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CLINICAL STUDY

# Autoimmune disease-related primary CNS lymphoma: systematic review and meta-analysis

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## Abstract

**Background** Recent studies suggest a relatively high prevalence of autoimmune disorders (AD) among primary CNS lymphoma (PCNSL) patients, however, the literature is limited to case reports. To gain a better understanding of AD-PCNSL we reviewed and analyzed all cases described in the literature.

**Methods** We searched the MEDLINE database using the search terms 'central nervous system lymphoma' or 'CNS lymphoma' along with AD-related terms. We selected 39 records for qualitative synthesis of data and identified 50 AD-PCNSL. Clinical, imaging and outcome data were collected. Overall survival (OS) was analyzed with the Kaplan–Meier method. Univariate and multivariate analyses were performed using log rank test and Cox proportional hazard model.

**Results** Most common AD were systemic lupus erythematosus (24%), multiple sclerosis (16%), and myasthenia gravis (14%). All patients had received immunosuppressants for their AD. Median interval from AD until PCNSL diagnosis was 108 months (range: 11–420). Male-to-female ratio was 0.42 and AD-PCNSL was diagnosed at a median age of 57 years (range: 2–88). On imaging lesions typically localized to the hemispheres (65%) and displayed peripheral enhancement (74%). Pathological evaluation revealed diffuse large-B-cell lymphoma (DLBCL) subtype (80%) and Epstein-Barr virus positivity (75%) in most AD-PCNSL. Median OS was 31 months. Age > 60 years ($p = 0.014$) was identified as a significant prognostic factor.

**Conclusions** AD requiring immunosuppression appear over-represented in the population of PCNSL patients. Aggressive polychemotherapy can accomplish long term OS in AD-PCNSL comparable to immunocompetent patients. Age > 60 may serve as a prognostic factor.

**Keywords** Primary CNS lymphoma · Autoimmune diseases · Epstein-barr virus · Immunosuppression · Brain tumor

## Introduction

Several autoimmune disorders (AD) were previously shown to be potential risk factors for non-Hodgkin Lymphoma (NHL). The hazard correlates with AD type, choice of immunosuppressants and inflammatory activity [1–4]. Primary central nervous system lymphoma (PCNSL) represents an extra nodal NHL that is confined to the central nervous system (CNS) at the time of diagnosis [5, 6]. Incidence of PCNSL currently stands at 0.44/100.000 [7]. In our clinical experience, relative incidence of AD amongst PCNSL patients is 5–10% [8]. A recent Scandinavian population based study suggested 29% of PCNSL patients had an underlying AD [9]. Although AD-related PCNSL presents with distinct clinical and pathological characteristics, data are scarce and limited to small case series [10, 11]. Clinical, radiological and pathological characteristics have not been

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defined in a larger cohort. Furthermore, it is unclear whether certain types of AD are overrepresented, and prognostic factors remain uncertain. To gain a better understanding of AD-PCNSL we conducted a comprehensive review and meta-analysis of cases described in the MEDLINE database.

## Material and methods

A comprehensive review of the literature on AD-related PCNSL was conducted searching the MEDLINE database in August 2019 according to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines [12]. 'Central nervous system lymphoma' or 'CNS lymphoma' were used as primary search terms. Boolean operator 'and' was applied together with AD-related search terms: 'Autoimmune', 'Immunosuppression', 'Immunosuppressed', 'Immunosuppressant', 'Arthritis', 'Crohn', 'Diabetes', 'Hyperthyroidism', 'Hypothyroidism', 'Lupus', 'Myasthenia', 'Multiple sclerosis', 'Sjögren', 'Thyroiditis', 'Uveitis', 'Azathioprine', 'Cyclosporine', 'Infliximab', 'Methotrexate', 'Mycophenolate', and 'Natalizumab'. Search terms including specific AD or immunosuppressants were selected based on high prevalence or a previously described association with PCNSL. Duplicates were removed and a total of 1103 articles underwent screening for eligibility. Case reports or series in English language reporting PCNSL in the setting of AD were included. Studies that only listed historical AD without providing clinical detail were not included. PCNSL with other underlying causes of immunosuppression (e.g. HIV infection) were excluded. Overall, a total of 39 articles were selected for qualitative synthesis of data (Supplementary Table 1). These studies reported a total of 50 cases of AD-PCNSL that are summarized in Supplementary Table 1. Clinical, radiological, pathological and outcome characteristics were collected. Overall survival (OS) was estimated using the Kaplan–Meier method. Univariate and multivariate analyses were performed using log rank tests and Cox proportional hazard models, respectively. The significance level was set at $p < 0.05$. Prism Version 8 and SPSS Version 25 were used for statistical analyses. Age at diagnosis was analyzed as a categorical variable in univariate analysis. The threshold was selected based on the international extranodal lymphoma study group prognostic scoring system for PCNSL [13].

## Results

### Cohort characteristics

AD distribution in this PCNSL cohort is shown in Fig. 1. Common ADs were systemic lupus erythematosus (SLE) (n = 12, 24%), multiple sclerosis (MS) (n = 8, 16%), myasthenia gravis (MG) (n = 7, 14%), rheumatoid arthritis (n = 6, 12%), autoimmune uveitis (n = 3, 6%) and myositis (n = 3, 6%). All ADs identified in this study can be found in Supplementary Table 1. Clinical characteristics are summarized in Table 1. All patients had received immunosuppressants for their respective ADs. Prescribed regimens prior to PNCSL diagnosis frequently included prednisone (n = 33, 69%), mycophenolate mofetil (MMF) (n = 20, 42%), azathioprine (n = 20, 42%), and methotrexate (n = 9, 19%). Median interval from AD to PCNSL diagnosis was 108 months (range 11–420). Male-to-female ratio in this study was 0.42. Among most common subgroups, a male predominance was observed in MS-PCNSL (male-to-female ratio: 2.5). Median age at PCNSL diagnosis was 57 years (range: 2–88).

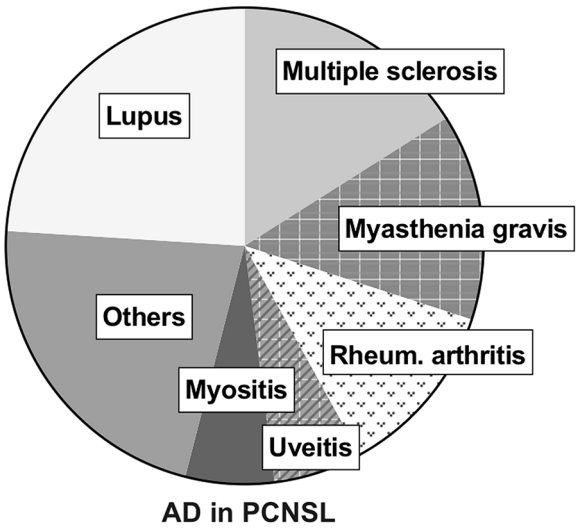


**Fig. 1** Distribution of autoimmune diseases in AD-PCNSL. Pie diagram illustrating the distribution of various autoimmune diseases (AD) in PCNSL. Systemic lupus erythematosus (24%) was the most common AD among PCNSL patients, followed by multiple sclerosis (16%), myasthenia gravis (14%), rheumatoid (rheum.) arthritis (12%), uveitis (6%) and myositis (6%)

### Radiological and pathological data

Radiological and pathological data are summarized in Table 2. Histology revealed diffuse large B-cell lymphoma (DLBCL) in the majority of cases (n = 37, 80%). Epstein-Barr-virus (EBV) status was reported in 36 cases and was positive in 27 of them (75%). Immunoglobulin heavy chain gene rearrangement (IgH-R) analysis revealed clonal disease in seven of ten subjects (70%). On neuroimaging studies multiple PCNSL lesions were noted in 24 cases (53%). Lymphomas were most frequently found in cerebral hemispheres (n = 28, 65%), the cerebellum (n = 8, 19%), and the brain stem (n = 5, 12%). Nearly all tumors showed contrast

**Table 1** Cohort characteristics and immunosuppression

| | N | (%) | | N | (%) |
|---|---|---|---|---|---|
| Gender | 47 | | Immuno-suppressants | 48 | |
| Female | 33 | (70) | Prednisone | 33 | (69) |
| Male | 14 | (30) | MMF | 20 | (42) |
| Age | 50 | | Azathioprine | 20 | (42) |
| Median at diagnosis, [range] | 57 y [2–88] | | Methotrexate | 9 | (19) |
| Interval of Immunosuppression | 47 | | Hydroxy- chloroquine | 6 | (13) |
| Median to diagnosis, [range] | 108 mo [11–420] | | Interferon-β | 5 | (10) |
| Survival data | 37 | | Natalizumab | 5 | (10) |
| Median OS [range] | 31 mo [1–139] | | Cyclo- phosphamide | 5 | (10) |
| | | | Infliximab | 2 | (4) |

*N* number of patients; *y* years; *mo* months; *OS* overall survival; *MMF* mycophenolate mofetil

**Table 2** Radiological and pathological data

| Imaging characteristics | N | (%) | Pathology characteristics | N | (%) |
|---|---|---|---|---|---|
| Number of lesions | 45 | | Histological subtype | 46 | |
| Single | 21 | (47) | DLBCL | 37 | (80) |
| Multiple | 24 | (53) | BCL not specified | 7 | (15) |
| Enhancement | 41 | | PTCL | 1 | (2) |
| Present | 40 | (98) | MALT | 1 | (2) |
| Enhancement patterns | 35 | | EBV status | 36 | |
| Peripheral | 26 | (74) | EBV positive | 27 | (75) |
| Diffuse | 7 | (20) | IgH-R | 10 | |
| Irregular | 2 | (6) | Positive | 7 | (70) |

*N* number of patients; *DLBCL* diffuse large B-cell lymphoma; *BCL* B-cell lymphoma; *MALT* mucosa associated lymphoid tissue; *PTCL* peripheral T-cell lymphoma; *EBV* Epstein-Barr virus; *IgH-R* immunoglobulin G heavy chain rearrangement

enhancement (n = 40, 98%) and a peripheral enhancement pattern was typically noted (n = 26, 74%). Supplementary Fig. 1 shows a typical AD-PCNSL lesion on MRI.

## Treatment and outcome

Treatment data are presented in Table 3. After PCNSL diagnosis immunosuppressants were reduced in all 27 patients for whom such information was available. Treatment frequently consisted of chemotherapy (Ch-Th) alone (n = 23, 55%), or administration of Ch-Th along with whole brain radiation therapy (WBRT) (n = 8, 19%). No additional treatment was provided in two patients (5%). Ch-Th regimens often included methotrexate (n = 19, 63%), rituximab (n = 18, 60%), or cytarabine (n = 8, 27%).

Survival data was available for 37 cases with a median follow-up of 8 months. Figure 2 presents Kaplan–Meier survival curves for AD-PCNSL. A median OS of 31 months was calculated. Median OS for SLE-, MS-, and MG- associated

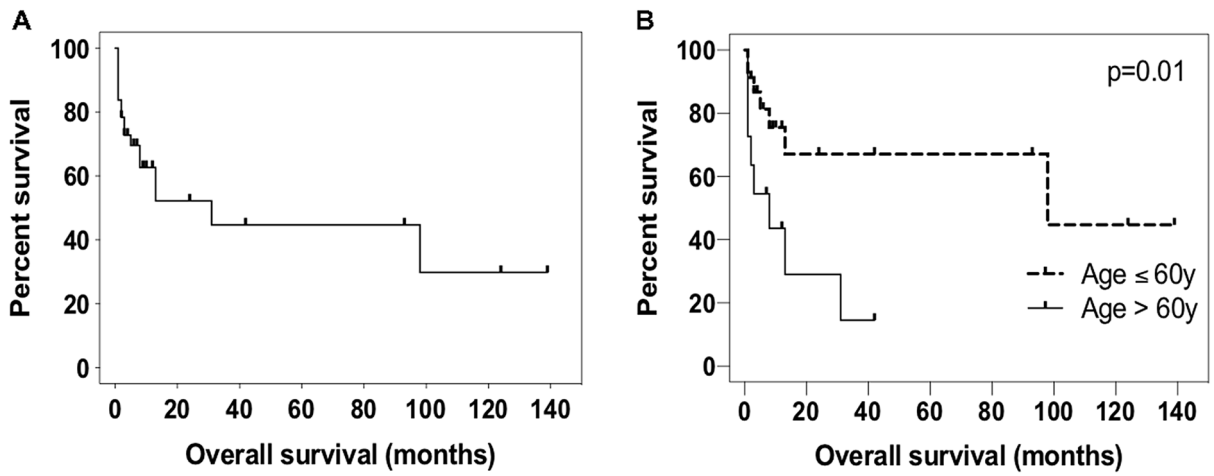


**Fig. 2** Overall survival and prognostic factors in AD-PCNSL. Kaplan–Meier survival curves **a** Overall survival of the entire autoimmune disease (AD)-related PCNSL cohort. Median overall survival was 31 months. **b** Age > 60 years at diagnosis (p = 0.014) is a significant predictor of inferior survival in AD-PCNSL

**Table 3** Treatment of AD-PCNSL

| | N | (%) | | N | (%) |
|---|---|---|---|---|---|
| Treatment | 42 | | Ch-Th drugs | 30 | |
| No treatment | 2 | (5) | Methotrexate | 19 | (63) |
| Ch-Th alone | 23 | (55) | Rituximab | 18 | (60) |
| Ch-Th + WBRT | 8 | (19) | Cytarabine | 8 | (27) |
| Ch-Th + ASCT | 2 | (5) | Temozolomide | 3 | (10) |
| WBRT alone | 2 | (5) | Vincristine | 3 | (10) |
| R alone | 2 | (5) | Cyclo-phosphamide | 3 | (10) |
| R + Ch-Th | 1 | (2) | Ifosfamide | 2 | (7) |
| R + WBRT | 1 | (2) | Thiotepa | 2 | (7) |
| Reduction of IS | 27 | | | | |
| Reduction | 27 | (100) | | | |

*N* number of patients; *Ch-Th*, chemotherapy; *WBRT* whole brain radiation therapy; *ASCT* autologous stem cell transplant; *R* resection; *IS* immunosuppressants

PCNSL, the three largest subgroups in this study, was 8, 5, and 25 months, respectively. However, differences between subgroups did not reach statistical significance. In univariate analysis age > 60 years at diagnosis ($p = 0.014$) was identified as a significant prognostic factors for AD-PCNSL. Patients with clonal IgH-R had a trend towards shorter OS ($p = 0.086$). Supplementary Table 2 summarizes all variables studied in univariate analysis. Significance was not reached in multivariate analysis.

## Discussion

To our knowledge, this review and meta-analysis presents the largest cohort of AD-PCNSL to date. The largest previous series included four or five patients only [8, 10, 11]. While the prevalence of AD in a PCNSL cohort was previously addressed in a Scandinavian and in a North American population based study, both studies did not present clinical characteristics of AD-PCNSL [4, 9]. As their study and our clinical experience suggest a high prevalence of AD among PCNSL patients, we aimed to better characterize AD-PCNSL in this study.

The most prevalent AD in the general population is type I diabetes (946/100,000), followed by hyperthyroidism (629/100,000), and rheumatoid arthritis (381/100,000) [14]. In comparison most common AD in this PCNSL meta-analysis were SLE, MS, and MG. Interestingly, all three conditions often display severe disease activity and hence require high intensity immunosuppressive treatment. As inflammatory activity, type and level of immunosuppression were previously correlated with an increased risk for lymphomagenesis, this may predispose to PCNSL [2, 15].

In line with Enblad et al., no PCNSL patient in this meta-analysis had a history of type I diabetes or hyperthyroidism [9]. Both conditions share lower systemic inflammatory activity and rare requirement of immunosuppressive treatment, distinguishing them from other AD found in the setting of PCNSL. In contrast to this study, Enblad et al. frequently identified hypothyroidism among AD-PCNSL [9]. Hypothyroidism and other conditions not requiring immunosuppressants may be underrepresented in this study due to a publication bias. In agreement with this notion, Enblad et al. identified AD-PCNSL without prior immunosuppressive treatment, whereas all patients in this series had received immunosuppressants [9]. Frequencies of AD identified in a recent North American population-based PCNSL study by Mahale et al. are not comparable to this series as only patients older than 65 years were included. However, they found significant associations between PCNSL and several AD included in this meta-analysis (SLE, MG, uveitis, psoriasis). [4].

Similar to other immunodeficiency-related PCNSL such as primary CNS post transplant lymphoproliferative disease (PCNS PTLD), a considerable portion of AD-PCNSL appears to occur in the setting of prior mycophenolate mofetil (MMF) or azathioprine treatment [8, 16, 17]. Although subject to ongoing controversial discussion both immunosuppressants were previously linked to lymphomagenesis [18, 19]. Whether the AD type, inflammatory activity, subsequent immunosuppressive treatment, or a combination of all three factors primarily contribute to development of AD-PCNSL warrants further investigation. The median interval of immunosuppression in AD-PCNSL of 9 years noted in this study was longer than previously reported in PCNS PTLD (4.4 years) [16]. This may reflect less severe immunosuppression on average in AD. In this study, median age at AD-PCNSL diagnosis was slightly older (57 years) than previously reported for PCNS PTLD (52 years) [17]. This could result from differences between age at AD diagnosis and at solid organ transplantation, but could also mirror a longer course of immunosuppression preceding AD-PCNSL diagnosis. A female predominance among AD-PCNSL in this meta-analysis (male-to-female ratio 0.42) is in line with similar gender differences in AD with the exception of MS-associated PCNSL. In MS male gender is correlated with a more aggressive disease course, which may contribute to a higher PCNSL risk [20].

Imaging characteristics of AD-PCNSL in this study resembled previous accounts of other immunodeficiency-related PCNSL. Similar to PCNS PTLD, AD-PCNSL in this study frequently presented as hemispheric, peripherally contrast enhancing lesions [8]. Pathological characteristics of AD-PCNSL are also in line with other immunodeficiency-related PCNSL. AD-PCNSL in this study were typically classified as DLBCL (80%) and EBV was identified in the

majority (75%) of tumors in agreement with 73% and 91% in PCNS PTLD, respectively [8]. In contrast to immunocompromised hosts EBV is normally not identified within the lymphomatous lesions in immunocompetent PCNSL patients [21]. This could suggest pathogenesis of AD-PCNSL differs from immunocompetent hosts and is typically EBV driven. However, there is a 'hit-and-run hypothesis' for EBV involvement in immunocompetent PCNSL, which proposes EBV induces lymphomagenesis, but is not needed for tumor maintenance and is hence lost from lymphoma cells [22].

In this meta-analysis, AD-PCNSL were typically found to be monoclonal (70%) as assessed with IgH-R analysis similar to reported 75% in PCNS PTLD [8]. Previous studies suggest that monoclonality as assessed with IgH-R analysis may provide an additional diagnostic tool that supports a lymphoma diagnosis [23]. This may prove especially valuable in the setting of AD with known CNS involvement (such as MS) that can mimick PCNSL. However, as IgH-R data was only available in a small subset of patients from this meta-analysis the diagnostic and prognostic utility of this method in AD-PCNSL warrants further investigation.

There is currently no consensus treatment for immunodeficiency-associated PCNSL. As in PCNS-PTLD, immunosuppressants were carefully reduced in AD-PCNSL patients included in this meta-analysis in order to improve immunosurveillance [8, 16, 17]. In line with PCNSL in immunocompetent patients, most AD-PCNSL were treated with high-dose methotrexate or rituximab based chemotherapy. Both drugs were previously shown to yield promising response rates in PCNS PTLD [17]. However, their efficacy could not be assessed in AD-PCNSL in this meta-analysis as treatment protocols were highly heterogeneous and clinical or radiographic responses were only rarely reported.

In contrast to PCNSL in immunocompetent hosts, it appears that AD-PCNSL patients more frequently underwent radiotherapy. In immunocompetent PCNSL the addition of WBRT to chemotherapy did not prolong overall survival while causing profound neurotoxicity [24]. At most centers WBRT is therefore not included in routine treatment protocols for PCNSL. However, administration of high dose polychemotherapy alone was likely not feasible in a subset of AD-PCNSL due to reduced kidney function as a result of renal involvement by systemic AD. This may explain the frequent addition of WBRT to treatment protocols in AD-PCNSL. Similar to the observation by Thiel et al. the addition of WBRT in AD-PCNSL did not prolong OS in this meta-analysis.

Recent studies suggest that EBV-positive systemic NHL are particularly susceptible to treatment with immune checkpoint inhibitors (ICI) [25, 26]. In line with this notion, Nayyar et al. recently demonstrated that EBV-positive PCNSL were associated with high PD1 expression levels [27]. Hence ICI might provide a promising novel avenue for the treatment of a subset of EBV-positive PCNSL. However out of concern for AD exacerbation patients with pre-existing autoimmune conditions were excluded from most clinical trials investigating ICI. Retrospective studies of patients with AD treated with checkpoint inhibitors demonstrated such exacerbations may be manageable and reversible with corticosteroid treatment [28]. They concluded that ICI can be considered in patients with AD when vigilant clinical monitoring is feasible. However, only few patients with severe autoimmune conditions such as SLE were included in these retrospective series which limits the ability to draw general conlusions with respect to AD-PCNSL. Continued immunosuppressive treatment in AD-PCNCSL patients may also impair the efficacy of ICI [29]. Notwithstading treatment with ICI should be investigated further in AD-PCNSL and could present an additional treatment option for patients who do not respond to standard methotrexate based polychemotherapy.

Mostly based on data from HIV-positive PCNSL, immunosuppression was linked to worse overall survival rates in PCNSL [30]. Our meta-analysis suggests that long term remission and survival can be accomplished with methotrexate and rituximab based polychemotherapy in AD-PCNSL similar to immuncompetent patients. Calculated median OS of AD-PCNSL in this study was 31 months. This is in agreement with previously reported survival in other immunosuppressed PCNSL cohorts such as PCNS PTLD ranging from 17 to 49 months [8, 16, 17]. However, previously reported median OS for immuncompetent PCNSL patients was not markedly better and ranged from 30 to 50 months [31]. Survival data from this meta-analysis is limited by the short median follow-up and should therefore be interpreted with caution. Future prospective studies are warranted to investigate the effect of AD on OS in PCNSL cohorts.

In this meta-analysis we show that overall survival in AD-PCNSL was primarly affected by age at diagnosis. This is in line with previous data from immunocompetent and immunosuppressed PCNSL cohorts. We previously showed that age > 60 years was a poor prognostic factor in a cohort of immunodeficiency-associated PCNSL [8]. It also represents the best established prognostic factor for PCNSL in immunocompetent patients and constitutes one variable of the international prognostic scoring system for PCNSL [5, 13]. Unfortunately, several other variables from this scoring system (lactate dehydrogenase serum levels, performance status, CSF protein levels) were rarely reported in studies included in this meta-analysis and could hence not be investigated in AD-PCNSL. Previously, we found that clonal IgH-R predicted shorter OS in immunodeficiency-associated PCNSL [8]. Despite showing a trend towards shorter OS in

AD-PCNSL significance levels were likely not reached in the present study as IgHR status was only available for 10 tumors.

## Limitations of this study

This meta-analysis has several limitations inherent to the case studies and retrospective series included in it. Clinical, radiological and pathological data may have been incomplete due to the retrospective nature of chart review. Data presentation and inclusion in analyzed case series was heterogeneous (heterogeneity bias), and we therefore explicitly provided the number of patients that were investigated in each analysis in tables and figures. As no standard treatment has been established for AD-PCNSL thus far, treatment regimens varied in cases included in this meta-analysis. The latter as well as the short median follow-up after diagnosis of PCNSL limit the generalizability of outcome data from this study. AD with mild disease activity not requiring immunosuppression may be underrepresented in this study due to a publication bias. This could have affected outcome analysis in this study as severe disease activity and resulting organ dysfunction likely led to therapeutic limitations in several cases. Despite, to our knowledge, presenting one of the largest AD-PCNSL series to date, the overall rather small size and heterogeneity of our series reduce its statistical power. Further studies in prospective cohorts are warranted to better characterize AD-PCNSL.

## Conclusions

AD often associated with severe disease activity and requiring high intensity immunosuppressive treatment such as MS, SLE or MG appear over-represented in PCNSL. The interval of immunosuppression preceding AD-PCNSL diagnosis was longer than in other settings of immunosuppression (e.g. solid organ transplantation). Otherwise clinical, pathological and radiological characteristics resemble other immunodeficiency-related PCNSL probably reflecting a shared EBV driven pathogenesis. Although no standard treatment has been established, most AD-PCNSL patients received methotrexate or rituximab-based chemotherapy. Our study suggests that long term remission and survival can be accomplished with such aggressive regimens. OS in AD-PCNSL was not markedly worse than previously reported for immuncompetent PCNSL cohorts. Age > 60 years may serve as prognostic factor for AD-PCNSL. Additional studies with a longer follow-up are warranted to better characterize outcome and prognostic factors.

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**Author contributions** LDK and JMB designed the study, analyzed and interpreted data, and drafted the manuscript. LDK conducted the review of literature. LDK, PK, JD and JMB critically revised, read and approved the final manuscript.

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**Data availability** Data will be shared by request from investigators.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** This study was approved by the institutional review board (IRB).

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