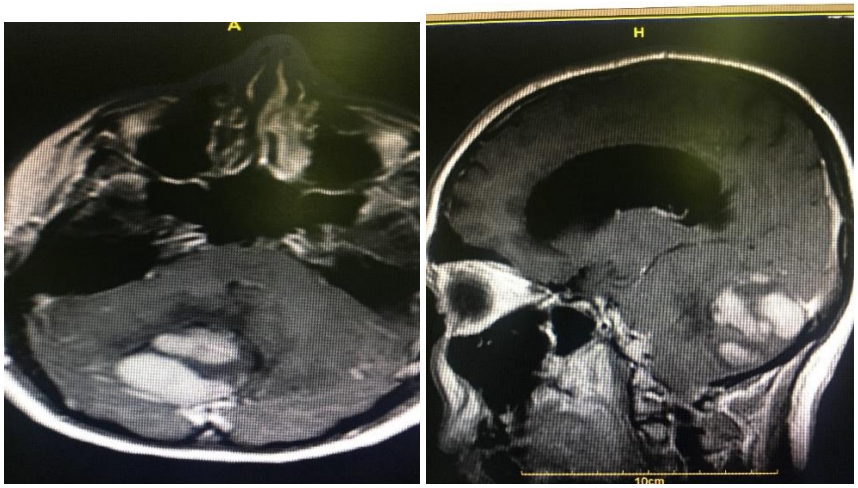

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Figure 2: A 14 y/o child with desmoplastic/nodular medulloblastoma
(A) Post-gadolinium axial T1- weighted MRI (B) Post-gadolinium sagittal T1- weighted MRI

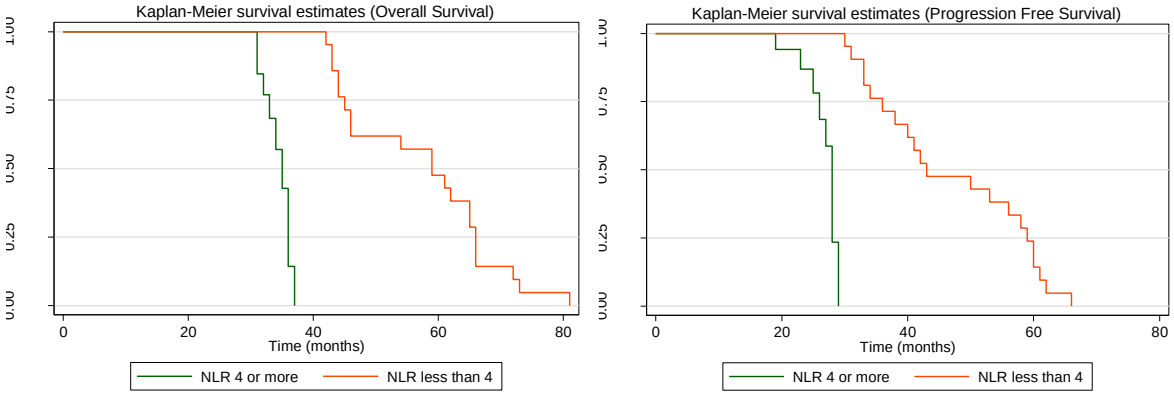

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Figure 3. Comparison of Kaplan- Meier estimates of survival between the patients with NLR>4 and NLR<4
(a) Overall survival (b) Progression free survival

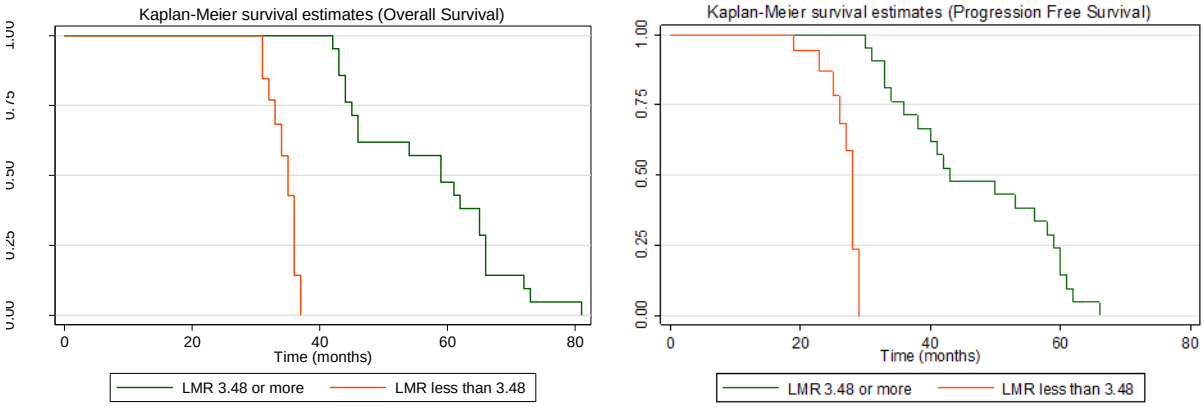

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Figure 4. Comparison of Kaplan- Meier estimates of survival between the patients with LMR>3.48 and LMR<3.48
(a) Overall survival (b) Progression free survival

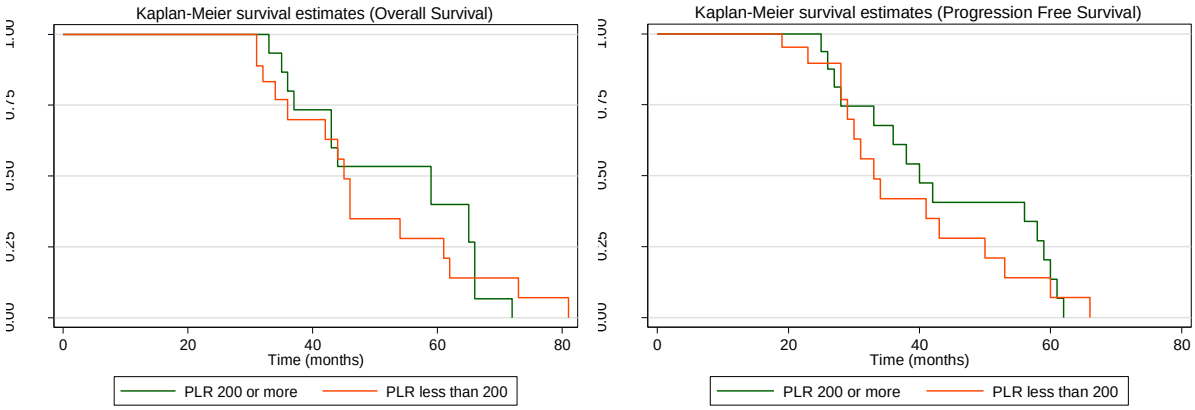

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Figure 5. Comparison of Kaplan- Meier estimates of survival between the patients with PLR>200 and PLR<200

(a) Overall survival (b) Progression free survival

Table 1: Basic characteristics of the study population

Variable	Frequency	Percent
Gender		
Male	27	62.8
female	16	37.2
Pathologic Variant		
Classic	25	58.1
Desmoplastic/nodular	11	25.6
Large-cell/anaplastic	5	11.6
Other differentiate	2	4.6
Clinical risk stratification		
Average-risk	27	62.8
High risk	16	37.2
Metastatic status		
M0: M0: no evidence of gross subarachnoid or hematogenous metastases	21	48.8
M1: microscopic CSF involvement	13	30.2
M2: gross nodular seeding intracranially beyond the primary site (in cerebellar/cerebral subarachnoid space, 3rd ventricle, or lateral ventricle(s))	6	13.9
M3: gross nodular seeding of spinal subarachnoid space	3	6.9
M4: metastases outside cerebrospinal axis	0	0
Tumor size		
T1:<3 cm in diameter	23	53.5
T2:≥3 in diameter	13	30.2
T3a: tumor > 3 cm and with extension into aquedauct of sylvius or foramen of luschka	5	11.63
T3b: tumor > 3 cm and with unequivocal extension into brainstem	2	4.65
T4: tumor > 3 cm with extension past the aqueduct of sylvius or past foramen magnum	0	0
Residual tumor		
<1.5 cm^2	27	62.8
>1.5 cm^2	12	27.9
Not available	4	9.3
CSF Shunting		
Yes	25	58.1
no	18	41.9
Radiotherapy		
Yes	38	88.4
No	5	11.6
Chemotherapy		
Yes	37	86.0
No	6	14.0

Table 2: Predictive factors of overall survival

	Crude estimates			Adjusted estimates		
Variable	HR	95%CI	p-value	HR	95%CI	p-value
Age	0.96	0.85, 1.10	0.609			
Gender (ref: male)	0.99	0.45, 2.16	0.975			
Pathologic Variant (ref:classic)						
Desmoplastic/nodular	0.21	0.85, 0.49	<0.0001			
Large-cell/anaplastic	3.27	-	-			
Other differentiate	2.18	-	1			
Clinical risk stratification(ref:Avrage)						
High risk	8.69	6.17, 12.5	<0.0001	4.94	2.45, 9.98	0.011
Metastasis (ref: M0)						
M1	1.08	0.47, 2.48	0.855			
M2	2.32	-	1			
M3	3.29	2.02, 5.37	0.014			
Tumor size(ref: T1:<3 cm in diameter)						
T2:≥3 in diameter	1.11	1.15, 1.07	<0.0001			
T3a:>3 cm& with extension	1.08	-*	-			
T3b:>3 cm with Unequivocal	1	-	-			
Residual tumor (ref: <1.5 cm^2)						
>1.5 cm^2	1.74	0.58, 5.21	0.322	0.26	0.05, 1.49	0.132
Not available	0.30	0.07, 1.37	0.121	0.42	0.06, 2.80	0.367
CSF Shunting (ref:yes)						
No	1.33	0.63, 2.79	0.45			
Radiotherapy (ref:yes)						
No	1	-	-			
chemotherapy(ref:yes)						
No	1.20	-	1			
Neutrophils to lymphocyte ratio	2.85	1.57, 4.80	<0.0001	2.14	1.14, 3.59	0.041
Lymphocyte to monocyte ratio	0.07	0.02, 0.25	<0.0001	0.05	0.01, 0.24	<0.0001
Platelet to lymphocyte ratio	0.98	0.97, 1.01	0.332	0.97	0.94, 1.01	0.094

*didn't reach to convergence due to lack of adequate sample size

Table 3: Predictive factors of progression free survival

	Crude estimates			**Adjusted estimates**		
Variable	HR	95%CI	p-value	HR	95%CI	p-value
Age	0.97	0.84, 1.11	0.632			
Gender (ref: male)	1.04	0.49, 2.22	0.911			
Pathologic Variant (ref:classic)						
Desmoplastic/nodular	0.09	0.03, 0.29	<0.0001			
Large-cell/anaplastic	4.56	-	-			
Other differentiate	2.36	-	-			
Clinical risk stratification (ref:Average)						
High risk	6.72	4.86, 12.19	<0.0001	3.26	1.44, 5.89	0.026
Metastasis (ref: M0)						
M1	1.49	0.66, 3.37	0.334			
M2	1.02	-	1			
M3	2.23	0.27, 8.67	0.458			
Tumor size(ref: T1:<3 cm in diameter)						
T2:≥3 in diameter	3.64	4.12, 7.11	0.001			
T3a:>3 cm& with extension	5.19	3.34, 19.87	0.007			
T3b:>3 cm with Unequivocal	1	-	-			
Residual tumor (ref: <1.5 cm^2)						
>1.5 cm^2	1.63	0.55, 4.84	0.382	0.31	0.06,1.57	0.159
Not available	0.54	0.15, 1.88	0.334	2.47	0.41, 4.93	0.325
CSF Shunting (ref:yes)						
No	1.09	0.52, 2.28	0.815			
Radiotherapy (ref:yes)						
No	5.87	-	1			
chemotherapy(ref:yes)						
No	1.17	-	1			
Neutrophils to lymphocyte ratio	2.69	1.75, 5.43	<0.0001	1.78	1.01, 3.65	0.03
Lymphocyte to monocyte ratio	0.14	0.03, 0.37	<0.0001	0.05	0.01, 0.41	0.005
Platelet to lymphocyte ratio	0.99	0.97, 1.01	0.355	0.97	0.94, 1.01	0.073

DISCUSSION

Medulloblastoma is one of the most common primary brain tumors in pediatrics[13]. Despite the development in the management of pediatric medulloblastoma, there is a high mortality rate in these children[4, 5]. Several studies have shown blood cell ratios as predictors of survival in various diseases, including brain tumors[14-16]. Very few studies have noticed the role of these indices in medulloblastoma[17]. Meanwhile, some studies demonstrated the significance of host immune response in the survival of patients with various cancers[18-20]. Han et al. (2015) retrospectively investigated 152 patients with glioblastoma. They found that higher pretreatment NLR levels were significantly associated with shorter overall survival in these patients (P = 0.037). Interestingly, their results showed that despite the correlation between NLR and PLR (R = 0.509, P < 0.001), NLR was a better prognostic factor in comparison with the PLR[21].

In 2017, Mitsuya et al. retrospectively evaluated 105 patients who underwent resection of brain metastases during a period of 8 years. In their study, lung, colon, breast, and uterus were the most common primary tumors. The median survival of their patients was about twelve months. The authors identified the NLR threshold value as five. Their results showed a remarkable difference in the median OS between patients with NLR < 5 and those with NLR ≥ 5 (p = 0.001)[9].

Arroyo et al. investigated the prognostic role of methylation-derived NLR (mdNLR) in 56 children with medulloblastoma. They found that elevated log-transformed mdNLR was associated with a higher likelihood of death in these patients [17].

There are several probable explanations to justify the role of NLR and LNR in cancer patient survival.

The pretumoral activity of neutrophils has been demonstrated. It has been shown that neutrophils secrete cytokines that are associated with tumor progression and treatment resistance, including tumor necrosis factor (TNF), vascular endothelial growth factor (VEGF), tumor necrosis factor, IL2, IL6, and other cytokines that contribute to cancer progression[22-25]. Therefore, an elevated neutrophil count could aid the promotion of rapid-growing, treatment-resistant tumors [24]. On the other hand, it has been demonstrated that tumors can release myeloid growth factors and, as a result, the elevated production of neutrophils [8, 26].

The antitumoral role of lymphocytes, especially helper T cells (Th) and natural killer cells, has been well defined. An elevated count of neutrophils suppresses the cytolytic activity of Th and natural killer cells and, as a result, helps the tumor progression [9, 27, 28].

Monocytes are other inflammatory cells that could promote the inflammatory process through up-regulation of inducible nitric oxide synthase expression [22, 29].

Following these findings, our results showed that patients with a higher NLR and a lower LMR are more likely to have a shorter PFS and OS.

Gasic et al., in 1968, first found the association between platelet number and metastatic cancer potential[30].

Some prior studies found that platelet-mediated inflammation contributes to cancer progression, so researchers have tested many platelet-based markers of inflammation in various cancers [20, 31].

Wang et al. (2018) investigated 112 glioma patients that underwent surgery at their center. They found that glioma patients with PLR ≥ 200 had a significantly shorter OS. However, the Cox regression model failed to spot PLR as an independent predictor for survival in their study [32].

Our results did not demonstrate any significant relationship between PLR and survival of children with medulloblastoma. This negative finding may reflect the influence of confounding factors, so it should be explored in larger, preferably prospective studies to clarify the potential prognostic relevance of PLR in medulloblastoma.

CONCLUSION

Our results suggest a higher preoperative NLR and a lower preoperative LMR as simple predictors of survival in pediatric medulloblastoma. These cost-effective and easily available ratios, along with previously established variables, could help to predict survival in pediatric medulloblastoma.

Limitations

The present study has several limitations. Neutrophilia is nonspecific and can occur in many conditions including subclinical infection, steroid administration, or even acute stress. Furthermore, this is a retrospective study with a small sample size that conducted in a single center. Moreover, molecular subtyping information was not available for any patients (e.g., WNT, SHH, Group 3, 4). As a result, we suggest large, multicenter prospective trials to evaluate the prognostic significance of NLR and LMR in pediatric medulloblastoma.

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