RESEARCH ARTICLE

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The Role of Pretherapeutic Diffusion-Weighted MR Imaging Derived Apparent Diffusion Coefficient in Predicting Clinical Outcomes in Immunocompetent Patients with Primary CNS Lymphoma: A Systematic Review and Meta-Analysis

Rahmad Mulyadi[1,2]*, Handoko Handoko[2,3], Ramdinal Aviesena Zairinal[2,4], Joedo Prihartono[5]

Abstract

Objective: This systematic review and meta-analysis aimed to confirm the role of Apparent Diffusion Coefficient (ADC) values in predicting the prognosis of PCNSL patients based on previous studies. **Methods:** A systematic review with meta-analysis was conducted on related articles PubMed, Scopus, Sciencedirect, Cochrane, DOAJ, and Embase databases with last updated search on November 30, 2021. This systematic review and meta-analysis included a total of four studies. **Result:** All studies that examined the association between pretherapeutic ADC values and OS and PFS discovered that lower ADC values were associated with significantly shorter OS and PFS. The analysis revealed that patients with low ADC values had a higher risk of death than those with high ADC values, with a pooled HR of 0.24 (95% CI: 0.10–0.56; Z = 3.26; p = 0.001). A meta-analysis of five data from three studies examining the association between ADC values and PFS was also conducted using a fixed-effects model due to the low heterogeneity values (I^2 = 4%; p = 0.38). The data analysis revealed that the pooled HR was 0.25 (95% confidence interval [CI]: 0.14–0.44, Z = 4.18; p 0.00001). **Conclusion:** Patients with low ADC values had significantly shorter overall survival and progression-free survival than those with high ADC values, so ADC values assessment prior to initial therapy administration can provide clinicians with valuable information about the prognosis of PCNSL.

Keywords: primary central nervous system lymphoma- lymphoma- prognosis- diffusion weighted imaging

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Introduction

Primary Central Nervous System Lymphoma (PCNSL) is an extra-nodal non-Hodgkin lymphoma (NHL) confined to the brain, spinal cord, leptomeninges, or eyes, in the absence of systemic lymphoma at the time of diagnosis. According to studies, PCNSL affects 4–7% of all brain tumors, 5% of all extra-nodal lymphomas, and less than 1% of all non-Hodgkin's lymphoma (Lauw et al., 2020). Around 90% of PCNSL cases exhibit histopathological features consistent with diffuse large B-cell lymphoma (DLBCL). The remainder is comprised of T-cell lymphoma (2%), Burkitt's lymphoma, and low-grade lymphoma (Löw et al., 2018). PCNSL was initially prevalent in immunocompromised populations, particularly in cases of human immunodeficiency virus/ acquired immunodeficiency syndrome (HIV/AIDS) (Shan and Hu, 2018; Song et al., 2021). PCNSL also has a poor prognosis in immunocompromised patients (Bayraktar et al., 2011). PCNSL has decreased in immunocompromised patients since the development of highly active antiretroviral therapy (HAART) (Lauw et al., 2020). Meanwhile, PCNSL has actually increased in prevalence in the immunocompetent population in recent years. However, the etiology and prognosis of PCNSL in immunocompetent individuals remain unclear (Rudresha et al., 2017; Shan and Hu, 2018).

While PCNSL is uncommon, it is highly aggressive and has a significant impact on morbidity and mortality (Song et al., 2021). Overall survival (OS) is estimated to be between 12 and 18 months (Liu et al., 2021). Over the last two decades, advancements in therapeutic strategies have improved patient prognoses but are not yet curative (Hoang-Xuan et al., 2015; Ahn et al., 2017; Liu et al., 2021). One of the reasons for the difficulty of PCNSL therapy is the limited number of agents that can cross the blood-

*[1]Department of Radiology, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia. [2]Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia. [3]Department of Radiation Oncology, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia. [4]Department of Neurology, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia. [5]Department of Community Medicine Pre Clinic, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia. *For Correspondence: dr_rahmad_radiologi@yahoo.com*

brain barrier (Khan et al., 2020). Currently, the treatment strategy for PCNSL includes high-dose chemotherapy (HD) methotrexate (MTX) in combination with other chemotherapeutic agents. Following chemotherapy, whole brain radiotherapy (WBRT) may be given, depending on the response to initial therapy (Hoang-Xuan et al., 2015). While chemotherapy and WBRT have been shown to be effective, the majority of patients continue to experience relapses within a short period of time, and the prognosis remains poor following treatment (Hoang-Xuan et al., 2015; Tao et al., 2021). WBRT, HD MTX, and the combination of multiple chemotherapeutic agents, on the other hand, can increase the risk of adverse events in patients (Hoang-Xuan et al., 2015).

Prognostic factors or biomarkers that can predict clinical outcomes, disease progression, and tumor recurrence after initial chemotherapy with HD MTX can help clinicians determine the next optimal therapeutic strategy (Barajas et al., 2010) (Barajas et al., 2010). However, the discussion regarding this matter still warrants further exploration (Baek et al., 2020; Khan et al., 2020).

There is currently no imaging biomarker that can accurately predict the prognosis of patients with PCNSL (Barajas et al., 2010). In a variety of neoplasms, diffusion weighted imaging (DWI) with apparent diffusion coefficient (ADC) has been used as an imaging biomarker. In comparison to conventional magnetic resonance imaging (MRI), DWI can visualize the water molecule's diffusion gradient. The microstructure of biological tissue can be reflected by ADC. According to this theory, there should be a correlation between tumor cell cellularity and ADC value (Zulfiqar et al., 2013). A recent study demonstrated that ADC derived from DWI calculation had an inverse relationship with histopathological features and tumor cell density in patients with PCNSL. A low ADC is associated with a higher proliferative index of the tumor (Schob et al., 2016; Schob et al., 2018; Chong et al., 2019; Hung et al., 2020; Khan et al., 2020). Numerous studies have indicated that low ADC values can be the single and independent predictor of poor clinical outcome and survival in patients with PCNSL (Barajas et al., 2010; Valles et al., 2013; Zhang et al., 2016; Chong et al., 2019; Baek et al., 2020). However, the ability of ADC values to predict clinical outcomes in patients is not fully understood, and studies regarding this matter have a relatively small sample size. Our systematic review and meta-analysis aimed to confirm the role of ADC values in predicting the prognosis of PCNSL patients based on previous studies.

Materials and Methods

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses were used to conduct this systematic review and meta-analysis (PRISMA) (Tawfik et al., 2019). The Patient, Intervention, Comparison, Outcomes (PICO) of this systematic review was:

P, Patients with confirmed diagnosis of PCNSL
I, Patients with low pretherapeutic ADC values
C, Patients with high pretherapeutic ADC values
O, OS and PFS

Based on the mentioned PICO, the question of the systematic review was "In patients with confirmed diagnosis of PCNSL, is there any association between pretherapeutic ADC values of the tumor with the OS and PFS of the patients?".

Studies were identified using the keywords "Apparent Diffusion Coefficient OR ADC OR Diffusion Weighted Imaging OR DWI" AND "primary central nervous system lymphoma" in six electronic databases: PubMed, Scopus, Sciencedirect, Cochrane, DOAJ, and Embase. The search took place between October 1, 2021, and November 30, 2021. The studies were reported in English and had no publication date restriction. The EndNote 9 application was used to filter for identical or duplicate articles.

Inclusion and Exclusion

The following criteria were used to determine study inclusion: full-text articles available; studies properly designated to assess prognosis, observational cohort or randomized controlled trial; target population, newly diagnosed PCNSL patients with histopathological confirmation; and availability of pretherapeutic ADC data. The study used cut-off values to classify patients as having a high or low ADC; Survival data are available in the form of overall survival (OS) and/or progression-free survival (PFS); hazard ratio (HR) and 95% confidence interval (CI) data are also available or can be calculated from the reported data.

Data Extraction

Three independent reviewers (a radiologist, a radiation-oncologist, and a neurologist) conducted data analysis and extraction. Disagreements were resolved through discussion. The first author's name, the year of publication, the location of the study, the number of samples, patient characteristics and therapy, ADC method data and explanations regarding the cut-off value used, as well as OS and PFS data, were extracted from each study (Table 1).

Statistical Analysis

In each study, MRI was performed on patients with PCNSL who had not previously received treatment. Following MRI examination, patients were divided into low pretherapeutic ADC group and high pretherapeutic ADC group based on the cut-off values determined in each study. Then, OS and/or PFS were compared between patients with low and high ADC values. If the p value is < 0.05, the difference is considered significant. HR quantifies the strength of the relationship between ADC values and OS and/or PFS. Because some articles omitted CI values, we estimated them using mathematical calculations based on previously reported methods (Altman and Bland, 2011). Pooled HR was calculated using RevMan 5 to determine the prognostic value of ADC values. Cochrane's Q test (Chi-squared test; Chi2) and Inconsistency tests were used to determine statistical heterogeneity (I^2). When I^2 is $< 50\%$, the pooled HR is estimated using a fixed-effects model; when $> 50\%$, the

pooled HR was estimated using a random-effects model.

Three reviewers independently assessed the quality and bias risks of the selected studies using the Quality in Prognosis Studies (QUIPS) assessment (Figure 1) (Hayden et al., 2013)

Results

Study Selection and Characteristics

Figure 2 depicts the flow chart diagram of the study selection process. We retrieved 1603 studies from six databases using the specified keywords. Following deduplication, titles and abstracts were screened from 1371 studies. We excluded 1357 due to irrelevant titles and abstracts and the abstracts were in languages other than English. Furthermore, 14 studies with relevant titles and abstracts were obtained, but two studies did not have full manuscripts available. Eventually, a total of 12 studies were chosen for review and detailed reading. Following a thorough review, eight studies were excluded because they did not include ADC values, lacked OS and/or PFS data, or used normalized ADC. This systematic review and meta-analysis included a total of four studies , (Barajas et al., 2010; Valles et al., 2013; Zhang et al., 2016; Baek et al., 2020).

The studies took place in three distinct countries (2 studies in the United States, 1 in South Korea, and 1 in China). Each study was a retrospective cohort study that was conducted between 2010 and 2020.

This systematic review and meta-analysis included a total of 123 patients. All studies used the same patient criteria: patients who had been newly diagnosed with PCNSL based on histopathological findings, were immunocompetent with a negative HIV status, and had been ruled out of having extra-central nervous system lymphoma. In the majority of studies, the histologic characteristic was DLBCL. Only one patient in the Zhang (2016). study exhibited T-cell lymphoma.

While all studies used HD MTX as an induction therapy, the use of chemotherapeutic agents and other adjunctive therapies varied. After complete response, Barajas (2010) and Valles (2013) used additional doses of MTX as consolidation chemotherapy. Baek (2020) used consolidation therapy consisting of high-dose chemotherapy followed by autologous stem cell transplantation (HD/ASCT). WBRT was used in all studies in patients with stable disease, progressive disease, or partial remission following HD MTX induction.

All studies reported objective outcome criteria. OS was described as the period between the day of initiation of treatment to death. PFS is the period between the day of initiation of the first treatment and the first recurrence.

Three studies used 1.5 T MRI scanners, (Barajas et al., 2010; Valles et al., 2013; Zhang et al., 2016) and one study used both 1.5T and 3T MRI scanners (Baek et al., 2020), with b values of 0 and 1000 sec/mm2. Each study used the ADC method with varying cut-off values, with the most commonly used cut-off value 384 x 10-6 mm2/s for the ADCmin method, as determined by Barajas (2010). Barajas (2010) used the ADCmean, ADCmin, and ADC25% methods, but ultimately focused on ADCmin and ADC25% methods, assuming that these methods accurately represent the cellular components in high-contrast tumors. Baek (2020) did not specify the method for determining the ADC value and cut-off, but the authors stated that they used the ADC value and cut-off determined by Barajas (2010) to categorize the patients into high and low ADC groups. Zhang (2016) used the ADCmean, ADC5%, and ADC95% methods, but the univariate analysis of ADC95% did not achieve statistical significance, and thus was excluded from the multivariate analysis.

Three studies were included in this systematic review and meta-analysis to assess the relationship between pretherapeutic ADC values and overall survival (OS) (Table 1). Three studies were included to assess the relationship between pretherapeutic ADC values and progression-free survival (PFS) (Table 2). All studies that examined the association between pretherapeutic ADC values and OS and PFS discovered that lower ADC values were associated with significantly shorter OS and PFS. In all of the studies reviewed, the HR was

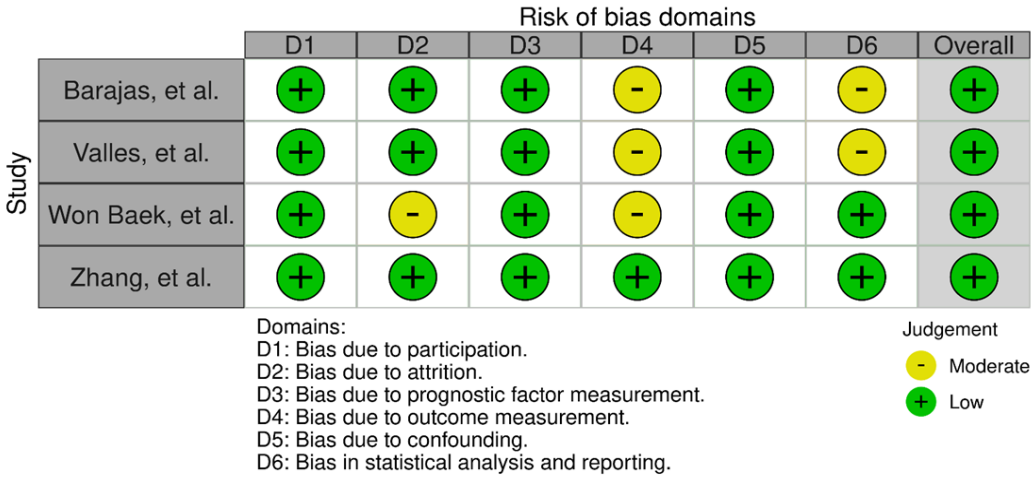

Figure 1. Assessment of Study Quality Using Quality in Prognosis Studies (QUIPS). From the overall assessment, all studies show a low bias.

Table 2. Data from Studies Regarding the Association of Pretherapeutic ADC Values with PFS in PCNSL Patients

Study (Year)	Regio	Study Design	Patients	Methods of ADC used	ADC Cut-off values used (10-6 mm2/s)	PFS (Low ADC group vs high ADC group)	Hazard Ratio (HR)	95%CI	p-value
Barajas et al. (2010)	United States	Cohort	18	$ADC_{25\%}$	692	Mean PFS 9.4 months vs 30 months; p = <0.01	0.21 (multivariate analysis)	0.05 - 0.86	0.03
				ADC_{min}	384		0.08 (multivariate analysis)	0.01 - 0.55	0.01
Valles et al. (2013)	United States	Cohort	25	ADC_{min}	384	Mean PFS 13.8 months vs 38.9 months; p = 0.04	0.24 (multivariate analysis)	0.08 - 0.71	<0.01
Zhang, et al. (2020)	China	Cohort	28	ADC_{mean}	800	Median PFS 5 months vs 12 months; p = 0.009	0.465 (multivariate analysis)	0.17 - 1.22	0.121
				$ADC_{5\%}$	500	Median PFS 4 months vs 15 months; p = 0.001	0.086 (multivariate analysis)	0.012 - 0.615	0.014

Table 1. Data from Studies Regarding the Association of Pretherapeutic ADC Values with OS of PCNSL Patients

Study (Year)	Regio	Study Design	Patients	Methods of ADC used	ADC Cut-off values used (10-6 mm2/s)	OS (Low ADC group vs high ADC group)	Hazard Ratio (HR)	95%CI	p-value
Barajas et al. (2010)	United States	Cohort	18	$ADC_{25\%}$	692	Mean OS 15.8 months vs 30.9 months; p = <0.01	0.12 (multivariate analysis)	0.02 - 0.71	0.02
				ADC_{min}	384		0.01 (multivariate analysis)	0.00 – 0.33	0.01
Valles et al. (2013)	United States	Cohort	25	ADC_{min}	384	Mean OS 12.1 months vs 20.1 months; p = 0.05	0.29 (multivariate analysis)	0.102 - 0.824	0.02
Dong Wo Baek et al. (2020)	South Korea	Cohort	52	Reference to Barajas et al.10	Reference to Barajas et al.10	OS at 3 year was shorter, (56.0±3.7% vs 76.5%±8.6%); p = 0.05	0.392 (multivariate analysis)	0.155 - 0.854	0.12

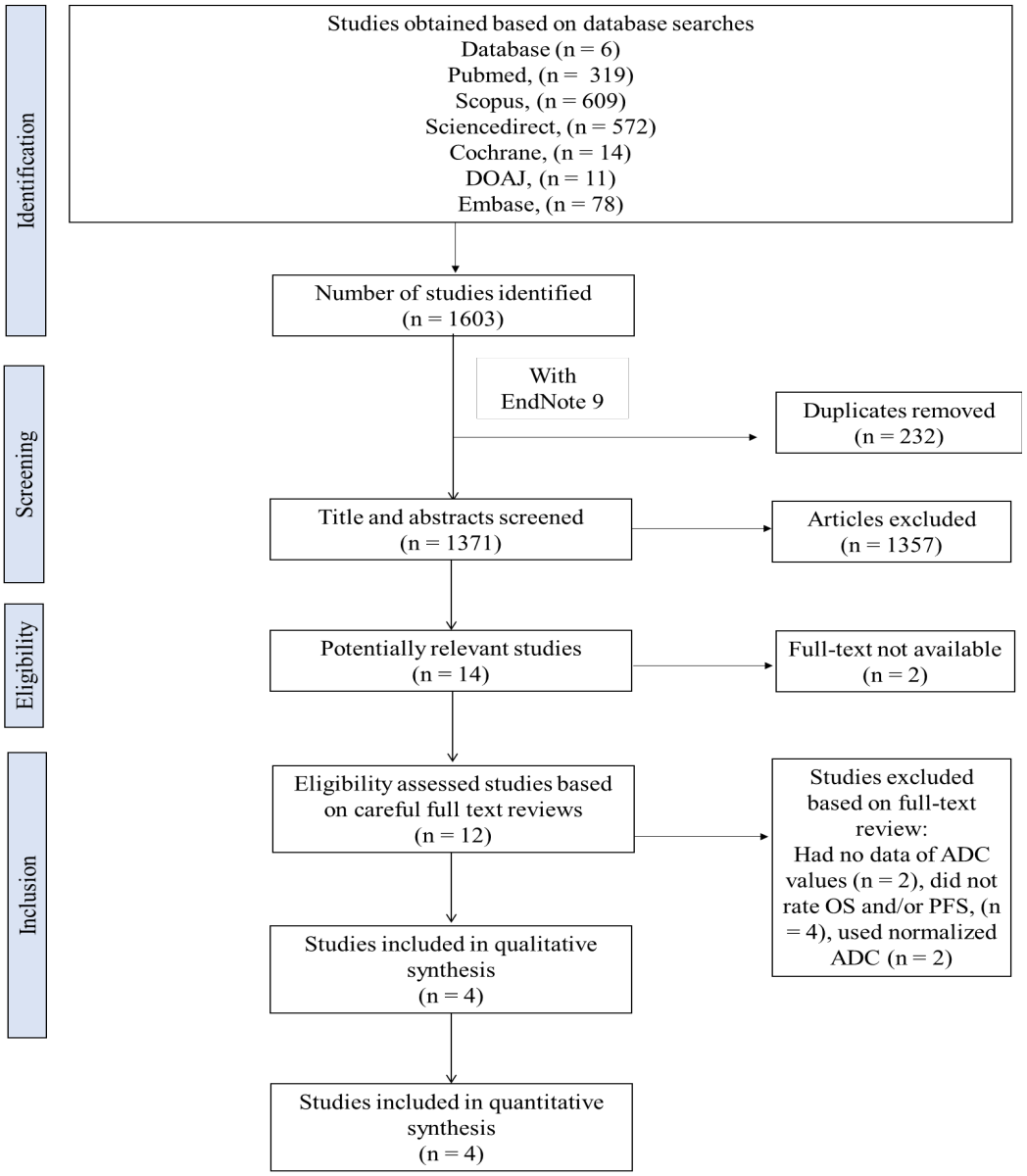

Figure 2. Flowchart of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). In the end, 4 studies were deemed suitable for inclusion in the analysis.

calculated using multivariate analysis and Kapplan-Meier curves. All studies matched their prognostic factors with other prognostic factors. Across all studies, multivariate analysis revealed that low ADC values were the single and independent predictor of OS. Except for calculations using the ADCmean from Zhang (2016), which did not reach statistical significance in multivariate analysis ($p > 0.05$), all low ADC values were also the single and independent prognostic factor for PFS.

Meta-analysis

OS and PFS are associated with Low ADC Value

A total of four data were analyzed to determine the relationship between ADC values and OS (Figure 3). Due to the low heterogeneity ($I2 = 42\%$; $p = 0.16$), the analysis was conducted using a fixed-effects model. The

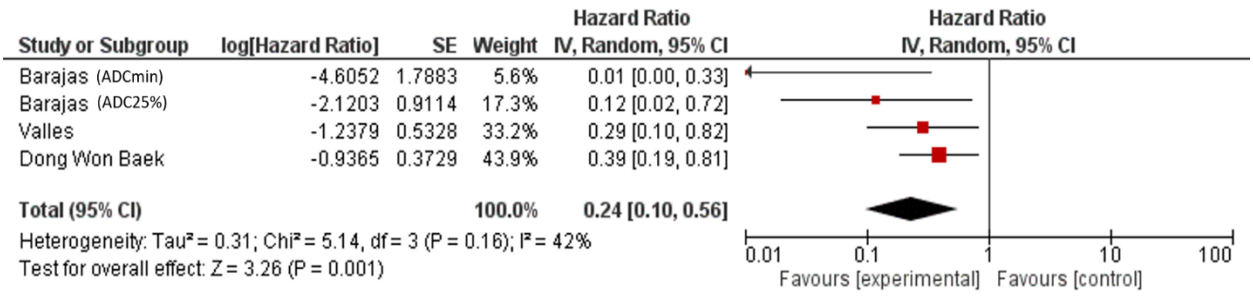

Figure 3. Forest Plot of Hazard Ratio (HR) combination using Fixed-Effect for Overall-Survival (OS).

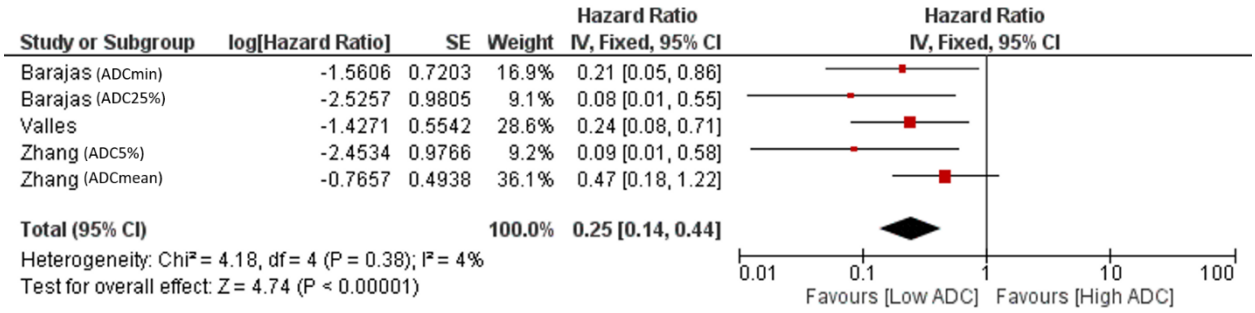

Figure 4. Forest Plot of Hazard Ratio (HR) combination using Fixed-effect for Progression-Free Survival (PFS).

analysis revealed that patients with low ADC values had a higher risk of death than those with high ADC values, with a pooled HR of 0.24 (95% CI: 0.10–0.56; Z = 3.26; p = 0.001).

A meta-analysis of five data from three studies examining the association between ADC values and PFS (Figure 4) was also conducted using a fixed-effects model due to the low heterogeneity values (I^2 = 4%; p = 0.38). The data analysis revealed that the pooled HR was 0.25 (95% confidence interval [CI]: 0.14–0.44, Z = 4.18; p=0.00001). Additionally, patients with low ADC had a greater risk of disease progression than those with high ADC.

Discussion

PCNSL is a highly aggressive cancer with a low rate of morbidity and mortality. OS is reported to have a life expectancy of only 12-18 months on average. Without therapy, OS is significantly shorter, ranging between 1.5 and 3.3 months. Since the introduction of HD-MTX-based chemotherapy, the prognosis for patients with PCNSL has improved significantly (16.3-66 months), with a 2-year OS rate of 42-80.8 percent (Liu et al., 2021).

Experts agree that HD MTX is the mainstay of therapy in the multimodal management of PCNSL cases. Chemotherapy regimens used in non-CNS lymphoma are ineffective because they cannot penetrate the blood-brain barrier, whereas MTX given at high doses has been shown to penetrate the blood-brain barrier (Grommes and Deangelis, 2017). Although some patients achieved complete remission (CR) following initial treatment with HD MTX, the reported relapse rate remains high (66.6%) (Yamanaka et al., 2017).

Combining HD-MTX and WBRT has been shown to improve response rate and prognosis, with a median OS of 30-60 months and a 5-year survival rate of 30% – 50% (Grommes and Deangelis, 2017). This improved prognosis, however, is associated with increased neurotoxicity as a result of the synergistic toxicity of HD-MTX and WBRT. Clinical manifestations of this neurotoxicity range from mild short-term memory impairment to more severe symptoms such as gait abnormalities, incontinence, and severe dementia, all of which can impair survivors' quality of life (Kasenda et al., 2016). The neurotoxic effects are even more severe and manifest more rapidly in the elderly patient population (Liu et al., 2021).

If clinicians can obtain information about prognosis, recurrence, or disease progression prior to initiating chemotherapy with HD MTX, it is not impossible for clinicians to determine a personalized therapy that is appropriate for each patient, especially in high-risk patients. For example, the clinician may determine that in patients with a low risk of disease progression, chemotherapy alone may be sufficient without the addition of WBRT. Meanwhile, in patients at high risk of disease progression, it may be necessary to continue radiation, HDC/ASCT, or even consider targeted agents in the event of relapse or recurrence (Ferreri et al., 2019). Thus, it is hoped that the clinical outcome of the patient will improve as well, and that side effects of treatment will be minimized.

Previously, the International Extra-nodal Lymphoma Study Group (IELSG) recommended a scoring system for predicting clinical outcomes in patients with extra-nodal lymphoma. The IELSG scoring system considers several factors, including age, Eastern Cooperative Oncology Group (ECOG) performance score, lactate dehydrogenase levels, protein concentration in cerebrospinal fluid (CSF), and involvement of inner brain structures (Grommes and Deangelis, 2017). However, implementation of this scoring system continues to present challenges and shortcomings. For instance, CSF examination is not always performed because it is time consuming, invasive, and carries a high risk of complications. Meanwhile, differences in the MRI sequence used, as well as the timing and dose of contrast administration, can affect the assessment of tumors and their response to therapy. Additionally, data on this subject are scarce. Additionally, there are insufficient studies examining the association between specific MRI images and the prognosis of PCNSL patients (Baek et al., 2020; Barajas et al., 2021).

Baek (2020) found that protein levels in the cerebrospinal fluid and the involvement of brain structures had no statistically significant relationship with patient survival. However, when Baek added a low ADC value as an independent variable to the IELSG scoring system, the authors discovered that the modified scoring system was capable of predicting OS significantly. The prognostic factors influencing PFS in patients with PCNSL remain unclear. Zhang (2016) demonstrated that PFS was not correlated by single or multiple lesions on conventional MRI, age, or gender. However, PFS was correlated by initial clinical performance status, Ki-67 expression, and ADC5% and ADCmean values.

DWI is a novel imaging technique that provides a

presentation of a tumor's microenvironment by assessing image contrast and tissue quantification based on differences in the proton movement of water molecules between tissues. Numerous studies have established DWI's utility in imaging malignancy. Currently, interest in the utility of DWI in assessing tumor response is increasing (Afaq et al., 2010).

Within the body, the diffusion of water molecules is restricted by a variety of barriers that vary according to the environment around the water molecules. The movement of protons from water molecules is inhibited in dense tissues (high cellularity), such as tumor tissue, by cell membranes, macromolecules, and extracellular space. Tissues with constrained water diffusion will exhibit a strong signal on the DWI image but a low ADC value. It is predictable, then, that tumor tissue has lower ADC values than normal tissue (Afaq et al., 2010). According to previous study, tumors with a high cell density, such as astrocytoma, lymphomas, and medulloblastomas, exhibit high DWI signals on b-value images and low ADC values due to cellularity and a high nuclear-to-cytoplasmic (N/C) ratio (Guo et al., 2002). Low ADC values derived from DWI were found to have an inverse relationship with the tumor proliferation index, suggesting that they may be used as noninvasive imaging biomarkers for determining the aggressiveness and grading of tumors pre-operatively (Li et al., 2015). For instances, the utility of ADC in differentiating high-grade from low-grade CNS tumors has been demonstrated in gliomas and meningiomas (Meyer et al., 2020; Wang et al., 2020).

Numerous studies have demonstrated a negative correlation between ADC values and the Ki-67 tumor proliferation index in patients with PCNSL (Schob et al., 2016; Schob et al., 2018; Chong et al., 2019; Hung et al., 2020; Khan et al., 2020). Ki-67 expression is strongly correlated with cell proliferation, growth, and aggressiveness and has been widely used as a marker of tumor proliferation in routine pathological examination. Additionally, Ki-67 has been widely used as a prognostic marker for cancer (Li et al., 2015). According to this, predictably, the ADC value in PCNSL can be used as a noninvasive surrogate marker for tumor cell proliferation. Because a low ADC value indicates increased cell proliferation, it may also be used to predict patient clinical outcomes (Valles et al., 2013).

The findings of our systematic review and meta-analysis of four retrospective cohort studies support the conclusion that ADC values obtained from DWI are the single and independent predictors of prognosis in immunocompetent PCNSL patients receiving initial HD MTX-based chemotherapy. When untreated PCNSL patients were divided into high and low ADC groups using the ADCmin, ADC25%, ADC5%, and ADCmean methods, it was discovered that patients with low ADC values had significantly shorter OS and PFS than those with high ADC values. These findings have the potential to pose a number of clinical implications. The DWI-ADC examination is noninvasive and low risk, and it can provide information on prognosis and relapse risk, allowing clinicians to determine second-line therapy strategies in high-risk patients, ultimately leading to improved clinical outcomes.

Several factors must be considered when interpreting these findings. To begin, the studies we included had a relatively small sample size and had retrospective nature. Currently, there are no randomized-controlled trial studies that can support these findings, yet. Second, while treatment modalities were generally consistent, additional therapy, consolidation, and rescue therapy might vary, affecting the clinical outcome of the patient. Third, both the ADC method used and the cut-off value varied, although slightly. According to Zhang (2016), the predictive values obtained using various ADC methods were not identical. The authors discovered that ADC5% and ADCmean were both significantly associated with decreased PFS. Multivariate analysis revealed that ADC5% could be an independent prognostic factor in patients with PCNSL. While the ADCmean might have predictive value for prognosis, it was not the only predictive, independent factor of PFS. Meanwhile, ADC95% did not demonstrate a statistically significant relationship with PFS, it was determined that it was insufficient for PCNSL prognostic stratification. The authors believe that the ADC5% derived from DWI is more accurate than other ADC methods in predicting clinical outcome in PCNSL patients. Fourth, several variables that affect the ADC calculation, such as the ROI assessment, the b-value, the spin-echo setting, the field strength, and the relaxation properties, can also affect the ADC value calculation. However, Ogura et al. (2015) previously reported that ADCs assessed using the same b-value would not differ even when using a different MRI machine and scanning parameters.

While our meta-analysis review has some disadvantages, it also has some advantages. Unfortunately, we were unable to control certain variables in a meta-analysis of retrospective studies, but fortunately, the cases and characteristics of the patients included in our included studies were generally homogeneous. The standard of care for PCNSL, HD MTX induction chemotherapy followed by WBRT based on response to therapy, was universally used in all of the studies we included. Finally, there has been no systematic review or meta-analysis of the effect of ADC values on the clinical outcome of PCNSL patients, and our meta-analysis is the first to do so.

In conclusion, the ADC value was found to be significantly corelated to the prognosis of patients with PCNSL. Patients with low ADC values had significantly shorter overall survival and progression-free survival than those with high ADC values. ADC values assessment prior to initial therapy administration can provide clinicians with valuable information about the prognosis of PCNSL patients non-invasively, so it is hoped that it can assist clinicians in selecting more appropriate second-line therapy, based on risk stratification and individually tailored to each patient, particularly in high-risk patients.

Author Contribution Statement

All authors were involved in planning the research. All authors were involved in the data acquisition, calculation, and analysis. RM drafted the manuscript, tables, and figures. All authors took part in revising the draft until

its completion.

Acknowledgements

Approval

This work has never been approved by any scientific body or registered in any dataset.

Ethical issue

There is no ethical issue to be handled.

Availability of data

Data used has been put into tables and figures.

Conflict of Interest

The authors report no conflicts of interest.

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