

Original Article

Is medulloblastoma associated with systemic immunomodulation? – A comparative analysis of preoperative inflammatory markers

Ravi Sharma¹, Varidh Katiyar¹, Hitesh Gurjar¹, Mehar Sharma², Revanth Goda¹, Zainab Vora³

Departments of ¹Neurosurgery, ²Pathology, and ³Radio diagnosis, All India Institute of Medical sciences, CNC, AIIMS, New Delhi, India.

E-mail: Ravi Sharma - aiims.ravisharma@gmail.com; *Hitesh Gurjar - hiteshgurjar@gmail.com; Varidh Katiyar - katiyar.varidh@gmail.com; Mehar Sharma - sharmamehar@yahoo.co.in; Revanth Goda - revanth2k7@gmail.com; Zainab Vora - zainab8@gmail.com



*Corresponding author:

Hitesh Gurjar,
Department of Neurosurgery,
All India Institute of Medical
Sciences, New Delhi, 720 CNC,
Delhi - 110029, India.

hiteshgurjar@gmail.com

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ABSTRACT

Background: We attempt to compare preoperative inflammatory markers among children with medulloblastoma and pilocytic astrocytoma and establish their diagnostic efficacy to distinguish these tumors.

Methods: Children (<18 years) with biopsy-proven medulloblastoma and pilocytic astrocytoma operated at our institute from January 2012 to January 2018 were enrolled in this study. The hematological parameters were compared between the two groups and with healthy controls. Children with a history of disease or medications that may confound these parameters were excluded from the study. Receiver operator characteristic curves were made to assess the diagnostic accuracy of markers found to be significant.

Results: Patients with medulloblastoma were found to have higher neutrophil-lymphocyte ratio (NLR), derived neutrophil-lymphocyte ratio (dNLR), platelet-lymphocyte ratio (PLR), and platelet counts compared with pilocytic astrocytoma. Absolute lymphocyte count (ALC) was significantly lower in medulloblastoma group as compared to healthy controls but not with pilocytic astrocytoma. NLR and dNLR demonstrated maximum diagnostic accuracy in distinguishing patients with medulloblastoma from healthy controls and pilocytic astrocytoma. Using a cutoff of 2.45 for NLR distinguishes medulloblastoma from healthy controls as well as pilocytic astrocytoma with a sensitivity of 75.5% and specificity of 66.7%. Similarly, dNLR cutoff of 1.47 distinguishes medulloblastoma from healthy controls with a sensitivity of 83% and specificity of 76% and a cutoff of 1.53 distinguishes medulloblastoma from pilocytic astrocytoma with a sensitivity of 81.1% and specificity of 81.8%. Combination of NLR and dNLR performed only marginally better than individual variables with area under the curve being 0.856 for medulloblastoma versus healthy controls and 0.86 for medulloblastoma versus pilocytic astrocytoma.

Conclusion: NLR and dNLR can be used as a preoperative predictive marker in medulloblastoma. There is decreased ALC in patients with medulloblastoma contributing to raised NLR and dNLR suggestive of systemic immunosuppression.

Keywords: Immunosuppression, Lymphopenia, Neutrophil-lymphocyte ratio

INTRODUCTION

Adult brain tumors have been found to be associated with systemic modulation of the immune system.^[4] In fact, pathological evaluation reveals important role of host leukocytes and macrophages in influencing the progression of neoplastic pathologies.^[6,10,19] Angiogenesis,

which is an important factor to sustain the growth of neoplasms, is also dependent on inflammatory cytokines and growth factors.^[5] Tumor-associated neutrophils have been proposed to play little antitumor role, if any. On the contrary, they are associated with progression of tumor and degeneration to a higher grade.^[6] Neutrophil counts (NCs) and neutrophil-lymphocyte ratios (NLRs) are found to be correlated to the prognosis of patients in many different malignancies.^[3,7,8,12-14,16] On the basis of these findings, there has been a recent surge in interest regarding the changes in the systemic inflammatory markers in the brain tumors as well. Although brain is an immunologically privileged site, it has been found in several studies that NC, NLR, and other hematological inflammatory markers are correlated with the grade of glioma in adult patients.^[23] NLR has been shown to not only correlate with the probability of a higher grade of tumor but it can also be used as a prognostic marker with higher NLR values associated with decreased survival.^[2,10,17] A few authors have also observed gliomas to be associated with immunosuppression.^[9] Lymphopenia is a contributing factor in the high NLR observed in glioblastoma patients apart from raised NC.^[23]

Although the pediatric population is different in terms of the common types and location of brain tumors, few recent studies have shown that the immunological parameters are altered in the pediatric brain tumors as well.^[21,22] NLR, mean platelet volume (MPV), and total leukocyte count (TLC) were found to be associated with the presence of intracranial tumor in pediatric population.^[21]

On this background, we attempt to compare these inflammatory markers among children with medulloblastoma (MB), pilocytic astrocytoma (PA), and healthy controls (HCs). We also aim to assess the efficacy of various inflammatory parameters and their combinations for differentiating medulloblastoma from pilocytic astrocytoma and healthy controls.

MATERIALS AND METHODS

Study design

The electronic medical records of pediatric population (<18 years) with biopsy-proven posterior fossa medulloblastoma and pilocytic astrocytoma operated at the Department of Neurosurgery, All India Institute of Medical Sciences, New Delhi, India, from January 2012 to January 2018 were collected and retrospectively analyzed. Patients who had recurrent tumor, had received preoperative chemotherapy and radiotherapy, preoperative hormonal replacement including glucocorticoids, history of infection or fever at the time of admission, history of autoimmune or hematological disease at the time of admission, history of serious hepatic, renal or cardiac dysfunction at the time of admission, history of medications which can alter blood

parameters, or whose complete data on preoperative blood counts and serum albumin levels were not available were excluded from the study. Informed written consent was obtained from the guardian/parents of the child. For the control group, we included children who came to annual health check-up at the periphery screening centers of our institute with noninfectious/nonmalignant conditions such as lipomas and scoliosis. This study was approved by the Institutional Ethics Committee.

Data collection

Information regarding the demographic and disease characteristics, including age, sex, and histopathology diagnosis, were retrieved from the hospital medical records and electronic database. Within 1 week before surgery, routine preoperative blood investigations were done. The TLC, NC, ALC, and PC were collected from the routine blood test, and albumin levels were collected from the hepatic function test. Other composite variables such as preoperative NLR (quotient of NC to LC), dNLR (quotient of NC to [TLC-NC]), PLR (ratio of PC to LC), and PNI (serum albumin (g/L) + 5 × total lymphocyte count) were calculated as described.

Statistical analysis

Statistical analysis was performed using the SPSS version 20. Initially, normality of the distribution of the variables was analyzed using the Kolmogorov-Smirnov test. Since almost all variables deviated significantly from normality, nonparametric statistics were used for estimates of central tendency and hypothesis testing. Continuous variables were presented as median with interquartile range (IQR). For comparison between groups, the Mann-Whitney U-test was used. NLR, dNLR, PLR, and PNI of MB group were compared with pilocytic astrocytoma and healthy controls. The diagnostic performance of NLR, dNLR, PLR, PNI, and their combinations was assessed by values of the area under the curve (AUC) obtained from the receiver operating characteristic (ROC) curve. Cutoff points were estimated using ROC curves for the variables which demonstrated significant diagnostic accuracy using the maximum Youden index as the criteria. Throughout the analysis, a two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Study population

A total of 53 patients with medulloblastoma, 66 with pilocytic astrocytoma located in the posterior fossa and a control group of 75 healthy children were included in the final analysis. The demographic characteristics for the study subjects are presented in Table 1. The age of patients with

Table 1: Preoperative characteristics of subjects with MB, PA, and HCs.

Characteristic	MB group (n=53)	PA group (n=66)	HCs (n=75)	P value
Age	8 (6–10)	8 (6–10)	8 (5–10)	*0.651 #0.459 \$0.642
Males (%)	36 (67.9%)	34 (51.5%)	40 (53.3%)	*0.092 #0.105 \$0.867
TLC (10 ⁹ /L)	8.4 (6.2–10.2)	8.75 (5.9–11)	8.8 (6.4–11)	*0.756 #0.757 \$0.992
ANC (10 ⁹ /L)	5.42 (4.15–6.66)	5.06 (3.08–6.38)	4.86 (3.71–6.48)	*0.198 #0.195 \$0.979
ALC (10 ⁹ /L)	1.18 (0.9–1.55)	1.38 (0.95–1.75)	1.43 (0.99–1.81)	*0.148 #0.045 \$0.58
PC (10 ⁹ /L)	217 (178–335)	210 (156–239)	210 (156–239)	*0.045 #0.029 \$0.89
Albumin (g/L)	42 (38–48)	45 (37–48)	44 (36–48)	*0.531 #0.742 \$0.764
NLR	2.8 (2.5–3.1)	2.1 (1.8–2.8)	1.9 (1.6–2.6)	*<0.001 #<0.001 \$0.404
dNLR	1.78 (1.63–2.03)	1.33 (1.22–1.5)	1.33 (1.22–1.44)	*<0.001 #<0.001 \$0.757
PLR	183.52 (123.27–301.9)	145.52 (103.5–205.27)	141.97 (101.07–234.03)	*0.036 #0.014 \$0.684
PNI	47.88 (43.5–54.19)	50.59 (43.37–56.56)	49.17 (42.5–56.77)	*0.37 #0.461 \$0.882

*MB versus PA, # MB versus HC, \$PA versus HC. All values are reported as median (interquartile range). MB: Medulloblastoma, PA: Pilocytic astrocytoma, HC: Healthy controls, NLR: Neutrophil-lymphocyte ratio, dNLR: Derived neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, ALC: Absolute lymphocyte count, TLC: Total leukocyte count

medulloblastoma ranged from 2.5 to 17 years, with median age being 8 years. The median age for patients with pilocytic astrocytoma and healthy controls was also 8 years. The sex distribution was also similar in all the three groups.

Comparison of preoperative inflammatory markers in medulloblastoma, pilocytic astrocytoma, and healthy controls

The preoperative inflammatory markers and comparisons between medulloblastoma, pilocytic astrocytoma, and healthy controls are detailed in Table 1. Patients with medulloblastoma had significantly higher NLR, dNLR, PLR, and platelet counts compared with healthy controls. Similarly, patients with medulloblastoma were found to have higher NLR, dNLR, PLR, and platelet counts compared

with pilocytic astrocytoma. ALC was significantly lower in medulloblastoma group as compared to healthy controls but not with pilocytic astrocytoma. However, there were no statistically significant differences in various preoperative inflammatory markers between the pilocytic astrocytoma and healthy control groups.

Evaluation of diagnostic efficacy of preoperative inflammatory markers and their combinations in patients with medulloblastoma versus healthy controls

For individual parameters, NLR and dNLR demonstrated maximum diagnostic accuracy in distinguishing patients with medulloblastoma from healthy controls, with AUC of ROC curve analysis of 0.783 and 0.848, respectively [Table 2, Figure 1]. Cutoffs of 2.45 for NLR and 1.47 for dNLR

were found to have best diagnostic accuracy in distinguishing medulloblastoma and healthy controls with Youden index of 0.422 and 0.59, respectively [Table 3]. Similar to the

differences noted in comparison between medulloblastoma and healthy controls, NLR and dNLR were the only two individual parameters which performed reasonably well for

Table 2: Diagnostic efficacy of NLR, dNLR, PLR, PNI, ALC, and their combinations in differentiating subjects with medulloblastoma, pilocytic astrocytoma, and healthy controls.

Characteristic	MB versus HC AUC (95% CI)	PA versus HC AUC (95% CI)	MB versus PA AUC (95% CI)
NLR	0.783 (0.705–0.861)	0.541 (0.445–0.636)	0.767 (0.683–0.851)
dNLR	0.848 (0.776–0.919)	0.515 (0.419–0.611)	0.851 (0.778–0.924)
PLR	0.627 (0.53–0.725)	0.52 (0.424–0.616)	0.612 (0.511–0.713)
PNI	0.462 (0.361–0.562)	0.507 (0.411–0.603)	0.452 (0.348–0.556)
ALC	0.604 (0.506–0.702)	0.527 (0.431–0.623)	0.577 (0.474–0.680)
NLR+dNLR	0.856 (0.788–0.923)	0.549 (0.453–0.645)	0.86 (0.79–0.93)
NLR+PLR	0.789 (0.713–0.866)	0.535 (0.44–0.631)	0.764 (0.68–0.848)
NLR+PNI	0.782 (0.704–0.86)	0.535 (0.44–0.631)	0.767 (0.683–0.851)
dNLR+PLR	0.842 (0.771–0.912)	0.513 (0.417–0.609)	0.849 (0.776–0.921)
dNLR+PNI	0.838 (0.763–0.914)	0.507 (0.411–0.603)	0.841 (0.764–0.919)
PLR+PNI	0.631 (0.535–0.727)	0.528 (0.432–0.623)	0.6 (0.497–0.702)
NLR+dNLR+PLR	0.855 (0.788–0.921)	0.542 (0.446–0.637)	0.856 (0.786–0.927)
NLR+PLR+PNI	0.788 (0.711–0.865)	0.535 (0.439–0.631)	0.766 (0.682–0.85)
NLR+PNI+dNLR	0.854 (0.786–0.922)	0.551 (0.455–0.647)	0.856 (0.784–0.929)
dNLR+PLR+PNI	0.844 (0.774–0.913)	0.524 (0.428–0.62)	0.849 (0.776–0.921)
NLR+dNLR+PLR+PNI	0.855 (0.79–0.921)	0.539 (0.443–0.635)	0.855 (0.785–0.926)

NLR: Neutrophil-lymphocyte ratio, dNLR: Derived neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, ALC: Absolute lymphocyte count,

Table 3: Diagnostic cutoff and sensitivity-specificity analysis of NLR, dNLR, and their combinations in differentiating subjects with medulloblastoma, pilocytic astrocytoma, and healthy controls.

Diagnostic marker	MB versus HC			MB versus PA		
	Cutoff	Sensitivity (%)	Specificity (%)	Cutoff	Sensitivity (%)	Specificity (%)
NLR	2.45	75.5	66.7	2.45	75.5	66.7
dNLR	1.47	83.0	76.0	1.53	81.1	81.8
NLR + dNLR (x)	0.407	81.1	78.7	0.428	79.2	78.8
Logit(x) = 0.978 x NLR + 3.014 x dNLR – 7.548				Logit(x) = 0.711 x NLR + 3.54 x dNLR – 7.596		

MB: Medulloblastoma, PA: Pilocytic astrocytoma, HC: Healthy controls, NLR: Neutrophil-lymphocyte ratio, dNLR: Derived neutrophil-lymphocyte ratio

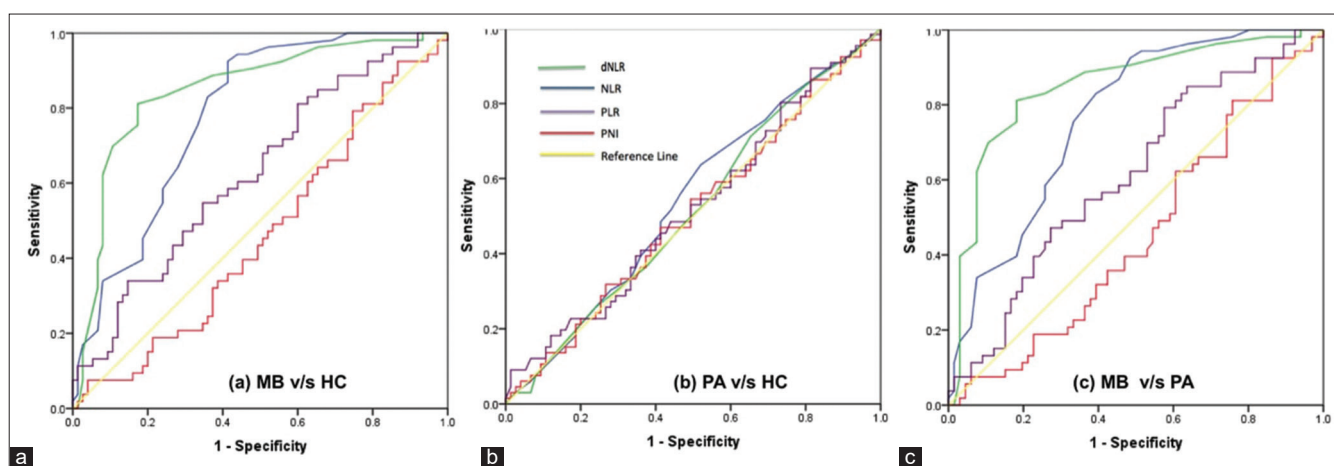


Figure 1: Receiver operating characteristic curves for individual variables for distinguishing between (a) medulloblastoma and healthy controls, (b) pilocytic astrocytoma and healthy controls, and (c) medulloblastoma and pilocytic astrocytoma.

distinguishing patients with medulloblastoma from those with pilocytic astrocytoma, with AUC of 0.767 and 0.851, respectively [Table 2, Figure 1] and at the cutoffs of 2.45 for NLR and 1.53 for dNLR had Youden index of 0.422 and 0.629, respectively [Table 3]. As previously, combinations of NLR and dNLR performed only marginally better than individual variables with AUC being 0.856 for medulloblastoma versus healthy controls and 0.86 for medulloblastoma versus pilocytic astrocytoma. Although ALC was found to be significantly lower in medulloblastoma group, it had a low AUC of 0.604 on ROC curve analysis [Table 2]. None of the other combinations performed any better NLR + dNLR and were not analyzed further. No significant difference was observed in any of the inflammatory markers between the pilocytic astrocytoma and healthy controls group. The ROC curves for the significant individual and combination variables are shown in Figure 2.

Statistical prediction model for medulloblastoma

The performance of different combinations of all the inflammatory parameters as a diagnostic marker for distinguishing among medulloblastoma, pilocytic astrocytoma, and healthy controls group was assessed by constructing logistic regression model followed by their ROC curve analysis. Only the combination of NLR and dNLR had substantial value over individual variables to predict medulloblastoma in comparison to pilocytic astrocytoma and healthy controls, as discussed previously. The equations describing the logistic regression model to combine NLR and dNLR for medulloblastoma versus pilocytic astrocytoma and medulloblastoma versus healthy controls group are given in Table 3.

DISCUSSION

There is recent surge of interest in the relationship between inflammation and tumor development and progression.^[20] In

fact, various blood inflammatory markers have been shown to be related to various malignancies. For example, preoperative NLR and PLR have been shown to help in early detection and prognosis in patients with colorectal cancer.^[11,15] Recently, such hematological parameters like NLR have been investigated not only as a predictive marker for the presence and grade of glial tumors but also as a prognostic marker in GBM. Raised NLR is found to be associated with poor prognosis in patients with GBM.^[2,10] Zheng *et al.*^[23] have even investigated the correlation between the hematological parameters with histopathological grade and found that NLR and dNLR are predictive of the WHO grade of glioma. Similarly, Han *et al.*^[10] observed prognostic significance of PLR in glioma patients.

In the light of these findings, several researchers have investigated the role of these blood markers in pediatric brain tumors as well.^[18,21,22] Tunturk *et al.*^[21] conducted a retrospective study of patients <3 years of age and found correlation of preoperative WBC count, NLR and MPV with the presence of CNS tumors. However, they included a wide range of malignant and benign tumors, and no association was found with the different histological types of pediatric brain tumors.

However, in another recent study conducted by Patel *et al.*,^[18] absolute lymphopenia and raised NLR was found in patients with medulloblastoma when compared with pilocytic astrocytoma. The authors attributed the lymphopenia to tumor-induced systemic immunosuppression. It is noteworthy that there were only 16 patients in each group in this study and ROC curve analysis was not done to define cutoffs for the same. In our study, we also found raised NLR to be associated with medulloblastoma both in comparison to pilocytic astrocytoma and healthy controls. However, we found significant lymphopenia in the medulloblastoma group when compared to healthy controls but not with pilocytic astrocytoma in contrast to Patel *et al.*^[18] who found ALC to be different between medulloblastoma and

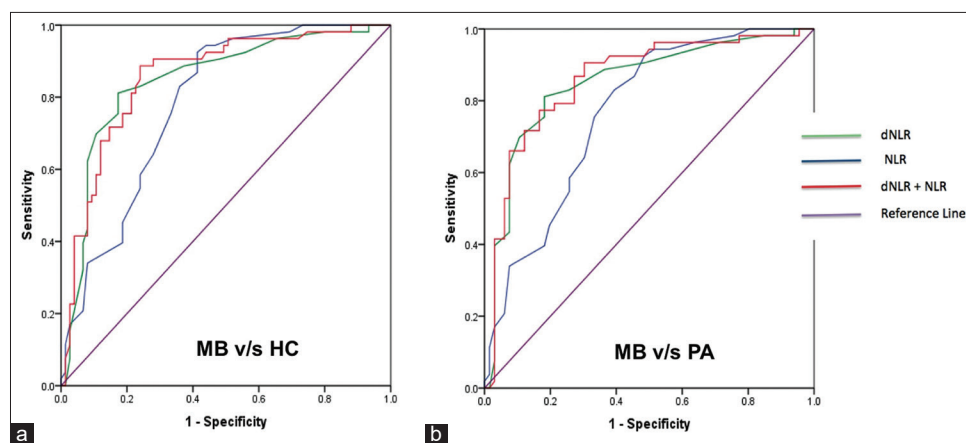


Figure 2: Receiver operating characteristic curves for significant individual and combination variables for distinguishing between (a) medulloblastoma and healthy controls and (b) medulloblastoma and pilocytic astrocytoma.

pilocytic astrocytoma. Thus, raised NLR, at least partially due to lymphopenia, seems to indicate systemic immune suppression in children with medulloblastoma.

Wilson *et al.*^[22] have attempted to evaluate the relation between the preoperative NC and NLR and the grade of different pediatric intracranial tumors. They included all the supratentorial and infratentorial tumors and compared the NC and NLR values among the low and high grades of all tumors collectively. Although this fails to provide significant clinical information for treatment or prognostication of any individual tumor type, it has provided great insight into the immunological alterations induced by neoplastic pathologies even at an immune privileged site like brain. They found that NC could predict the histological grade of tumors and though NLR was also correlated, it fell short of statistical significance. We have attempted to evaluate these parameters, specifically in the most common high-grade and low-grade pediatric brain tumors which are medulloblastoma and pilocytic astrocytoma, respectively, and compare them with that of healthy controls. We have found that the primary factor leading to raised NLR is decreased in the ALC. The probable mechanism behind tumor induced lymphopenia is secretion of immunosuppressive cytokines such as IL-10, IL-2, and TGF- β .^[1]

We analyzed the diagnostic efficiency of the various markers using ROC curves and found NLR and dNLR to be the only significant factor that can accurately predict medulloblastoma vis-à-vis pilocytic astrocytoma or healthy controls. ALC had considerably less accuracy with maximum Youden index of only 0.236 to distinguish medulloblastoma from healthy controls, though it was found to be significantly different. We observed that the correlation of NLR and dNLR could primarily be ascribed to neutrophilia rather than lymphopenia in our sample. NLR cutoffs of 2.45 and 2.45 and dNLR cutoffs of 1.47 and 1.53 had a good predictive accuracy for medulloblastoma when compared to pilocytic astrocytoma or healthy controls, respectively, in the pediatric population. Out of the combined markers, only NLR and dNLR combination was found to have significant predictive value. Although no other hematological marker was found to be of value in our study, their relevance cannot be ruled out based on the existing literature. Although Patel *et al.*^[18] did not do ROC curve analysis to identify the accuracy and appropriate cutoffs of NLR and ALC to predict medulloblastoma, their positive findings certainly lay ground for future investigation of the same. A prospective study with larger sample size must be done to not only accurately identify the significant variables but also to establish the diagnostic cutoffs for the same. The sensitivity and specificity of individual and combined parameters must be defined for this finding to be of clinical relevance. Further, the pathophysiological mechanisms behind these immunological perturbations must be studied in detail to elucidate its cause and effect relationship with tumor development and progression.

This study suffers from a few limitations. The most important drawback of the study being the symptomatology of these tumors commonly being vomiting and the treatment patient received for vomiting which possibly can affect immunological status of the patient, but we tried to exclude the patients who had a history of infection or who had received antibiotics before admission. The other drawbacks of the study are that the sample size of the study was small and this might have been the reason that a few markers failed to show significant correlation. This was a unicentric retrospective case-control study, in which we attempted to eliminate the possible sources of bias. However, large prospective studies with stringent selection criteria to eliminate bias are needed to verify the findings and provide a more accurate estimation of the diagnostic accuracy and cutoffs of these parameters. Considering the difference in the behavior of various molecular subtypes of medulloblastoma, it would be interesting to note the efficacy of these parameters in differentiating these subtypes. We did not include this analysis as this information was not available for some of our patients and the remaining number was too small to be of any statistical value. We have also not analyzed the long-term outcomes of the patients and thus the possible role of the parameters as a prognostic marker due to lack of follow-up data of the patients.

Apart from these limitations, we would like to discuss the clinical relevance of our study. Although the role of these biomarkers has been extensively studied in the adult glioblastoma patients, there is not much literature on the most common pediatric high-grade tumor, medulloblastoma. There is a study evaluating all the pediatric intracranial SOLs and evaluating the role of these parameters in predicting grade of these tumors irrespective of the histological type of tumor.^[22] Another study has evaluated the role of these parameters in medulloblastoma with respect to pilocytic astrocytoma but not with healthy controls.^[18] Furthermore, the authors did not evaluate the diagnostic accuracy and cutoffs for the significant factors identified in their study, probably because of small sample size, which would have been of a more direct clinical importance. Thus, ours is the first study which evaluates the role of immunological parameters in predicting medulloblastoma with respect to both pilocytic astrocytoma and healthy controls and also attempts to provide ROC curve analysis to assess diagnostic efficiency and cutoffs of the factors found to be significant.

CONCLUSION

The current evidence strongly suggests the interrelationship between immunological alterations and the pathogenesis and progression of medulloblastoma. It seems that NLR and dNLR can complement the imaging features in diagnosis of medulloblastomas in children similar to GBM in adults. However, the quantitative details of these findings and the underlying pathophysiologic mechanisms have not been

clearly elucidated. Our study gives an important directive for future research in the involvement of immune system and prognostic value of these factors in medulloblastoma patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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