



The Correlation Between Apparent Diffusion Coefficient (ADC) and Relative Cerebral Blood Volume (rCBV) with Ki-67 Expression in Central Nervous System Lymphoma

Nguyen Duy Hung^{#1,2}, Nguyen Minh Duc^{ib #3,4,*}, Ta Hong Nhung¹, Le Thanh Dung², Bui Van Giang^{1,5} and Nguyen Duy Hue^{1,2}

¹Department of Radiology, Hanoi Medical University, Hanoi, Vietnam

²Department of Radiology, Viet Duc Hospital, Hanoi, Vietnam

³Department of Radiology, Pham Ngoc Thach University of Medicine, Ho Chi Minh City, Vietnam

⁴Department of Radiology, Children's Hospital 2, Ho Chi Minh City, Vietnam

⁵Department of Radiology, National Cancer Hospital, Hanoi, Vietnam

* Corresponding author: Department of Radiology, Pham Ngoc Thach University of Medicine, Ho Chi Minh City 700000, Vietnam. Email: bsnguyenminhdudc@pnt.edu.vn

These authors are contributed equally as the first author.

Received 2020 July 26; Revised 2020 October 13; Accepted 2020 October 14.

Abstract

Background: Central nervous system (CNS) lymphoma presents as the dense infiltration of tumor cells in the perivascular space and blood-brain barrier disruption, on histopathological examination. The Ki-67 expression has been significantly correlated with tumor proliferation and is considered to be a prognostic factor.

Objectives: This study aimed at analyzing the correlations among the apparent diffusion coefficient (ADC), the relative cerebral blood volume (rCBV), and the Ki-67 proliferation index in CNS lymphoma.

Methods: From August 2019 to March 2020, 26 patients (14 men and 12 women) who underwent biopsy or surgery and were histologically confirmed as CNS lymphoma were included in this retrospective study. Diffusion and perfusion acquisitions were performed in 26 and 10 examinations, respectively. The Ki-67 proliferation index was available for all cases.

Results: The mean tADC, rADC, and rCBV values were $0.61 \pm 0.12 \times 10^{-3} \text{ mm}^2/\text{s}$, 0.73 ± 0.14 , and 1.1 ± 0.32 , respectively. Negative correlations were identified between both tADC and rADC and the Ki-67 proliferation index ($r = -0.656$, $P < 0.01$ and $r = -0.540$, $P < 0.01$, respectively). No significant correlations were found between rCBV values and the Ki-67 proliferation index, between rCBV and rADC, or between rCBV and tADC.

Conclusions: tADC and rADC values can be used as noninvasive indicators to predict cell proliferation in CNS lymphoma.

Keywords: Lymphoma, Cerebral Blood Volume, Diffusion

1. Background

Central nervous system (CNS) lymphoma is a rare non-Hodgkin's lymphoma that can be divided into primary and secondary groups (1). Primary CNS lymphoma is defined as the presence of disease in the CNS, without systemic involvement at the time of diagnosis, and accounts for 80% to 90% of all CNS lymphoma cases, 5% of all brain tumors, and 1% of non-Hodgkin's lymphoma cases (2). In contrast, secondary CNS lymphoma, including lesions in both the CNS and other organs at the time of diagnosis, often occurs 5-12 months after the diagnosis of systemic lymphoma (2). CNS lymphoma presents as the dense infiltration of tumor cells in the perivascular space and blood-brain barrier disruption, on histopathological examination (3). Ki-67 ex-

pression has been significantly correlated with tumor proliferation and is considered to be a prognostic factor (4-6).

Diffusion-weighted imaging and perfusion-weighted imaging can be used to assess the tumor cell density and angiogenesis, and providing important information for the diagnosis and treatment planning of intracranial tumors. CNS lymphoma generally presents low values for the apparent diffusion coefficient (ADC) and relative cerebral blood volume (rCBV), due to hypercellularity and the absence of angiogenesis characteristics (7-9). Moreover, the correlation between ADC values and the Ki-67 proliferation index may represent an additional noninvasive indicator for use in the diagnosis and prognosis of CNS lymphoma (10).

A previous study has reported increased ADC values in

response to tumor cell proliferation inhibitors (11). However, studies examining the correlation between ADC values and the Ki-67 proliferation index are limited (10, 12). In addition, few studies have examined the correlation between rCBV values and the Ki-67 proliferation index in CNS lymphoma, although several studies have examined this correlation for other intracranial tumors (13, 14).

2. Objectives

This study aimed at analyzing the correlations between ADC and rCBV values and the Ki-67 proliferation index in CNS lymphoma.

3. Methods

3.1. Study Population

From August 2019 to March 2020, 26 patients (14 men and 12 women, aged 18 to 82 years, with an average age of 58 years) who underwent biopsy or surgery at Viet Duc and National Cancer hospitals, with the histopathological confirmation of CNS lymphoma, were included in this retrospective study. The patients underwent magnetic resonance imaging (MRI), with results showing intracranial masses, with solid portions larger than 10 mm in diameter. Diffusion acquisitions were performed in 26 examinations, and perfusion acquisitions were performed in 10 examinations. Immunohistochemistry results for the Ki-67 proliferation index were available for all cases. We did not collect patients diagnosed as CNS lymphoma without histopathological findings and treated by chemotherapy before MRI scanning. Ethical clearance received from the institute ethics committee (Ref: 2967/Q-DHYHN), with a waiver of informed consent.

3.2. Imaging Technique

The MRI examinations were conducted on 1.5 Tesla Siemens Avanto (Siemens Medical Systems, Erlangen, Germany), 1.5 Tesla Hitachi Echelon (Hitachi Medical Corporation, Tokyo, Japan), 1.5 Tesla Philips Ingenia (Philips Healthcare, Best, Netherlands), and 3.0 Tesla GE SIGNA Pioneer (GE Healthcare, Chicago, IL, USA), using a head coil. The conventional sequences included: non-enhanced axial or sagittal T1-weighted images, axial fluid-attenuated inversion recovery (FLAIR) images, axial T2 gradient-echo images, contrast-enhanced T1 volumetric images, reconstructed in the axial, coronal, and sagittal planes.

Axial diffusion-weighted images, with 2 b-values of 0 and 1,000 s/mm², were performed with the following parameters: 240-mm field of view (FOV), 5-mm slice thickness, repeat time (TR)/echo time (TE): 4,500/102 ms, and

matrix: 192 × 192. ADC images were automatically calculated.

Perfusion acquisition was performed before contrast-enhanced T1 volumetric acquisition. The T2 gradient-echo echo-planar sequence was used with the following parameters: 230 × 230-mm FOV, 5-mm slice thickness, TR/TE: 500/40 ms, matrix: 144 × 256, and 1-mm slice spacing. A dynamic series of 10 sets, with a 1-s delay between each set, was acquired, and the first 3 sets were acquired before contrast injection. A bolus of contrast agent, at a dose of 0.1 mmol/kg (Dotarem, Guerbet, France) and a rate of 5 mL/s, was administered using a power injector through an 18-20 G intravenous catheter, during the fourth set. Afterward, a bolus of 20 mL saline was immediately injected, at the same rate.

3.3. Image Analysis

The ADC and CBV values were independently analyzed on a Ziostation 2 version 2.9.7.2 (Ziosoft Inc, Tokyo, Japan), by 2 senior radiologists. The Ki-67 proliferation index was blinded. Any disagreement between the 2 investigators was solved by consensus. For multifocal lesions, the ADC, CBV, and Ki-67 proliferation index values were all measured and counted on the same lesion.

On the ADC map, the ADC values were evaluated by drawing a 10-20-mm² region of interest (ROI) within the solid portion of the tumor, taking care to avoid necrotic, hemorrhagic, cystic, or calcific areas and blood vessels, and tumoral ADC (tADC) and relative ADC (rADC) values were calculated. The tADC value was calculated as the average of 3 ROIs placed within the solid portion that showed the lowest signal on the ADC map (Figure 1). The mean ADC value of the opposite white matter was calculated as the average of 3 ROIs placed within the normal white matter, at the same level as the tumor (Figure 1). The rADC value was calculated as the ratio between the values of the tADC and the mean ADC of the opposite white matter.

On the CBV map, the tumoral CBV value was evaluated by placing a 10-20 mm² ROI within the most vascular proliferative area, corresponding to the highest color spectrum, and avoiding large vessels and the choroid plexus. In the control area, the ROI was placed within the normal white matter, at the same level as the tumor (Figure 1). rCBV was calculated as the ratio between the tumoral CBV and the CBV in the control area.

3.4. Statistical Analysis

SPSS version 20.0 software was used to analyze data (IBM Corp, New York, USA). Quantitative variables are described as the mean and standard deviation. Categorical variables are described as the number and percentage. The

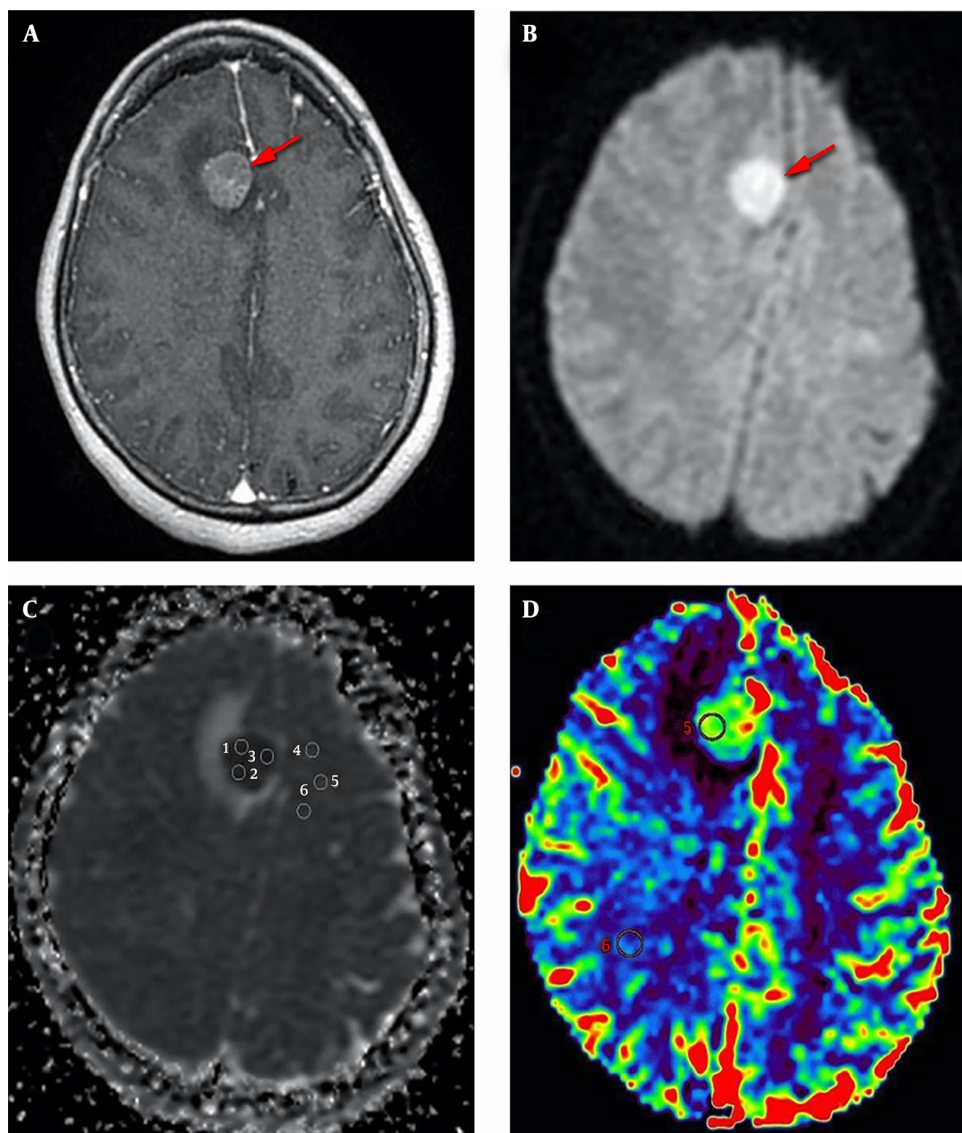


Figure 1. A 62-year-old female with right frontal secondary CNS lymphoma. An axial, contrast-enhanced, and T1-weighted; image (a) shows a homogenous enhancement (arrow). An axial diffusion-weighted image, with b-values of $1,000 \text{ s/mm}^2$ (b), shows a homogenous hyperintensity. ADC map (c) shows 3 ROIs were placed within the lowest signal area of the mass, and 3 additional ROIs were placed within the opposite normal white matter. CBV map (d) shows an ROI was placed within the most vascular proliferative area of the mass, corresponding to the highest color spectrum, and another ROI was placed within the normal white matter.

correlations between the tADC, rADC, rCBV, and Ki-67 proliferation index were determined using the Spearman rank correlation test, with the level of significance set to $P < 0.05$.

4. Results

4.1. Study Population

Overall, multifocal lesions (65.4%) were more common than unifocal lesions (36.6%). Primary CNS lymphoma was

identified in 18 (69.2%) patients, and secondary CNS lymphoma was found in 8 (30.8%) patients.

The average lesion size was $32.88 \pm 12.7 \text{ mm}$ (13-47 mm). Diffusion restriction was detected in all cases. The mean tADC value was $0.61 \pm 0.12 \times 10^{-3} \text{ mm}^2/\text{s}$ ($0.41\text{-}0.90 \times 10^{-3} \text{ mm}^2/\text{s}$). The mean rADC value was 0.73 ± 0.14 (0.46-1.04). The mean rCBV value was 1.1 ± 0.32 (0.60-1.75).

4.2. Histological Characteristics

Non-Hodgkin’s lymphoma was identified in all cases, including 25 cases with diffuse large B-cell lymphoma and 1 case with small lymphocytic lymphoma. All samples were positive for Ki-67, with a mean proliferation index of $65.96 \pm 18.0\%$ (ranging from 20% to 90%).

4.3. Correlations Between the tADC and rADC Values and the Ki-67 Proliferation Index Values

All 26 cases, with available tADC, rADC, and Ki-67 proliferation index data were used to analyze the correlations among these values, which are presented in Table 1. Negative correlations were identified between the tADC value and the Ki-67 proliferation index ($r = -0.656, P < 0.01$) (Figure 2) and between the rADC value and the Ki-67 proliferation index ($r = -0.540, P < 0.01$) (Figure 3), indicating that lower tADC and rADC values are associated with increases in the Ki-67 proliferation index.

Table 1. Correlations Between the tADC and rADC Values and the Ki-67 Proliferation Index

	Spearman’s rho	P Value
tADC and Ki-67	-0.656	< 0.001
rADC and Ki-67	-0.540	0.004

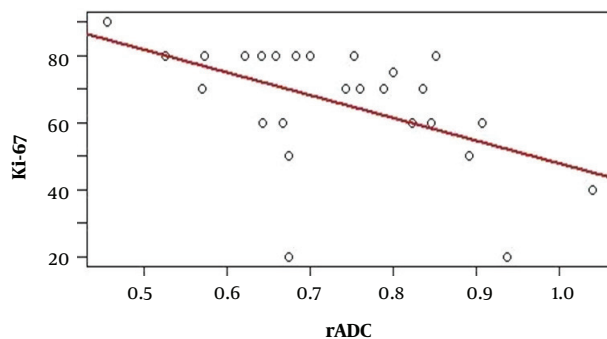


Figure 2. Linear relationship between tADC values and the Ki-67 proliferation index, which presented a significant negative correlation.

4.4. Correlations Among the tADC, rADC, and rCBV Values and the Ki-67 Proliferation Index

We analyzed 10 cases with available tADC, rADC, rCBV, and Ki-67 proliferation index data to determine the correlations among these values, which are presented in Table 2. No significant correlations were identified between the rCBV value and the Ki-67 proliferation index ($r = 0.117, P > 0.05$), between rCBV value and the rADC value ($r = -0.139, P > 0.05$), or between the rCBV value and the tADC value ($r = -0.097, P > 0.05$).

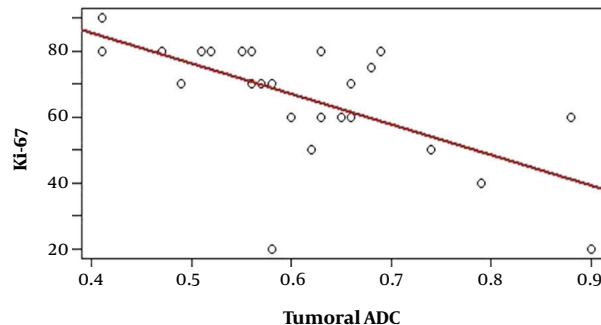


Figure 3. Linear relationship between rADC values and the Ki-67 proliferation index, which presented a significant negative correlation

Table 2. Correlations Among the tADC, rADC, and rCBV Values and the Ki-67 Proliferation Index

	Spearman’s rho	P Value
rCBV and Ki-67	0.117	0.748
rCBV and rADC	-0.139	0.701
rCBV and tADC	-0.097	0.789

5. Discussion

Previous research demonstrated the ADC values representing tumor density and proliferation (11). However, experiments exploring the association between the ADC values and the Ki-67 proliferation index in CNS lymphoma were not widespread (10, 12). In addition, the association between rCBV values and Ki-67 proliferation index in CNS lymphoma has been tested in a few reports (13, 14). In this analysis, we noted that no substantial correlations between the rCBV value and the Ki-67 proliferation index were reported, and significantly negative correlations with the ADC parameters and Ki-67 proliferation index in CNS lymphoma were observed.

Previously, CNS lymphoma was found to be strongly associated with immunocompromised states, particularly human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS). More recently, the increased occurrence of CNS lymphoma has been reported in immunocompetent patients, in both sexes, and across all ages (15). CNS lymphoma tends to occur in the elderly, with a peak incidence among patients 50-70 years in age, in immunocompetent individuals, and in young immunocompromised patients, with a male predominance (1). Our study population presented a similar distribution, with a mean age of 58 years, ranging from 18 to 82 years (the 50-70-year-old age group accounted for 57.7% of our cohort), and a male to female ratio of 1.17:1. Diffuse large B-cell lymphoma represents 95% of all CNS lymphoma cases, and the

remainder consisted of low-grade B-cell lymphoma, T-cell lymphoma, and Burkitt lymphoma (1, 16). Based on immunohistochemistry results, CNS lymphoma is characterized by a high Ki-67-positive rate (50%–70%), (17), Chacko et al. (18) in a study of 73 primary CNS lymphomas found that the Ki-67 proliferation index from 60% to 98%. A study by Schob et al. (12) reported a mean Ki-67 proliferation index of 76.19% in 21 primary CNS lymphoma samples. The results of this study, were similar to previous findings, with 25 cases of diffuse large B-cell lymphoma and 1 case of small lymphocytic lymphoma, which is a subtype of low-grade B-cell lymphoma. The Ki-67 proliferative index in the present study varied from 20% to 90%, with an average of $65.96\% \pm 18.0\%$, which was lower than that reported by Schob et al. study and more variable than that reported by Chacko et al. This discrepancy may be due to differences in the cell counting process, as Ki-67 positive cells were manually counted in the current study, whereas Schob et al. used an automatic counting tool. In addition, the present study included both primary and secondary CNS lymphoma groups, whereas the studies by Chacko et al. and Schob et al. only included primary CNS lymphoma.

CNS lymphoma often presents with restricted diffusion, with low ADC values during the diffusion acquisition. Previous studies have demonstrated that the ADC values of CNS lymphoma are significantly lower than those for glioblastoma, anaplastic astrocytoma, and metastatic lesions (19–23). The results of Matuszewska et al. (24), in a study of 16 CNS lymphomas found in 12 patients, showed that all lesions presented with restricted diffusion, with tADC and rADC values as low as $0.54 \times 10^{-3} \text{ mm}^2/\text{s}$ and 0.71, respectively and no significant differences were identified between primary and secondary CNS lymphomas. Lee et al. (19) reported tADC and rADC values as low as $0.595 \pm 0.228 \times 10^{-3} \text{ mm}^2/\text{s}$ and 0.86 ± 0.26 , respectively. The lowest tADC values reported by the studies performed by Yamashita et al. (20), Calli et al. (21), and Neska-Matuszewska et al. (22) were $0.61 \pm 0.13 \times 10^{-3} \text{ mm}^2/\text{s}$, $0.51 \pm 0.09 \times 10^{-3} \text{ mm}^2/\text{s}$, and $0.57 \pm 0.12 \times 10^{-3} \text{ mm}^2/\text{s}$, respectively. Doskaliyev et al. (23) obtained tADC values as low as $0.717 \pm 0.094 \times 10^{-3} \text{ mm}^2/\text{s}$ and $0.390 \pm 0.081 \times 10^{-3} \text{ mm}^2/\text{s}$, with b values of 1,000 and 4,000, respectively. Our study identified a mean tADC value of $0.61 \pm 0.12 \times 10^{-3} \text{ mm}^2/\text{s}$, which is comparable to the results reported by Lee et al. (19), Yamashita et al. (20), and Neska-Matuszewska et al. (22); however, this result is higher than those reported by Neska-Matuszewska et al. (24) and Calli et al. (21) and lower than the result reported by Doskaliyev et al. (23). These disagreements among various studies are likely due to differences in the study populations and ROI settings. Several studies have reported that ADC values are negatively correlated with cell proliferation. Schob et al. (12) found that the lowest, the mean,

and the highest ADC values all reflected cell division, based on the positive expression of Ki-67. Jung et al. (10) studied the correlation between rADC values and the positive expression of Ki-67 in 50 patients with primary CNS lymphoma and detected a negative correlation between these 2 values. Our study identified negative correlations between the tADC values and the Ki-67 proliferation index ($r = -0.656, P < 0.01$) and between the rADC values and the Ki-67 proliferation index ($r = -0.540, P < 0.01$). According to these results, tADC values are more strongly correlated with Ki-67 expression than rADC values. The ADC values of normal white matter tend to increase with age; therefore tADC values may better reflect tumor cell proliferation (25). Based on this correlation, ADC values can be used as an additional non-invasive predictor of tumor cell proliferation, which can provide additional information for the prognosis and evaluation of chemical treatment responses, particularly among patients treated with cell proliferation inhibitors.

According to previous studies, CNS lymphoma presents with low rCBV values, due to the absence of tumoral angiogenesis (6, 9, 26). In a study of 12 CNS lymphomas, Hartmann et al. (9) reported a mean rCBV of 1.29 ± 0.18 , whereas Hakyemez et al. (27) reported a mean rCBV value of 1.1 ± 0.32 . In contrast, the rCBV values reported by Lee et al. (8) and Neska-Matuszewska et al. (24) were 1.68 and 1.58, respectively. Furthermore, Lee et al. (8) and Neska-Matuszewska et al. (24) found no significant differences between the mean rCBV values measured in primary and secondary CNS lymphoma groups. The mean rCBV in our study was 1.1 ± 0.32 (0.60–1.75), which is similar to those reported by Hartmann et al. (9), Hakyemez et al. (27), Abul-Kasim et al. (26), and Blasel et al. (28) but is lower than those reported by Lee et al. (8) and Neska-Matuszewska et al. (24). Despite the divergence among study results, several authors have determined that the rCBV values for CNS lymphoma are significantly lower than those for glioblastoma, meningioma, and metastasis (9, 21, 22, 26, 27, 29). The rCBV value has been proven to serve as a valuable indicator for the grading and prognosis of some intracranial tumors, based on studies examining the correlation between rCBV values and the Ki-67 proliferation index. Ginat et al. (14) found a positive correlation between rCBV values and the Ki-67 proliferation index in meningioma and determined that rCBV values can be used to distinguish atypical meningioma from anaplastic meningioma. A positive correlation between these 2 values was also detected in a study of high-grade glioma (13). However, our study showed no correlation between rCBV values and the Ki-67 proliferation index in CNS lymphoma ($r = 0.117, P = 0.748$). This result may be due to the growth patterns associated with CNS lymphoma, which is characterized by angiotropism or angiocentric

phenomena, with the migration of tumor cells along or within blood vessels, which differs from the angiogenesis associated with glioma or meningioma, during which the formation of new blood vessels occurs (14, 29). Although the presence of vascular endothelial growth factor has been reported in CNS lymphoma, angiogenesis appears to independently occur from the proliferation of tumor cells (30, 31). In a histological study of 32 patients with primary CNS lymphoma, Roser et al. (31) found no correlation between vascularity and proliferation.

The present study had some limitations. Firstly, the study included small sample size, particularly for rCBV data. Secondly, primary and secondary CNS lymphomas are different; however, in this study due to the small sample size, we could not perform the comparison of subgroups of lymphoma. Although no correlation was observed between rCBV and ADC values, further studies with larger sample sizes must be performed to validate these findings. Thirdly, the manual counting of Ki-67-positive cells may have affected the final results, and future studies should consider the use of automatic counting. Finally, the investigation of the correlations among rCBV, ADC, and Ki-67 should be performed within subgroups of CNS lymphomas.

5.1. Conclusion

The negative correlations between tADC and rADC values and the Ki-67 proliferation index indicated that these values can be used as non-invasive indicators for the prediction of the degree of cell proliferation occurring in CNS lymphoma. Further studies should be performed to validate the present findings.

Footnotes

Authors' Contribution: NDH and NMD contributed equally to this article as the first authorship. NDH and NMD gave a substantial contribution to acquisition, analysis, and data interpretation. NDH and NMD prepared, drafted, and revised the manuscript critically for important intellectual content. Each author gave the final approval of the version to be published and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interests: There are no conflicts of interest to declare.

Ethical Approval: The institutional review board of Hanoi Medical University approved this retrospective study (Ref: 2967/QD-DHYHN).

Funding/Support: There is no funding/support.

References

- Green K, Hogg JP. *Cancer, Central Nervous System Lymphoma*. Treasure Island (FL): StatPearls Publishing; 2020.
- Newton HB. *Handbook of neuro-oncology neuroimaging*. Academic Press; 2016.
- Rubenstein JL, Gupta NK, Mannis GN, Lamarre AK, Treseler P. How I treat CNS lymphomas. *Blood*. 2013;**122**(14):2318–30. doi: [10.1182/blood-2013-06-453084](https://doi.org/10.1182/blood-2013-06-453084). [PubMed: [23963042](https://pubmed.ncbi.nlm.nih.gov/23963042/)]. [PubMed Central: [PMC3790503](https://pubmed.ncbi.nlm.nih.gov/PMC3790503/)].
- Liu J, Wang Y, Liu Y, Liu Z, Cui Q, Ji N, et al. Immunohistochemical profile and prognostic significance in primary central nervous system lymphoma: Analysis of 89 cases. *Oncol Lett*. 2017;**14**(5):5505–12. doi: [10.3892/ol.2017.6893](https://doi.org/10.3892/ol.2017.6893). [PubMed: [29113178](https://pubmed.ncbi.nlm.nih.gov/29113178/)]. [PubMed Central: [PMC5656017](https://pubmed.ncbi.nlm.nih.gov/PMC5656017/)].
- Cho U, Oh WJ, Hong YK, Lee YS. Prognostic Significance of High Ki-67 Index and Histogenetic Subclassification in Primary Central Nervous System Lymphoma. *Appl Immunohistochem Mol Morphol*. 2018;**26**(4):254–62. doi: [10.1097/PAL.0000000000000424](https://doi.org/10.1097/PAL.0000000000000424). [PubMed: [27490760](https://pubmed.ncbi.nlm.nih.gov/27490760/)].
- Salles G, de Jong D, Xie W, Rosenwald A, Chhanabhai M, Gaulard P, et al. Prognostic significance of immunohistochemical biomarkers in diffuse large B-cell lymphoma: a study from the Lunenburg Lymphoma Biomarker Consortium. *Blood*. 2011;**117**(26):7070–8. doi: [10.1182/blood-2011-04-345256](https://doi.org/10.1182/blood-2011-04-345256). [PubMed: [21536860](https://pubmed.ncbi.nlm.nih.gov/21536860/)].
- Haldorsen IS, Espeland A, Larsson EM. Central nervous system lymphoma: characteristic findings on traditional and advanced imaging. *AJNR Am J Neuroradiol*. 2011;**32**(6):984–92. doi: [10.3174/ajnr.A2171](https://doi.org/10.3174/ajnr.A2171). [PubMed: [20616176](https://pubmed.ncbi.nlm.nih.gov/20616176/)].
- Lee IH, Kim ST, Kim HJ, Kim KH, Jeon P, Byun HS. Analysis of perfusion weighted image of CNS lymphoma. *Eur J Radiol*. 2010;**76**(1):48–51. doi: [10.1016/j.ejrad.2009.05.013](https://doi.org/10.1016/j.ejrad.2009.05.013). [PubMed: [19500931](https://pubmed.ncbi.nlm.nih.gov/19500931/)].
- Hartmann M, Heiland S, Harting I, Tronnier VM, Sommer C, Ludwig R, et al. Distinguishing of primary cerebral lymphoma from high-grade glioma with perfusion-weighted magnetic resonance imaging. *Neuroscience Letters*. 2003;**338**(2):119–22. doi: [10.1016/s0304-3940\(02\)01367-8](https://doi.org/10.1016/s0304-3940(02)01367-8).
- Jung G, Kim YZ. Analysis of Relative Apparent Diffusion Coefficient Value of Intracranial Primary Central Nervous System Lymphoma and its Correlation with Ki-67 Positive Rate. *J Clin Res Oncol*. 2019;**2**(2):1–6.
- Chen Y, Zhong J, Wu H, Chen N. The clinical application of whole-body diffusion-weighted imaging in the early assessment of chemotherapeutic effects in lymphoma: the initial experience. *Magn Reson Imaging*. 2012;**30**(2):165–70. doi: [10.1016/j.mri.2011.09.019](https://doi.org/10.1016/j.mri.2011.09.019). [PubMed: [22133288](https://pubmed.ncbi.nlm.nih.gov/22133288/)].
- Schob S, Meyer J, Gawlitza M, Frydrychowicz C, Muller W, Preuss M, et al. Diffusion-Weighted MRI Reflects Proliferative Activity in Primary CNS Lymphoma. *PLoS One*. 2016;**11**(8). e0161386. doi: [10.1371/journal.pone.0161386](https://doi.org/10.1371/journal.pone.0161386). [PubMed: [27571268](https://pubmed.ncbi.nlm.nih.gov/27571268/)]. [PubMed Central: [PMC5003362](https://pubmed.ncbi.nlm.nih.gov/PMC5003362/)].
- Jain KK, Sahoo P, Tyagi R, Mehta A, Patir R, Vaishya S, et al. Prospective glioma grading using single-dose dynamic contrast-enhanced perfusion MRI. *Clin Radiol*. 2015;**70**(10):1128–35. doi: [10.1016/j.crad.2015.06.076](https://doi.org/10.1016/j.crad.2015.06.076). [PubMed: [26152879](https://pubmed.ncbi.nlm.nih.gov/26152879/)].
- Ginat DT, Mangla R, Yeane G, Wang HZ. Correlation of diffusion and perfusion MRI with Ki-67 in high-grade meningiomas. *AJR Am J Roentgenol*. 2010;**195**(6):1391–5. doi: [10.2214/AJR.10.4531](https://doi.org/10.2214/AJR.10.4531). [PubMed: [21098200](https://pubmed.ncbi.nlm.nih.gov/21098200/)].
- Olson JE, Janney CA, Rao RD, Cerhan JR, Kurtin PJ, Schiff D, et al. The continuing increase in the incidence of primary central nervous system non-Hodgkin lymphoma: a surveillance, epidemiology, and end results analysis. *Cancer*. 2002;**95**(7):1504–10. doi: [10.1002/cncr.10851](https://doi.org/10.1002/cncr.10851). [PubMed: [12237919](https://pubmed.ncbi.nlm.nih.gov/12237919/)].

16. Rubenstein JL, Treseler P, O'Brien JM. Pathology and genetics of primary central nervous system and intraocular lymphoma. *Hematol Oncol Clin North Am.* 2005;19(4):705-17. vii. doi: [10.1016/j.hoc.2005.05.012](https://doi.org/10.1016/j.hoc.2005.05.012). [PubMed: [16083831](https://pubmed.ncbi.nlm.nih.gov/16083831/)].
17. Osborn AG, Salzman KL, Jhaveri MD, Barkovich AJ. *Diagnostic imaging: brain E-book.* Elsevier Health Sciences; 2015.
18. Patel B, Chacko G, Nair S, Anandan J, Chacko AG, Rajshankar V, et al. Clinicopathological correlates of primary central nervous system lymphoma: experience from a tertiary care center in South India. *Neurol India.* 2015;63(1):77-82. doi: [10.4103/0028-3886.152658](https://doi.org/10.4103/0028-3886.152658). [PubMed: [25751474](https://pubmed.ncbi.nlm.nih.gov/25751474/)].
19. Lee SC, Moon W, Choi JW, Roh HG, Bak SH, Yi JG, et al. Differentiation between Primary Central Nervous System Lymphoma and Glioblastoma: Added Value of Quantitative Analysis of CT Attenuation and Apparent Diffusion Coefficient. *J Korean Soc Magn Reson Med.* 2012;16(3):226. doi: [10.13104/jksmrm.2012.16.3.226](https://doi.org/10.13104/jksmrm.2012.16.3.226).
20. Yamashita K, Yoshiura T, Hiwatashi A, Togao O, Yoshimoto K, Suzuki SO, et al. Differentiating primary CNS lymphoma from glioblastoma multiforme: assessment using arterial spin labeling, diffusion-weighted imaging, and (1)(8)F-fluorodeoxyglucose positron emission tomography. *Neuroradiology.* 2013;55(2):135-43. doi: [10.1007/s00234-012-1089-6](https://doi.org/10.1007/s00234-012-1089-6). [PubMed: [22961074](https://pubmed.ncbi.nlm.nih.gov/22961074/)].
21. Calli C, Kitis O, Yunten N, Yurtseven T, Islekel S, Akalin T. Perfusion and diffusion MR imaging in enhancing malignant cerebral tumors. *Eur J Radiol.* 2006;58(3):394-403. doi: [10.1016/j.ejrad.2005.12.032](https://doi.org/10.1016/j.ejrad.2005.12.032). [PubMed: [16527438](https://pubmed.ncbi.nlm.nih.gov/16527438/)].
22. Neska-Matuszewska M, Bladowska J, Sasiadek M, Zimny A. Differentiation of glioblastoma multiforme, metastases and primary central nervous system lymphomas using multiparametric perfusion and diffusion MR imaging of a tumor core and a peritumoral zone-Searching for a practical approach. *PLoS One.* 2018;13(1). e0191341. doi: [10.1371/journal.pone.0191341](https://doi.org/10.1371/journal.pone.0191341). [PubMed: [29342201](https://pubmed.ncbi.nlm.nih.gov/29342201/)]. [PubMed Central: [PMC5771619](https://pubmed.ncbi.nlm.nih.gov/PMC5771619/)].
23. Doskaliyev A, Yamasaki F, Ohtaki M, Kajiwara Y, Takeshima Y, Watanabe Y, et al. Lymphomas and glioblastomas: differences in the apparent diffusion coefficient evaluated with high b-value diffusion-weighted magnetic resonance imaging at 3T. *Eur J Radiol.* 2012;81(2):339-44. doi: [10.1016/j.ejrad.2010.11.005](https://doi.org/10.1016/j.ejrad.2010.11.005). [PubMed: [21129872](https://pubmed.ncbi.nlm.nih.gov/21129872/)].
24. Neska-Matuszewska M, Zimny A, Bladowska J, Sasiadek M. Diffusion and perfusion MR patterns of central nervous system lymphomas. *Adv Clin Exp Med.* 2018;27(8):1099-108. doi: [10.17219/acem/73894](https://doi.org/10.17219/acem/73894). [PubMed: [29975467](https://pubmed.ncbi.nlm.nih.gov/29975467/)].
25. Engelter ST, Provenzale JM, Petrella JR, DeLong DM, MacFall JR. The effect of aging on the apparent diffusion coefficient of normal-appearing white matter. *AJR Am J Roentgenol.* 2000;175(2):425-30. doi: [10.2214/ajr.175.2.1750425](https://doi.org/10.2214/ajr.175.2.1750425). [PubMed: [10915688](https://pubmed.ncbi.nlm.nih.gov/10915688/)].
26. Abul-Kasim K, Maly P, Strombeck A, Svensson J, Sundgren PC. Perfusion Weighted MR Imaging may Differentiate Primary CNS Lymphoma from other Homogeneously Enhancing Brain Tumors. *Neuroradiol J.* 2008;21(5):637-44. doi: [10.1177/197140090802100505](https://doi.org/10.1177/197140090802100505). [PubMed: [24257004](https://pubmed.ncbi.nlm.nih.gov/24257004/)].
27. Hakyemez B, Erdogan C, Bolca N, Yildirim N, Gokalp G, Parlak M. Evaluation of different cerebral mass lesions by perfusion-weighted MR imaging. *J Magn Reson Imaging.* 2006;24(4):817-24. doi: [10.1002/jmri.20707](https://doi.org/10.1002/jmri.20707). [PubMed: [16958061](https://pubmed.ncbi.nlm.nih.gov/16958061/)].
28. Blasel S, Jurcoane A, Bahr O, Weise L, Harter PN, Hattingen E. MR perfusion in and around the contrast-enhancement of primary CNS lymphomas. *J Neurooncol.* 2013;114(1):127-34. doi: [10.1007/s11060-013-1161-z](https://doi.org/10.1007/s11060-013-1161-z). [PubMed: [23695516](https://pubmed.ncbi.nlm.nih.gov/23695516/)].
29. Goyal P, Kumar Y, Gupta N, Malhotra A, Gupta S, Gupta S, et al. Usefulness of enhancement-perfusion mismatch in differentiation of CNS lymphomas from other enhancing malignant tumors of the brain. *Quant Imaging Med Surg.* 2017;7(5):511-9. doi: [10.21037/qims.2017.09.03](https://doi.org/10.21037/qims.2017.09.03). [PubMed: [29184763](https://pubmed.ncbi.nlm.nih.gov/29184763/)]. [PubMed Central: [PMC5682400](https://pubmed.ncbi.nlm.nih.gov/PMC5682400/)].
30. Takeuchi H, Matsuda K, Kitai R, Sato K, Kubota T. Angiogenesis in primary central nervous system lymphoma (PCNSL). *J Neurooncol.* 2007;84(2):141-5. doi: [10.1007/s11060-007-9363-x](https://doi.org/10.1007/s11060-007-9363-x). [PubMed: [17406788](https://pubmed.ncbi.nlm.nih.gov/17406788/)].
31. Roser F, Saini M, Meliss R, Ostertag H, Samii M, Bellinzona M. Apoptosis, vascularity, and proliferation in primary central nervous system lymphomas (PCNSL): a histopathological study. *Surg Neurol.* 2004;62(5):393-9. discussion 399. doi: [10.1016/j.surneu.2003.11.038](https://doi.org/10.1016/j.surneu.2003.11.038). [PubMed: [15518841](https://pubmed.ncbi.nlm.nih.gov/15518841/)].