Soluble TIM-3 and galectin-9 serve as additional diagnostic biomarkers in primary central nervous system lymphoma

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ORIGINAL COMMUNICATION

Soluble TIM-3 and galectin-9 serve as additional diagnostic biomarkers in primary central nervous system lymphoma

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Abstract

Background Primary central nervous system lymphoma (PCNSL) is a rare and aggressive B-cell lymphoma in which early diagnosis remains challenging. Although cerebrospinal fluid (CSF) B-cell-associated factors including soluble interleukin-2 receptor subunit alpha (IL-2RA) are known diagnostic markers, they often reflect neuroinflammation and are insufficient on their own to reliably differentiate PCNSL from neuroimmunological diseases. On the other hand, CSF immune checkpoint molecules reflect neuro-immune regulation and remain incompletely evaluated as biomarkers for PCNSL. We aimed to determine whether CSF immune checkpoint molecules can serve as additional diagnostic and prognostic biomarkers for PCNSL alongside B-cell-associated factors.

Methods In this retrospective cohort study, CSF samples from 33 patients with PCNSL and 85 patients with control diseases, including neuroimmunological diseases and other brain tumors, were analyzed using a bead-based multiplex immune-assay. Correlations between markers were evaluated using Spearman's rank correlation and hierarchical clustering. Diagnostic performance was assessed using logistic regression modeling. Progression-free survival (PFS) was analyzed using the Kaplan–Meier method.

Results CSF levels of B-cell-associated factors (interleukin-10, C–X–C motif chemokine ligand 13, and IL-2RA) and immune checkpoint molecules (Fas ligand, T-cell immunoglobulin and mucin domain 3 (TIM-3), and galectin-9) were significantly elevated in PCNSL compared with control diseases. Correlation and cluster analysis identified two distinct marker clusters: B-cell-associated factors and immune checkpoint molecules. Two-marker diagnostic models combining IL-10 and immune checkpoint molecules demonstrated superior diagnostic performance. Higher levels of B-cell-associated factors showed a non-significant trend towards shorter PFS.

Conclusions CSF TIM-3 and galectin-9 represented additional diagnostic biomarkers for PCNSL alongside B-cell-associated factors.

Keywords LYMPHOMA · CSF · Biomarkers · Neuromyelitis optica · Myelin oligodendrocyte glycoprotein antibody-associated disease

Introduction

Primary central nervous system lymphoma (PCNSL) is a rare subtype of B-cell non-Hodgkin lymphoma confined to the central nervous system (CNS), involving the brain, leptomeninges, eyes, or spinal cord without systemic involvement. Although PCNSL is generally responsive to high-dose methotrexate-based chemotherapy and radiotherapy, recurrence is common and overall prognosis remains poor [1]. Early and accurate diagnosis is, therefore, crucial. While brain biopsy remains the diagnostic gold standard, it is

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invasive and associated with serious complications, such as intracranial hemorrhage and permanent neurological deficits [2]. Consequently, reliable and minimally invasive diagnostic examinations for PCNSL are required.

Several cerebrospinal fluid (CSF) proteins, such as interleukin-10 (IL-10), C–X–C motif chemokine ligand 13 (CXCL13), and interleukin-2 receptor subunit alpha (IL-2RA), have been proposed as the diagnostic and prognostic biomarkers for PCNSL [3–5]. These cytokines, chemokines, and their receptors are produced not only by malignant B cells [3, 6] but also by activated non-neoplastic B cells in inflammatory conditions [7–10]. Accordingly, these B-cell-associated factors, including CSF IL-10, CXCL13, and IL-2RA, reflect neuroinflammation and are also frequently elevated in acute neuroimmunological diseases such as neuromyelitis optica spectrum disorders (NMOSD) [11–13], complicating differential diagnosis. Moreover, PCNSL can present with steroid-responsive symptoms and various radiological findings that mimic neuroimmunological diseases [14]. At present, the available evidence on diagnostic biomarkers for PCNSL is insufficient and application of these markers in clinical practice is limited [15, 16].

Previous studies have investigated immune checkpoint molecules in PCNSL. In particular, programmed cell death protein 1 (PD-1) and its ligand PD-L1 have been examined in several studies [17, 18]. Another study evaluated related immune biomarkers including PD-1 and Fas ligand (FasL) in CSF of patients with PCNSL [19], but their diagnostic utility for PCNSL has not been well evaluated. CSF immune checkpoint molecules reflect neuro-immune regulation and may play a pivotal role in helping clinicians distinguish PCNSL from inflammatory diseases, when B-cell-associated factors alone are insufficient. In addition, prognostic biomarkers of PCNSL remain poorly defined and need to be evaluated.

This study aimed to determine whether CSF immune checkpoint molecules can serve as additional diagnostic biomarkers for PCNSL compared with neuroimmunological diseases when assessed alongside B-cell-associated factors. We also evaluated the prognostic relevance of these proteins in patients with PCNSL.

Methods

Study population

This is a retrospective cohort study that included patients treated at Kobe University between January 2015 and March 2025. Eligible patients were ≥ 18 years old and had CSF samples available for analysis. Thirty-three patients with PCNSL, 34 with NMOSD, 10 with myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), and 7 with tumefactive demyelinating lesion (TDL), 6 with neurosarcoidosis, 2 with primary CNS vasculitis (PCNSV), 4 with neuro-Behçet's disease, 6 with glioblastoma, 5 with metastatic brain tumor, and 11 with idiopathic normal pressure hydrocephalus (iNPH) were included. PCNSL was diagnosed based on brain biopsy. NMOSD and MOGAD were diagnosed in accordance with established diagnostic criteria [20, 21], while TDL was diagnosed based on the clinical course and imaging findings. Neurosarcoidosis (5 probable and 1 possible), PCNSV (1 definite and 1 probable), and neuro-Behçet's disease (3 definite and 1 probable) were diagnosed according to the established diagnostic criteria [22–24]. Glioblastoma was diagnosed based on brain biopsy and metastatic brain tumor was diagnosed based on the clinical course and imaging findings. iNPH was diagnosed as possible iNPH according to established guidelines [25]. CSF samples from patients with NMOSD, MOGAD, TDL, neurosarcoidosis, PCNSV, and neuro-Behçet's disease were obtained within 3 months of the clinical attack. CSF samples were acquired by lumbar puncture after informed consent was obtained.

CSF analysis

CSF samples were centrifuged immediately and stored at − 80 °C. After thawing, samples were analyzed using a custom bead-based multiplex immune-assay kit (LEGENDplex™; BioLegend) [26]. We simultaneously measured levels of IL-10, CXCL13, IL-2RA, FasL, programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1), cytotoxic T-lymphocyte antigen 4 (CTLA-4), T-cell immunoglobulin and mucin domain 3 (TIM-3), galectin-9, lymphocyte activation gene 3 (LAG-3), transforming growth factor b (TGF-b), B7.2, and 4-1BB.

Statistical analysis

We used Holm-adjusted pairwise Fisher's exact test to compare the proportions of categorical variables (such as sex), and Kruskal–Wallis test followed by Holm-adjusted Dunn's test to compare the medians of continuous variables (such as age and levels of evaluated proteins) between diseases. Receiver-operating characteristic (ROC) curves were created, and the area under the curve (AUC) values were calculated to evaluate the diagnostic accuracy of evaluated proteins. Spearman's rank correlation was used to measure the degree of correlation between proteins, and hierarchical clustering was performed based on 1 − Spearman's correlation coefficient using the complete linkage method. Logistic regression analysis was used to generate two-marker diagnostic models. Cut-off of the diagnostic markers were determined using the Youden index derived from ROC analysis. Progression-free survival (PFS) was determined as the interval from diagnosis to disease progression, recurrence,

or last follow-up evaluation and was estimated using the Kaplan–Meier method with comparisons by the log-rank test. Data are presented as medians [interquartile range (IQR)] or box plots as appropriate. The threshold for significance was $p < 0.05$. All statistical analyses were conducted using R version 4.4.1 with RStudio version 2022.07.2.

Results

Clinical and CSF features of patients

Demographic, clinical, and CSF characteristics were compared among PCNSL, neuroimmunological diseases (NMOSD, MOGAD, TDL, neurosarcoidosis, PCNSV, and neuro-Behçet's disease), other brain tumors (glioblastoma and metastatic brain tumor), and iNPH groups and summarized in Table 1. Age differed significantly among the groups; post hoc analyses showed that patients with PCNSL were significantly older than those with neuroimmunological diseases (Supplemental Table 1). Overall differences in prior steroid exposure were observed; post hoc analyses showed that patients with PCNSL received less steroid treatment compared to patients with neuroimmunological diseases. CSF leukocyte counts and protein concentrations also differed significantly; post hoc tests showed that PCNSL had higher CSF leukocyte counts than other brain tumors and iNPH, and that PCNSL had higher CSF protein levels than all other groups.

CSF TIM-3 and galectin-9 were identified as diagnostic markers for PCNSL

CSF levels of IL-10, CXCL13, IL-2RA, FasL, TIM-3, and galectin-9 were significantly higher in PCNSL compared with neuroimmunological diseases (Fig. 1A–F, Supplemental Fig. 1). Although CSF levels of IL-10, CXCL13, IL-2RA, FasL, and galectin-9 were significantly higher in PCNSL compared with other brain tumors, TIM-3 levels did not significantly differ between PCNSL and other brain tumors. Other markers were also analyzed in CSF samples. However, these markers showed limited discriminatory ability between PCNSL and the other diseases groups (Supplemental Fig. 2). ROC analysis demonstrated high diagnostic accuracy for CSF IL-10, CXCL13, IL-2RA, and FasL (Fig. 1G–I). CSF TIM-3 and galectin-9 showed moderate diagnostic accuracy.

Diagnostic markers for PCNSL were divided into B-cell-associated factors and immune checkpoint molecules

Next, we studied the correlations between the CSF marker levels in PCNSL patients. To this extent, we classified these six markers into two groups: B-cell-associated factors (IL-10, CXCL13, and IL-2RA) and immune checkpoint molecules (FasL, TIM-3, and galectin-9), and examined the characteristics of these two groups.

Correlation analysis revealed B-cell-associated factors showed strong positive correlations with each other, whereas immune checkpoint molecules also demonstrated significant intercorrelations (Fig. 2A–P). In contrast, correlations between these two groups were relatively weak. Hierarchical clustering identified two distinct marker clusters: B-cell-associated factors and immune checkpoint molecules (Fig. 2Q).

Combining two marker clusters demonstrated superior diagnostic performance for PCNSL than using single markers

We then applied the logistic regression models to the diagnostic markers data to generate two-marker diagnostic models (Table 2). Univariate analysis showed that IL-10 had the lowest Akaike and Bayesian information criteria. Two-marker models of IL-10 plus immune checkpoint molecules (FasL, TIM3, or galectin-9) had high diagnostic performance (AUC = 0.990–0.991). In addition, among IL-10-negative PCNSL patients, TIM-3 and galectin-9 were elevated in 2 of 2 patients (Supplemental Table 2).

Table 1 Demographic and clinical characteristics

Baseline characteristics	PCNSL ($n=33$)	Neuroimmunological diseases ($n=63$)	Other brain tumors ($n=11$)	iNPH ($n=11$)
Age; years, median (IQR)	73 (68–77)	54 (41–68)	66 (55–71)	74 (73–78)
Female; no. (%)	16 (48)	40 (63)	2 (18)	5 (45)
Prior steroid exposure; no. (%)	1 (3.0)	16 (25)	2 (18)	0 (0)
CSF leukocyte; (/uL) median (IQR)	4 (2–7)	4 (1–12)	0 (0–1)	0 (0–1)
CSF protein; (mg/dL) median (IQR)	79 (48–156)	45 (36–53)	38 (35–73)	38 (33–47)

CSF, cerebrospinal fluid; iNPH, idiopathic normal pressure hydrocephalus; IQR, interquartile range; PCNSL, primary central nervous system lymphoma.

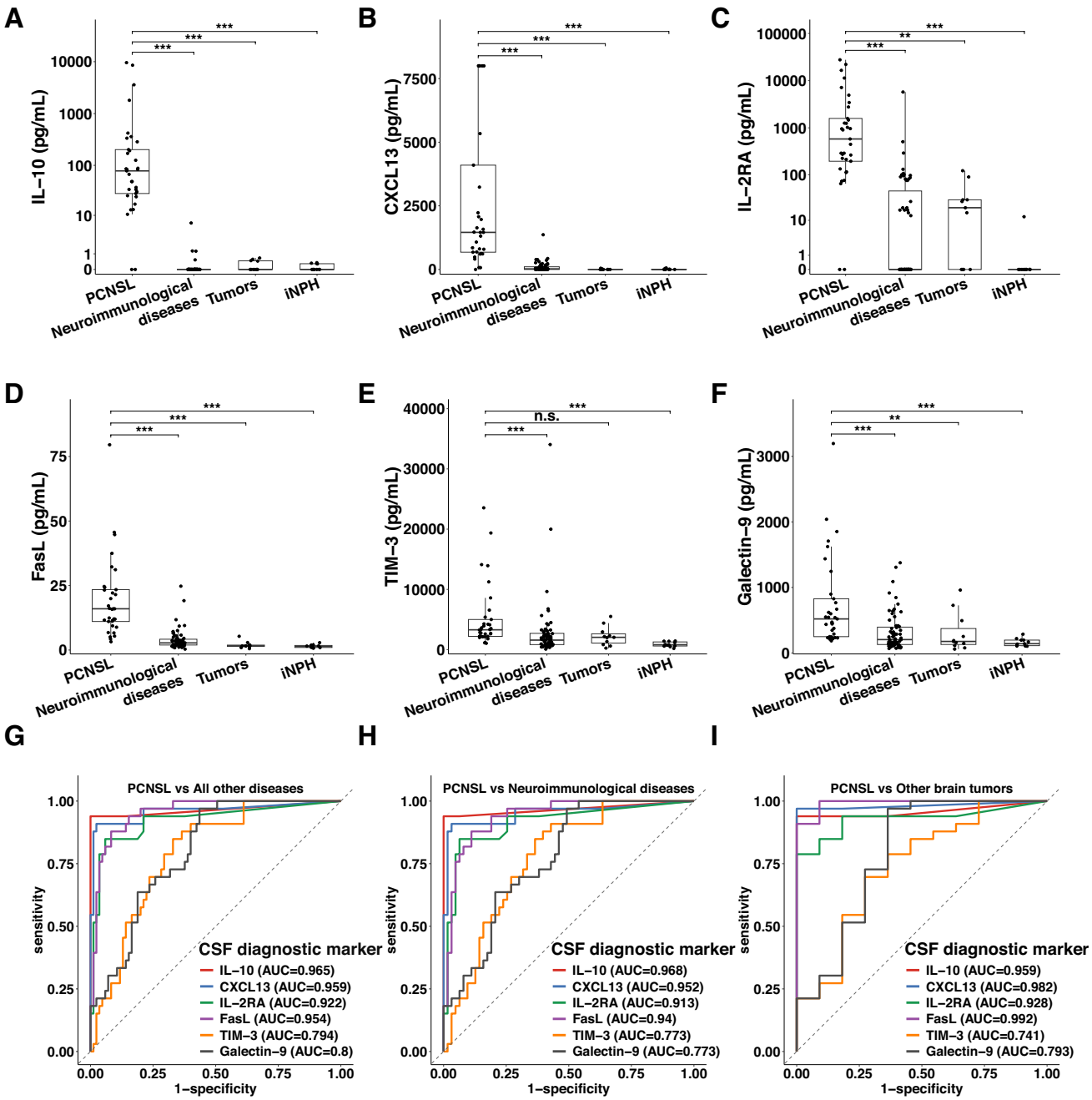

Fig. 1 Accuracy of CSF diagnostic markers for PCNSL. Boxplots depicted the distribution of CSF IL-10 (**A**), CXCL13 (**B**), IL-2RA (**C**), FasL (**D**), TIM-3 (**E**), and galectin-9 (**F**) levels in PCNSL, neuroimmunological diseases, other brain tumors, and iNPH patients. Median values were represented by the horizontal bar, IQR by boxes, 1.5×IQR by whiskers, and individual values by dots. IL-10 and IL-2RA are shown on a logarithmic scale due to the highly skewed distribution with a large proportion of zero or low values and a small number of extremely high values. The *y*-axis is displayed on a logarithmic scale after log10 transformation of IL-10 and IL-2RA concentrations with the addition of a constant of 1, while tick labels indicate the original values in pg/mL. **, adjusted $p < 0.01$. ***, adjusted $p < 0.001$. n.s., not significant. Holm-adjusted Dunn's tests were used to compare PCNSL with the other groups. **G–I** ROC curves showed the diagnostic performance of CSF IL-10, CXCL13, IL-2RA, FasL, TIM-3, and galectin-9 for distinguishing PCNSL from different disease groups. The corresponding AUC values were shown. **G** PCNSL versus all other diseases. **H** PCNSL versus neuroimmunological diseases. (I) PCNSL versus other brain tumors. AUC values were shown in the legends of each panel AUC, area under the curve; CSF, cerebrospinal fluid; CXCL13, C–X–C motif chemokine ligand 13; FasL, Fas ligand; IL-2RA, interleukin-2 receptor chain alpha; IL-10, interleukin-10; iNPH, idiopathic normal pressure hydrocephalus; IQR, interquartile range; PCNSL, primary central nervous system lymphoma; ROC, Receiver operating characteristic; TIM-3, T-cell immunoglobulin and mucin domain 3

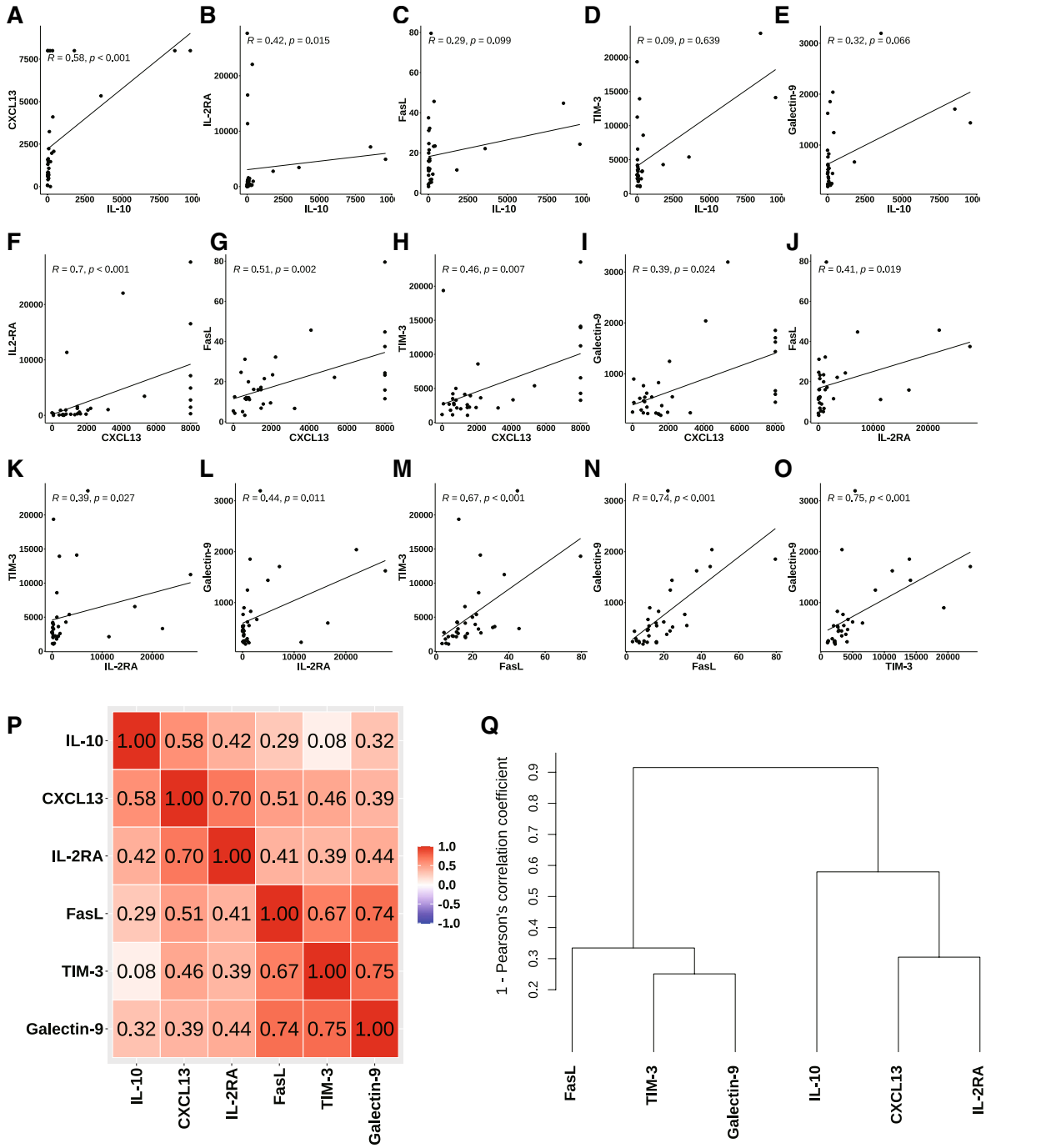

Fig. 2 Correlations and clustering of diagnostic markers in PCNSL. Scatter plots and correlation analyses showed correlations between IL-10 and CXCL13 (**A**), IL-10 and IL-2RA (**B**), IL-10 and FasL (**C**), IL-10 and TIM-3 (**D**), IL-10 and galectin-9 (**E**), CXCL13 and IL-2RA (**F**), CXCL13 and FasL (**G**), CXCL13 and TIM-3 (**H**), CXCL13 and galectin-9 (**I**), IL-2RA and FasL (**J**), IL-2RA and TIM-3 (**K**), IL-2RA and galectin-9 (L), FasL and TIM-3 (**M**), FasL and galectin-9 (**N**), and TIM-3 and galectin-9 (**O**). Spearman's rank correlation was used to measure the degree of correlation between CSF diagnostic markers. **P** Correlation matrix showed Spearman's rank correlation coefficients between CSF diagnostic markers in PCNSL patients. **Q** Hierarchical clustering of CSF diagnostic markers in PCNSL patients based on Spearman's rank correlation coefficients. Clustering was performed using 1 − Spearman's correlation coefficient as the distance metric with the complete linkage method. CSF, cerebrospinal fluid; CXCL13, C–X–C motif chemokine ligand 13; FasL, Fas ligand; IL-2RA, interleukin-2 receptor chain alpha; IL-10, interleukin-10; PCNSL, primary central nervous system lymphoma; TIM-3, T-cell immunoglobulin and mucin domain 3

Table 2 Performance of diagnostic models for PCNSL based on diagnostic markers

Markers included in the model	Performance index					
	AIC	BIC	AUC	RMSE	R^2	*p* value
IL-10	**24.9**	**30.4**	0.965	0.136	0.906	0.002
CXCL13	53.3	58.8	0.959	0.223	0.733	< 0.001
IL-2RA	113.1	118.7	0.923	0.361	0.310	0.006
FasL	72.3	77.8	0.954	0.283	0.593	< 0.001
TIM-3	136.4	142.0	0.794	0.431	0.073	0.018
Galectin-9	122.8	128.3	0.799	0.409	0.179	< 0.001
IL-10 + CXCL13	26.7	35.0	0.980	**0.135**	**0.908**	
IL-10 + IL-2RA	26.8	35.1	0.973	**0.135**	0.907	
IL-10 + FasL	26.5	34.8	0.990	0.139	0.905	
IL-10 + TIM-3	26.7	35.0	0.989	0.140	0.903	
IL-10 + Galectin-9	26.2	34.6	**0.991**	0.141	0.904	
CXCL13 + IL-2RA	54.8	63.1	0.952	0.223	0.733	
CXCL13 + FasL	52.9	61.2	0.974	0.220	0.746	
CXCL13 + TIM3	51.1	59.4	0.940	0.204	0.767	
CXCL13 + Galectin-9	55.1	63.4	0.940	0.223	0.735	
IL-2RA + FasL	73.6	81.9	0.956	0.280	0.600	
IL-2RA + TIM3	115.0	123.3	0.887	0.362	0.308	
IL-2RA + Galectin-9	112.9	121.2	0.909	0.364	0.312	
FasL + TIM3	56.6	64.9	0.950	0.247	0.700	
FasL + Galectin-9	68.5	76.8	0.961	0.269	0.631	
TIM-3 + Galectin-9	123.7	132.0	0.790	0.408	0.186	

Logistic regression analysis including the diagnostic markers data was performed to generate single-marker and two-marker diagnostic models for PCNSL

Bold indicates the best metrics for diagnostic performance among models

AIC, Akaike information criterion; AUC, the area under the ROC curve; BIC, Bayesian information criterion; CXCL13, C–X–C motif chemokine ligand 13; FasL, Fas ligand; IL-2RA, interleukin-2 receptor chain alpha; IL-10, interleukin-10; PCNSL, primary central nervous system lymphoma; R^2, *R*-squared; RMSE, root-mean-squared error; TIM-3, T-cell immunoglobulin and mucin domain 3

CSF TIM-3 and galectin-9 were not associated with prognosis in PCNSL

Furthermore, we analyzed the prognosis of PCNSL patients. We divided the patients into two groups according to the median value of the diagnostic markers. Although not statistically significant, higher levels of B-cell-associated factors were associated with shorter PFS (Fig. 3). No significant association was observed between immune checkpoint molecules and PFS.

Discussion

This retrospective single-center study investigated CSF diagnostic and prognostic markers for PCNSL using a bead-based multiplex immune-assay. Both B-cell-associated factors (IL-10, CXCL13, and IL-2RA) and immune checkpoint molecules (FasL, TIM-3, and galectin-9) were significantly elevated in PCNSL. Notably, two-marker models combining IL-10 with immune checkpoint molecules demonstrated superior diagnostic performance. Furthermore, B-cell-associated factors—but not immune checkpoint molecules—showed a trend towards association with poor prognosis of PCNSL patients.

We newly identified elevated CSF levels of TIM-3 and galectin-9 in PCNSL patients. TIM-3 is an immune checkpoint receptor that primarily binds to galectin-9 and exhausts immune cells such as T cells, and it is involved in the regulation of inflammation in the central nervous system [27]. A previous study has demonstrated expression of TIM-3 on tumor cells and tumor-associated macrophages, while galectin-9 is expressed on tumor-associated macrophages and glial cells [28]. Given ongoing therapeutic investigations targeting immune checkpoints [29], TIM-3 and galectin-9 may represent biologically meaningful diagnostic and potentially therapeutic targets. Our findings strengthen existing evidence supporting CSF profile in PCNSL and expand the diagnostic biomarker landscape by identifying immune checkpoint molecules including TIM-3 and galectin-9 as potential complementary markers to B-cell-associated factors.

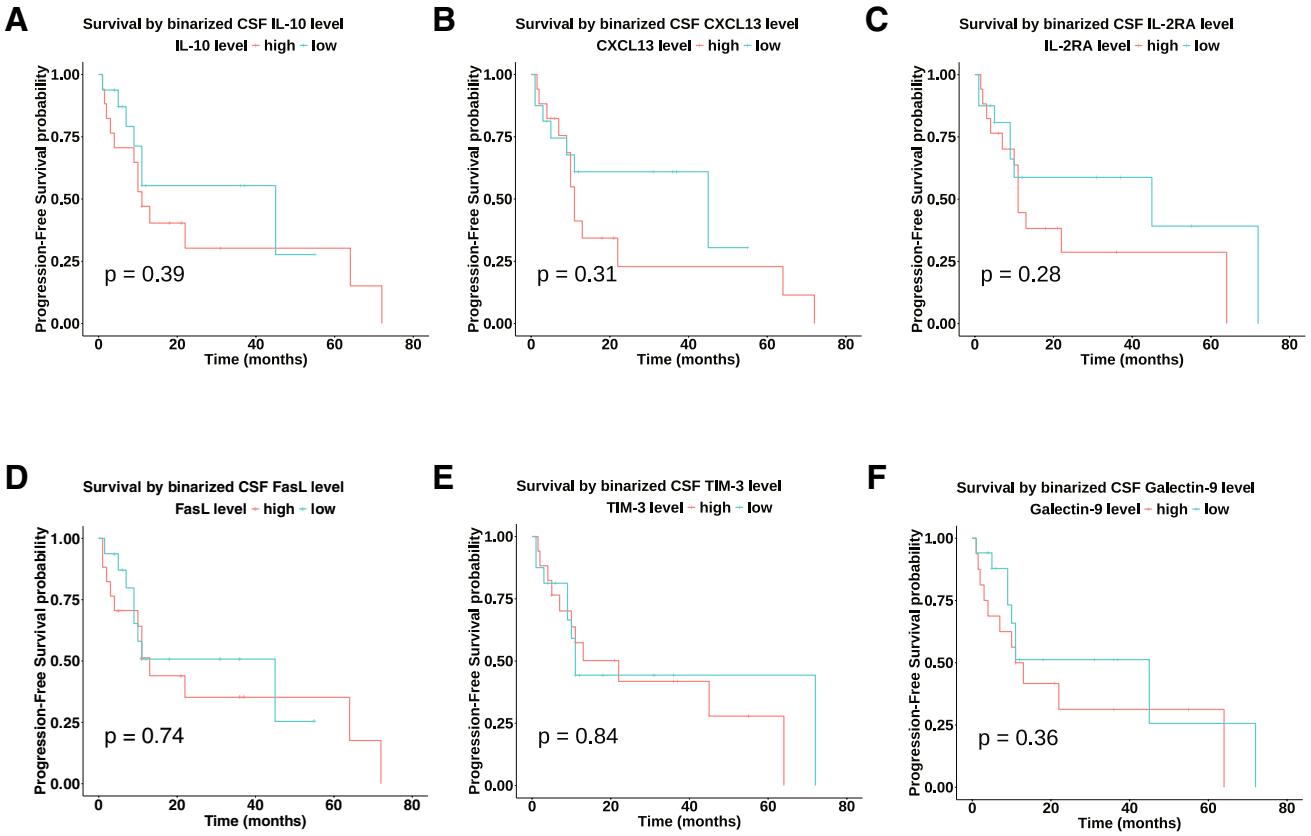

Fig. 3 Comparison of PFS in PCNSL according to diagnostic marker levels. Kaplan–Meier curves for PFS in PCNSL patients were compared according to CSF IL-10 (**A**), CXCL13 (**B**), IL-2RA (**C**), FasL (**D**), TIM-3 (**E**), and galectin-9 (**F**) levels. PFS was compared using the log-rank test. CSF, cerebrospinal fluid; CXCL13, C–X–C motif chemokine ligand 13; FasL, Fas ligand; IL-2RA, interleukin-2 receptor chain alpha; IL-10, interleukin-10; PCNSL, primary central nervous system lymphoma; PFS, progression-free survival; TIM-3, T-cell immunoglobulin and mucin domain 3

CSF TIM-3 did not significantly differ between PCNSL and other brain tumors (glioblastoma and metastatic brain tumor), which may reflect shared immune checkpoint activation in tumor microenvironment. TIM-3 may serve as a diagnostic marker for differentiating PCNSL from neuroimmunological diseases rather than other brain tumors.

In contrast to earlier reports [17, 18], we did not detect significant differences in CSF PD-1 or PD-L1 levels. This discrepancy may be attributable to methodological differences, and further validation using multiple approaches such as enzyme-linked immunosorbent assays is warranted.

Several studies have reported associations between CSF IL-10 and CXCL13 levels and prognosis in PCNSL [3–5]. Consistent with these observations, we found a trend towards shorter PFS in patients with higher levels of B-cell-associated factors. These B-cell-associated factors may contribute to the microenvironment of PCNSL and reflect activation and expansion of lymphoma [30–32]. On the contrary, immune checkpoint molecules had no association with prognosis in PCNSL. This result is biologically plausible, because immune checkpoint molecules may be derived not only from tumor cells but also from compensatory upregulation in response to antitumor immune activity.

Although CSF analysis may provide important diagnostic information, brain biopsy remains necessary for most patients with suspected PCNSL. Nevertheless, CSF markers may serve as a useful tool to raise suspicion for PCNSL and help distinguish PCNSL from inflammatory or other neoplastic conditions. In addition, these markers may be particularly helpful in patients for whom brain biopsy is difficult or contraindicated.

Several limitations of the present study should be acknowledged. First, differences in sex, age, and prior steroid exposure may have influenced diagnostic marker levels. Second, the diagnostic models for diagnostic markers in PCNSL were developed using a relatively small sample size and a retrospective study design. Prospective studies with larger, multicenter cohorts are needed to establish clinical applicability.

Conclusions

CSF TIM-3 and galectin-9 serve as additional diagnostic biomarkers for PCNSL when used in conjunction with B-cell-associated factors. Future prospective, multicenter studies are warranted to validate whether immune checkpoint molecules can be complementary biomarkers and improve non-invasive diagnostic strategies for PCNSL.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-026-13791-4.

Author contributions SN and NC contributed to the conception and design of the study. All authors contributed to acquisition of data. SN contributed to statistical analysis. All authors contributed to drafting the manuscript.

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Data availability All the datasets analyzed and all the reagents used or generated during this study are available from the corresponding author on reasonable request.

Declarations

Conflicts of interest NC has received honoraria for lectures from Biogen Japan, Novartis, Tanabe Pharma, Chugai Pharmaceutical, and Alexion Pharmaceuticals. The other authors declare no competing interests.

Consent for publication Not applicable.

Ethics approval The protocol was approved by Kobe University Clinical Research Ethical Committee (B250069) in accordance with the Declaration of Helsinki. Because the research involved the use of existing clinical data, informed consent was obtained through an opt-out process. Study information was publicly available on the institutional website, providing patients with the opportunity to withdraw their data from the analysis.

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