Diagnostic Biomarkers in Cerebrospinal Fluid in Primary Central Nervous System Lymphoma: A Protocol for Systematic Review and Meta-analysis

Lili Zhou1,2, Hai Yi1*, Dan Chen1, Qian Zhang1, Fangyi Fan1, Ling Qiu1, Nan Zhang1, Yi Su1

1Department of Hematology, General Hospital of Western Theater Command, People's Liberation Army, Chengdu, Sichuan, China
2The Second Stationed Outpatient Department, General Hospital of Western Theater Command, People's Liberation Army, Chengdu, Sichuan, China

*Corresponding Author

DOI: https://doi.org/doi/03.2022-33862439/A3

Abstract

**Background:** Primary central nervous system lymphoma (PCNSL) is a highly aggressive non-Hodgkin’s lymphoma with an unfavorable prognosis. Currently, the diagnosis of PCNSL relies on brain excisional biopsy, which is an invasive procedure that carries the risk of complications such as intracranial hemorrhage and functional impairment. Finding effective biomarkers will help us to diagnose PCNSL faster and safer.

**Methods:** A systematic review and meta-analysis will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) 2015 guidelines. We will search databases including PubMed, Cochrane Library, Medline, Web of Science, EMBASE, and CNKI. Studies that demonstrated the diagnostic value of certain biomarkers in cerebrospinal fluid (CSF) in PCNSL will be included. The standardized mean difference (SMD) and their 95% confidence intervals (CI) will be calculated for quantitative values. The outcomes are the mean difference in biomarker levels in CSF between PCNSL patients and controls.

**Discussion:** In this systematic review and meta-analysis, we will analyze biomarkers in cerebrospinal fluid for the diagnosis of PCNSL. This research can help us to identify biomarkers with diagnostic value for PCNSL, making the diagnosis of PCNSL easier, faster, and safer.

**Systematic review and meta-analyses registration:** PROSPERO CRD42020218143.

**Keywords:** Diagnostic biomarkers, cerebrospinal fluid, primary central nervous system lymphoma, systematic review, meta-analysis

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: info@plascipub.com

Address for correspondence: Prof. Hai Yi, Department of Hematology, General Hospital of Western Theater Command, People’s Liberation Army, No. 270 Rongdu Avenue, Jinniu District, Chengdu 610083, Sichuan, China. E-mail: yihaimail@163.com

Submitted: 02 Nov 2021, Accepted: 08 Jan 2022, Published: 29 Mar 2022

How to cite this article: Zhou, L., Yi, H., Chen, D., Zhang, Q., Fan, F., Qiu, L., Zhang, N., & Su, Y. (2022). Diagnostic Biomarkers in Cerebrospinal Fluid in Primary Central Nervous System Lymphoma: A Protocol for Systematic Review and Meta-analysis. Cancer Translational Medicine, 8(1), 16–24.
BACKGROUND

Primary central nervous system lymphoma (PCNSL) is a rare subtype of non-Hodgkin's lymphoma that tends to occur in older people with a median age of 65 years. The common primary sites are the brain, leptomeninges, spinal cord, and eyes, without infiltration of other parts. PCNSL can occur in immunocompromised individuals, such as HIV-infected hosts and post organ transplant recipients. In recent years, an increasing number of cases in immunocompetent hosts have been reported. PCNSL is particularly the activated B cell-like (ABC) subtype, characterized by constitutive activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, which is frequently accompanied by myeloid differentiation factor 88 (MYD88) and CD79B mutations. PCNSL is a highly aggressive malignant lymphoma with an unfavorable prognosis. It responds poorly to conventional chemotherapy, and the overall 5-year survival rate is only approximately 33%. Combination chemotherapy with high-dose methotrexate, whole-brain radiotherapy, and autologous hematopoietic stem cell transplantation can benefit PCNSL patients. In recent years, novel targeted therapeutics have emerged as potential treatments for PCNSL.

AIM AND OBJECTIVES

The aim of this systematic review and meta-analysis is to evaluate the diagnostic performance of frequently reported biomarkers in CSF in PCNSL patients, with an objective to identify promising biomarkers that will help us to diagnose PCNSL faster and safer.

METHODS

This “systematic review and meta-analysis” was registered on the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42020218143) on the 29th of November 2020. This systematic review and meta-analysis will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) 2015 guidelines [Additional file 1].

Eligibility criteria

Type of studies

This review will include all types of studies with human subjects that evaluate the diagnostic value of biomarkers in CSF in PCNSL. Case reports, letters, animal studies, and laboratory studies will be excluded.

Type of participants

Patients with PCNSL diagnosis according to histopathology will be included, regardless of sex, age, race, ethnicity, involvement site, host immune status, and severity of PCNSL. Patients with secondary central nervous system lymphoma will be excluded.

Type of index test

The results of the index tests that use CSF-based tumor cells, tumor DNA, and proteins in the detection of PCNSL will be considered for analysis.

Types of intervention

Several cytokines and gene mutations in CSF are reported to be associated with the diagnosis of PCNSL. The concentration or properties of the following biomarkers in the CSF of PCNSL patients and controls will be evaluated in this study.

The clinical manifestations of PCNSL patients are nausea, headache, vomiting, limb weakness, etc. Imaging examinations such as computed tomography (CT) and magnetic resonance imaging (MRI) can find intracranial space-occupying lesions. Several studies have reported that PCNSL has certain changes in imaging features, such as lesions that are mostly located in the supratentorial area, MRI hypointense on T1-weighted images, isohypointense on T2-weighted images, homogeneous enhancement and restricted diffusion, little associated vasogenic edema, and no central necrosis, which can be distinguished from other tumor types such as glioma. However, brain biopsy is still the gold standard for diagnosis. Nevertheless, brain biopsy is an invasive procedure that carries the risk of complications such as intracranial hemorrhage and functional impairment. The procedure may also be challenging because of the difficulty in reaching deep tumor sites. Exploring a high-efficiency and less invasive diagnostic strategy is an urgent need for the diagnosis of PCNSL.

Recently, several studies have shown that certain diagnostic biomarkers could be detected in cerebrospinal fluid (CSF) and peripheral blood in PCNSL patients, providing ideas for the diagnosis of PCNSL without brain excisional biopsy. These biomarkers include tumor cells, tumor DNAs, and proteins. CSF biomarkers have better sensitivity and auxiliary diagnostic value for PCNSL than blood biomarkers. Because lumbar puncture is routine and less traumatic in patients with intracranial lesions, CSF biomarkers are potentially the most suitable biomarkers for PCNSL diagnosis.
Biomarkers: MiR-21, miR-19, miR-30c, miR-92a, transmembrane activator, and calcium modulator and cyclophilin ligand interactor (TACI), B cell maturation antigen (BCMA), soluble IL-2 receptor (sIL-2R), interleukin-6 (IL-6), interleukin-10 (IL-10), β2-microglobulin (β2-MG), the C-X-C motif chemokine ligand 13 (CXCL13), T cell immunoglobulin and mucin domain 1 (Tim-1), neopterin (Npt), a proliferation inducing ligand (APRIL), B cell activating factor (BAFF), CD79B, myeloid differentiation factor 88 (MYD88), circulating U2 small nuclear RNA fragments (RNU2-1f), soluble CD27, osteopontin (OPN), antithrombin III (AT III).

Types of outcome measures
Diagnostic value of the biomarkers in CSF in the diagnosis of PCNSL will be measured by calculating the mean difference in biomarker levels between PCNSL patients and controls.

Data sources and search strategy
A literature search will be performed in multiple electronic databases, including PubMed, Cochrane Library, Medline, Web of Science, EMBASE, and CNKI, from their inception to October 30, 2020. There are no language restrictions. The search strategy of Medline is shown in Additional file 2. Other databases will be used by a similar strategy.

Data collection and analysis

Study selection
Two reviewers (FF and LQ) will evaluate the titles and abstracts by searching information sources independently. The full text of potential articles will be assessed by both reviewers if the eligibility of an article cannot be decided by only screening the title and abstract. Any disagreements regarding the eligibility of studies will be adjudicated by a discussion with a third reviewer (YS).

Data extraction
Two reviewers (HY and FF) will extract the data from each included study independently by using a standardized form. The items extracted from the studies will be the first author, study title, publication year, regions, study design, sample size and controls, detection methods, biomarkers and levels, diagnostic value, value type, sensitivity, and specificity. If there will be any missing data, then we will contact the authors for additional information. Any disagreements will be resolved through discussion, and the standardized forms will be checked by NZ.

Risk of bias in individual studies
The quality of the included studies and risk of bias will be assessed independently by two reviewers (HY and FF) using Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria. The quality assessment evaluates the risk of bias and concerns regarding the applicability of all included studies. The results of the quality assessment and studies with a high, low, or unclear risk of bias will be displayed in a table.

Data synthesis

Statistical analysis
The mean and standard deviation of biomarker levels from individual studies will be collected to calculate the standardized mean difference (SMD) and their 95% confidence interval (CI). Heterogeneity will be evaluated by Cochran’s Q test and inconsistency index value (I²). If there is no heterogeneity (I²<40%, p>0.05), we will use a fixed-effects model for the meta-analysis; otherwise, the random-effects model will be chosen. All statistical analyses will be conducted using STATA version 15.0.

Subgroup analysis
To further understand the heterogeneity, we will perform subgroup analyses as follows:
1. The type of biomarkers (tumor cells, tumor DNA, and proteins).
2. Detection methods (Droplet Digital PCR, Next Generation Sequencing, ELISA).

Sensitivity analysis
To determine the stability of the study, we will perform a sensitivity analysis. Studies with a high risk of bias on overall effects will be excluded.

Assessment of reporting bias
Funnel plots, as well as associated regression tests, will be used to test publication bias.

Confidence in cumulative evidence
The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) will be used to assess the strength of evidence.

DISCUSSION
We will evaluate the role of all the reported biomarkers in CSF in patients with PCNSL in this systematic review and meta-analysis. Additionally, we intend to clarify the optimal concentrations of certain biomarkers for diagnosis. By subgroup analyses, we will compare the different types of biomarkers and the different detection methods for the diagnosis of PCNSL. We hope the findings of this study will help us recognize the significance of liquid biopsy of CSF in
PCNSL patients, making the diagnosis of PCNSL easier, faster, and safer and improving the quality of life.

**LIST OF ABBREVIATIONS**

PCNSL: Primary central nervous system lymphoma  
CSF: Cerebrospinal fluid  
ABC: Activated B cell-like  
NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells  
BTK: Bruton tyrosine kinase  
CT: computed tomography  
MRI: Magnetic resonance imaging  
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols  
QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies  
DNA: Deoxyribonucleic acid  
PCR: Polymerase chain reaction  
ELISA: Enzyme-linked immunosorbent assay

**ETHICS APPROVAL AND CONSENT TO PARTICIPATE**

This study is a systematic review and meta-analysis, and the results are based on previously published evidence, and hence is exempted from the need for approval from the ethics committee.

**FINANCIAL SUPPORT AND SPONSORSHIP**

This work is supported by the Science and Technology Project of Sichuan to Hai Yi (No. 2018JY0583), Scientific Research Project of Sichuan Health Commission to Hai Yi (No. 18PJ358), and Youth Innovation Project of Sichuan Medical Research to Hai Yi (No. Q17004). The sponsors are not involved in design, data collection, data analysis and interpretation, or writing the manuscript.

**CONFLICTS OF INTEREST**

The authors declare that they have no conflicts of interest.

**REFERENCES**

1. Citterio G, Reni M, Gatta G, Ferreri AJM. Primary central nervous system lymphoma. *Crit Rev Oncol Hematol* 2017;113:97-110.
2. Gupta NK, Nolan A, Omuro A, Reid EG, Wang CC, Mannis G, Jglal M, Chavez JC, Rubinstein PG, Griffin A, Abrams DI, Hwang J, Kaplan LD, Luce JA, Volberding P, Treseler PA, Rubenstein JL. Long-term survival in AIDS-related primary central nervous system lymphoma. *Neuro Oncol* 2017;19(1):99-108.
3. Grommes C, DeAngelis LM. Primary CNS Lymphoma. *J Clin Oncol* 2017;35(21):2410-8.
4. Ho KG, Grommes C. Molecular profiling of primary central nervous system lymphomas - predictive and prognostic value? *Curr Opin Neurol* 2019;32(6):886-94.
5. Han CH, Batchelor TT. Diagnosis and management of primary central nervous system lymphoma. *Cancer* 2017;123(22):4314-24.
6. Kasenda B, Schorb E, Fritsch K, Finke J, Illerhaus G. Prognosis after high-dose chemotherapy followed by autologous stem-cell transplantation as first-line treatment in primary CNS lymphoma-a long-term follow-up study. *Ann Oncol* 2012;23(10):2670-5.
7. Martinez-Calle N, Poynton E, Alchawaf A, Kassam S, Horan M, Rafferty M, Kelsey P, Scott G, Culligan DJ, Buckley H, Lim YJ, Ng L, McCulloch R, Rowntree C, Wright J, McKay P, Eyre TA, Smith J, Osborne W, Yallop D, Linton K, Fox CP, Cwynarski K. Outcomes of older patients with primary central nervous system lymphoma treated in routine clinical practice in the UK: methotrexate dose intensity correlates with response and survival. *Br J Haematol* 2020;190(3):394-404.
8. Holdhoff M, Ambady P, Abdelaziz A, Sarai G, Bonekamp D, Blakeley J, Grossman SA, Ye XB. High-dose methotrexate with or without rituximab in newly diagnosed primary CNS lymphoma. *Neurology* 2014;83(3):235-9.
9. Houillier C, Taillandier L, Dureau S, Lamy T, Laadhari M, Chinot O, Moluço-Chabrot C, Soubeiran P, Gressin R, Choquet S, Damaj G, Thyss A, Abraham J, Delwail V, Gyan E, Sanhes L, Cornillon J, Garidi R, Delmer A, Tanguy ML, Al Jijakli A, Morel P, Bourquard P, Moles MP, Chauchet A, Gastinne T, Constans JM, Langer A, Martin A, Moisson P, Lacomblez L, Martin-Duverneuil N, Delgadillo D, Turbiez I, Feuvret L, Cassoux N, Toutou V, Ricard D, Hoang-Xuan K, Soussain C. Radiotherapy or Autologous Stem-Cell Transplantation for Primary CNS Lymphoma in Patients 60 Years of Age and Younger: Results of the Intergroup ANOCEF-GOELAMS Randomized Phase II PRECIS Study. *J Clin Oncol* 2019;37(10):823-33.
10. Illerhaus G, Schorb E, Kasenda B. Novel agents for primary central nervous system lymphoma: evidence and perspectives. *Blood* 2018;132(7):681-8.
11. Grommes C, Younes A. Ibrutinib in PCNSL: The Curious Cases of Clinical Responses and Aspergillosis. Cancer Cell 2017;31(6):731-3.

12. Ghesquieres H, Chevrier M, Laadhari M, Chinot O, Choquet S, Molouco-Chabrot C, Beauchesne P, Gressin R, Morschhauser F, Schmitt A, Gyan E, Hoang-Xuan K, Nicolas-Virelizier E, Cassoux N, Toutou V, Garff-Tavernier ML, Savignoni A, Turbiez I, Soumelis V, Houillier C, Soussain C. Lenalidomide in combination with intravenous rituximab (REVRI) in relapsed/refractory primary CNS lymphoma or primary intraocular lymphoma: a multicenter prospective 'proof of concept' phase II study of the French Oculo-Cerebral lymphoma (LOC) Network and the Lymphoma Study Association (LYSA). Ann Oncol 2019;30(4):621-8.

13. Cheng G, Zhang J. Imaging features (CT, MRI, MRS, and PET/CT) of primary central nervous system lymphoma in immunocompetent patients. Neurul Sci 2019;40(3):535-42.

14. van der Meulen M, Dirven L, Habets EJJ, van den Bent MJ, Taphoorn MJB, Bromberg JEC. Cognitive functioning and health-related quality of life in patients with newly diagnosed primary CNS lymphoma: a systematic review. Lancet Oncol 2018;19(8):e407-e418.

15. Khatab S, Spliet W, Woerdeman PA. Frameless image-guided stereotactic brain biopsies: emphasis on diagnostic yield. Acta Neurochir 2014;156(8):1441-50.

16. Kerbauy MN, Moraes FY, Lok BH, Ma J, Kerbauy LN, Spratt DE, Santos FP, Perini GF, Berlin A, Chung C, Hamerschlak N, Yahalom J. Challenges and opportunities in primary CNS lymphoma: A systematic review. Radiother Oncol 2017;122(3):352-61.

17. Yu X, Li Z, Shen J, Chan MT, Wu WK. Role of microRNAs in primary central nervous system lymphomas. Cell Prolif 2016;49(2):147-53.

18. Hiemcke-Jiwa LS, Minnema MC, Radersma-van Loon JH, Jiwa NM, de Boer M, Leguit RJ, Weger RA, Huibers MM. The use of droplet digital PCR in liquid biopsies: A highly sensitive technique for MYD88 p.(L265P) detection in cerebrospinal fluid. Hematol Oncol 2018;36(2):429-35.

19. Zheng XH, Li P, Dong QQ, Duan YH, Yang SB, Cai ZH, Chen F, Li WB. MicroRNAs as diagnostic biomarkers in primary central nervous system lymphoma: a systematic review and meta-analysis. Front Oncol 2021;11:743542.

20. Bobillo S, Crespo M, Escudero L, Mayor R, Raheja P, Carpio C, Rubio-Perez C, Tazon-Vega B, Palacio C, Carabia J, Jimenez I, Nieto JC, Montoro J, Martinez-Ricarte F, Castellvi J, Simo M, Puigdefabregas L, Abrisqueta P, Bosch F, Seoane J. Cell free circulating tumor DNA in cerebrospinal fluid detects and monitors central nervous system involvement of B-cell lymphomas. Haematologica. 2021;106(2):513-21.

21. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;350:g7647.

22. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155(8):529-36.

23. Kumarasamy C, Devi A, Jayaraj R. Prognostic value of microRNAs in head and neck cancers: a systematic review and meta-analysis protocol. Syst Rev 2018;7(1):150.

DISCLAIMER
All claims made in this article are exclusively those of the writers, and do not necessarily reflect the views of their connected organizations, the publisher, editors, or reviewers. The publication does not guarantee or promote any product that may be evaluated in this article or any claim made by its producer.
### Additional file 1. PRISMA-P 2015 Checklist.

| Section and topic | # | Checklist item | Information reported | Page number(s) |
|-------------------|---|----------------|----------------------|---------------|
| **ADMINISTRATIVE INFORMATION** | | | Yes | No | |
| Identification | 1a | Identify the report as a protocol of a systematic review | √ | Page 1 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | | |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | √ | Page 1 |
| Authors: | | | Yes | No | |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | √ | Page 1 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | √ | Page 4 |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | | Page 4 |
| Support: | | | Yes | No | |
| Sources | 5a | Indicate sources of financial or other support for the review | √ | Page 4 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | √ | Page 4 |
| Role of sponsor/funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | √ | Page 4 |
| **INTRODUCTION** | | | Yes | No | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | √ | Page 2 |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | √ | Page 2 |
| **METHODS** | | | Yes | No | |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | √ | Page 2 |
**Information sources** | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | √ | Page 3 |
---|---|---|---|---|
**Search strategy** | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | √ | Page 3 and Additional File 2 |

**Study records:**

| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | √ | Page 3 |
| Selection process | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | √ | Page 3 |
| Data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | √ | Page 3 |

**Data items** | 12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | √ | Page 3 |

**Outcomes and prioritization** | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | √ | Page 3 |

**Risk of bias in individual studies** | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | √ | Page 3 |

**Data synthesis** | 15a | Describe criteria under which study data will be quantitatively synthesised | √ | Page 3 |
| 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I², Kendall’s τ) | √ | Page 3 |
| 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | √ | Page 3 |
| 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | √ | Page 3 |

**Meta-bias(es)** | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | √ | Page 3 |

**Confidence in cumulative evidence** | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | √ | Page 3 |

*Page number according to pdf version of the manuscript*

*From: Shamseer L, Moher D, Clarke M, Gherzi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;350:g7647.*
Additional file 2. Search strategy applied in MEDLINE database

**MiR-21, miR-19, miR-30c, miR-92a**

Primary central nervous system lymphoma OR PCNSL AND ("biological"[All Fields] AND "markers"[All Fields]) OR "biomarker"[All Fields]) OR CSF[All Fields] OR cerebrospinal[All Fields]) AND (MiR-21 OR miR-19 OR miR-30c OR miR-92a)

**TACI**

Primary central nervous system lymphoma OR PCNSL AND ("biological"[All Fields] AND "markers"[All Fields]) OR "biomarker"[All Fields]) OR CSF[All Fields] OR cerebrospinal[All Fields]) AND ("transmembrane activator and calcium modulator and cyclophilin ligand interactor" OR TACI)

**BCMA**

Primary central nervous system lymphoma OR PCNSL AND ("biological"[All Fields] AND "markers"[All Fields]) OR "biomarker"[All Fields]) OR CSF[All Fields] OR cerebrospinal[All Fields]) AND ("B cell maturation antigen" OR BCMA)

**sIL-2R**

Primary central nervous system lymphoma OR PCNSL AND ("biological"[All Fields] AND "markers"[All Fields]) OR "biomarker"[All Fields]) OR CSF[All Fields] OR cerebrospinal[All Fields]) AND ("soluble IL-2 receptor" OR sIL-2R)

**IL-6, IL-10**

Primary central nervous system lymphoma OR PCNSL AND ("biological"[All Fields] AND "markers"[All Fields]) OR "biomarker"[All Fields]) OR CSF[All Fields] OR cerebrospinal[All Fields]) AND ("interleukin-6" OR IL-6 OR "interleukin-10" OR IL-10)

**β2-MG**

Primary central nervous system lymphoma OR PCNSL AND ("biological"[All Fields] AND "markers"[All Fields]) OR "biomarker"[All Fields]) OR CSF[All Fields] OR cerebrospinal[All Fields]) AND ("β2-microglobulin" OR β2-MG)

**CXCL13**

Primary central nervous system lymphoma OR PCNSL AND ("biological"[All Fields] AND "markers"[All Fields]) OR "biomarker"[All Fields]) OR CSF[All Fields] OR cerebrospinal[All Fields]) AND ("the C-X-C motif chemokine ligand 13" OR CXCL13)

**Tim-1**

Primary central nervous system lymphoma OR PCNSL AND ("biological"[All Fields] AND "markers"[All Fields]) OR "biomarker"[All Fields]) OR CSF[All Fields] OR cerebrospinal[All Fields]) AND ("T cell immunoglobulin and mucin domain 1" OR Tim-1)
Npt

Primary central nervous system lymphoma OR PCNSL AND (("biological"[All Fields] AND "markers"[All Fields]) OR "biomarker"[All Fields]) OR CSF[All Fields] OR cerebrospinal[All Fields]) AND ("neopterin" OR Npt)

APRIL

Primary central nervous system lymphoma OR PCNSL AND (("biological"[All Fields] AND "markers"[All Fields]) OR "biomarker"[All Fields]) OR CSF[All Fields] OR cerebrospinal[All Fields]) AND ("a proliferation inducing ligand" OR APRIL)

BAFF

Primary central nervous system lymphoma OR PCNSL AND (("biological"[All Fields] AND "markers"[All Fields]) OR "biomarker"[All Fields]) OR CSF[All Fields] OR cerebrospinal[All Fields]) AND ("B cell activating factor" OR BAFF)

CD79B

Primary central nervous system lymphoma OR PCNSL AND (("biological"[All Fields] AND "markers"[All Fields]) OR "biomarker"[All Fields]) OR CSF[All Fields] OR cerebrospinal[All Fields]) AND ("cluster of differentiation 79B" OR CD79B)

MYD88

Primary central nervous system lymphoma OR PCNSL AND (("biological"[All Fields] AND "markers"[All Fields]) OR "biomarker"[All Fields]) OR CSF[All Fields] OR cerebrospinal[All Fields]) AND ("myeloid differentiation factor 88" OR MYD88)

RNU2-1f

Primary central nervous system lymphoma OR PCNSL AND (("biological"[All Fields] AND "markers"[All Fields]) OR "biomarker"[All Fields]) OR CSF[All Fields] OR cerebrospinal[All Fields]) AND ("circulating U2 small nuclear RNA fragments" OR RNU2-1f)

Soluble CD27

Primary central nervous system lymphoma OR PCNSL AND (("biological"[All Fields] AND "markers"[All Fields]) OR "biomarker"[All Fields]) OR CSF[All Fields] OR cerebrospinal[All Fields]) AND ("soluble cluster of differentiation 27" OR "soluble CD27")

OPN

Primary central nervous system lymphoma OR PCNSL AND (("biological"[All Fields] AND "markers"[All Fields]) OR "biomarker"[All Fields]) OR CSF[All Fields] OR cerebrospinal[All Fields]) AND ("osteopontin" OR OPN)

AT III

Primary central nervous system lymphoma OR PCNSL AND (("biological"[All Fields] AND "markers"[All Fields]) OR "biomarker"[All Fields]) OR CSF[All Fields] OR cerebrospinal[All Fields]) AND ("Antithrombin III" OR AT III)