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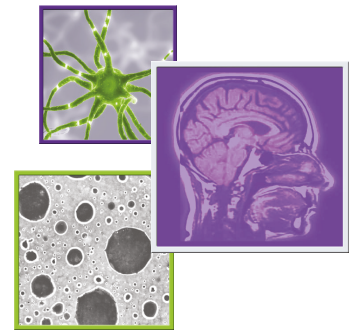

Systemic inflammatory biomarkers in primary central nervous system lymphoma versus high-grade glioma: exploratory, comparative and correlative analysis

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Aim: To assess systemic inflammatory biomarkers in non invasive differential diagnosis of primary central nervous system lymphoma (PCNSL) from high-grade glioma (HGG). **Materials & methods:** Patients with similar morphology (PCNSL or HGG) on conventional neuro-imaging were included. Systemic inflammatory indices were calculated from pretreatment complete blood counts and liver function tests and compared against histopathology as reference standard. **Results:** Mean values of absolute lymphocyte count and prognostic nutritional index were significantly different between PCNSL (n = 42) versus HGG (n = 16). Area under receiver operating characteristics curve for absolute lymphocyte count and prognostic nutritional index in the diagnosis of PCNSL was 0.70 and 0.72 respectively suggesting fair and acceptable diagnostic accuracy. **Conclusion:** Systemic inflammatory biomarkers complement established clinico-radiological features and aid in the differential diagnosis of PCNSL from HGG.

Plain language summary: There exists a complex interplay between cancer and inflammation that can manifest as increased inflammatory biomarkers in blood. However, utility of systemic inflammatory biomarkers in the non invasive differential diagnosis of primary brain lymphoma from high-grade glioma is generally lacking. Two simple serum biomarkers, absolute lymphocyte count and prognostic nutritional index, easily derived from routine pretreatment blood tests have fair correlation and acceptable diagnostic accuracy in differentiating brain lymphoma from glioma in patients with similar morphology on MRI.

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Keywords: diagnosis • high-grade glioma • imaging • inflammation • PCNSL

Primary central nervous system lymphoma (PCNSL) is a rare form of non-Hodgkin lymphoma that only affects the brain, leptomeninges, spinal cord or eyes without any evidence of systemic involvement [1,2]. Multi parametric contrast-enhanced MRI supplemented with spectroscopy, diffusion and perfusion techniques is the recommended first-line imaging modality for assessment and characterization of intracranial lesions including suspected PCNSL. In immunocompetent adults with PCNSL, MRI shows single or multiple solid lesions in the supra-tentorial brain (mostly located in the deep peri-ventricular regions including basal ganglia, thalamus, midbrain and corpus callo-

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sum) with intense, homogenous, contrast enhancement without necrosis, restricted diffusion and variable peri-focal edema [3]. Metabolic imaging using FDG-PET/CT is being increasingly used as an adjunctive modality in the diagnostic and staging evaluation of patients with PCNSL [4–7]. Lymphomatous lesions typically demonstrate increased FDG-avidity on PET/CT with higher maximum standardized uptake values (SUVmax) and tumor/normal tissue (T/N) ratios compared with non lymphomas providing acceptably high diagnostic accuracy [5,8,9]. In addition, pretreatment whole-body FDG-PET/CT has also been demonstrated to be a valuable single-stop imaging modality for staging in PCNSL [5,10]. The identification of systemic lymphoma in patients with disease apparently confined to the CNS has major diagnostic, prognostic and therapeutic implications. Notwithstanding the substantially higher (nearly twice as much) glucose metabolism in lymphomas compared with high-grade gliomas (HGGs), there exists modest overlap in SUVmax and T/N ratios between the two, rendering differential diagnosis difficult. It is therefore necessary to have adjunctive cerebrospinal fluid-based and/or blood-based biomarkers [11,12] that can complement radiological features for reliable non invasive diagnosis of PCNSL.

A complex interplay exists between cancer and inflammation [13,14] that is demonstrable in the tumor microenvironment on tissue-biopsy in various solid tumors and hematological malignancies. This is often reflected in the systemic circulation which can be captured in the form of systemic inflammatory markers in the peripheral blood [15,16]. Some of the most widely studied systemic inflammatory biomarkers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR) and red-cell distribution width – coefficient of variation (RDW-CV) can be easily derived from blood tests obtained routinely in the work-up of patients with cancer. Prognostic nutritional index (PNI) – a composite score [17] based on serum albumin and lymphocyte count reflecting nutritional and inflammatory state respectively has also emerged as a prognostic biomarker in various cancers [18,19]. The CNS has long been considered an immune-privileged organ with its parenchymal cells (i.e., neurons, astrocytes, microglia and oligodendrocytes) being separated from rest of body by a blood–brain barrier. However, accumulating evidence shows that brain is quite immune competent due to participation of microglia and astrocytes in immune response. Brain does not have a typical lymphatic circulation and normally lacks lymphoid aggregation raising questions regarding the origins of PCNSL locally within the brain [20]. It is still unclear whether PCNSL truly originates within the CNS or whether it is part of a systemic lymphoma that escapes from the immune system and grows in the CNS sanctuary. B-cells recruited to the brain in the case of an immune reaction may stay for extended periods and eventually transform while residing within the CNS. On the other hand, it has also been hypothesized that B-cells might have transformed to a malignant state outside the CNS (in a secondary lymphoid organ) and survive in an immunologically aberrant CNS which otherwise should have been eradicated by an intact immune system [21,22]. Vast majority of patients with PCNSL harbor B-cell receptors specific for autoantigens predominantly expressed in the CNS providing an attractive explanation for CNS tropism of the disease [23]. Considering above plausibility, systemic inflammation is likely to play some role in PCNSL etiopathogenesis. Data on systemic inflammatory biomarkers in PCNSL including differentiating them from HGG with similar imaging morphology is generally lacking. This exploratory post-hoc subset analyses of a prospective imaging study in suspected PCNSL compares and correlates systemic inflammatory biomarkers (derived from routinely performed blood investigations) to aid in the non invasive differential diagnosis of PCNSL from HGG.

Materials & methods

The present exploratory, comparative and correlative analysis of systemic inflammatory biomarkers was done retrospectively as a sub study of a larger prospective observational imaging study [5].

Study population

Consecutive patients registered at an academic neuro-oncology unit of a tertiary-care comprehensive cancer center with clinico radiological suspicion of PCNSL on conventional neuro imaging (MRI) accrued on a prospective imaging study testing the diagnostic performance of pre-treatment whole-body FDG-PET/CT were eligible. Conventional neuro imaging comprised of multi parametric contrast-enhanced MRI supplemented with additional diffusion, perfusion and spectroscopy techniques if available to aid in the non invasive differential diagnosis of PCNSL from HGG. These patients underwent whole-body FDG-PET/CT to characterize and quantify glucose metabolism (SUVmax and T/N ratio) in the suspected intracranial lesion(s). The study was limited to immunocompetent adults and patients with known immunodeficiency syndrome such as HIV infection were considered ineligible. All patients had undergone extensive pre-anesthetic check-up, documentation of any pre-existing illness

including review of ongoing medication and comprehensive hematological/biochemical evaluation prior to the neurosurgical procedure. Histopathology obtained either from stereotactic biopsy or open neurosurgical debulking was used as the reference standard. Only patients with pathologically confirmed diagnosis of PCNSL or HGG were included provided pretreatment complete blood count (CBC) and liver function test (LFT) reports were also available for data extraction and analysis. If relevant blood tests had been performed multiple times, the sample collected closest (just prior) to the procedure was used for extraction and calculation of systemic inflammatory ratios/indices.

Blood parameters

All blood samples had been collected from peripheral veins of patients in ethylene diamine tetra-acetic acid tubes for hemogram and plain/clot activator tubes for serum biochemistry prior to the neuro-surgical procedure. Blood counts were performed on automated blood counters (Advia 2120i, Siemens Medical Solutions, Germany) by using flow-cytometry for total cell counts including platelet count. Cytochemical-myeloperoxidase method and basophil channel method were used for obtaining differential cell counts. Serum biochemistry was also processed on auto-analyzers (AU5800, Beckman Coulter, CA, USA) with albumin levels being measured using modified Doumas and Rodkey method that captures the absorbance of albumin-bromocresol green complex bichromatically (proportional to the albumin concentration in the given sample). All blood tests were performed in an accredited institutional laboratory with stringent quality control standards. Total leucocyte count (TLC) along with differential count of its components such as absolute neutrophil count (ANC), absolute lymphocyte count (ALC) and absolute monocyte count (AMC) were extracted from available CBC reports and expressed in 10^9 cells/l. Platelet counts were also extracted and expressed in 10^9 cells/l. RDW-CV was calculated by dividing the standard deviation (SD) of mean red blood cell size by mean corpuscular volume of the red blood cells × 100 and expressed as a percentage with normal range between 11 and 15%. Serum albumin levels were extracted from available pre-treatment LFT reports and expressed in g/dl. Systemic inflammatory markers such as NLR (ANC/ALC), PLR (platelet count/ALC) and LMR (ALC/AMC) were calculated simply as ratios of respective absolute cell counts. PNI was defined and computed as 10 × serum albumin (g/dl) + 5 × ALC (10^9 cells/l). Besides evaluating various inflammatory ratios/indices, components of CBC along with serum albumin were also analyzed individually for diagnostic correlation.

Statistical analysis

Mean values with respective SD for all blood parameters as described above were extracted for all the included patients. Normality testing for all continuous variables was done using Shapiro–Wilk test. Blood parameters were then compared between PCNSL versus HGG using Mann–Whitney U test for non parametric data and independent samples *t*-test for normally distributed data. Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and overall accuracy with corresponding 95% CI were calculated for assessing the diagnostic performance of blood-based parameters including systemic inflammatory indices. Receiver operating characteristics (ROC) curves were generated for parameters that successfully differentiated between the two with optimal cut-off values identified and corresponding area under the curve (AUC) calculated to demonstrate diagnostic performance. Any p-value < 0.5 was considered as statistically significant. All statistical analysis was performed on SPSS software (version 21.0; SPSS Inc., IL, USA). The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was duly reviewed and approved by the Institutional Ethics Committee III of Tata Memorial Centre, India (ECR149/Inst/MH/2013) and written informed consent was obtained from all study participants. The study received financial support from the institution through a competitive intramural research grant.

Results

The flow of participants through the study is depicted in a flow-diagram (Figure 1). A total of 80 patients with clinico-radiological suspicion of PCNSL were consented and accrued between October 2014 and June 2017 on the prospective PET-PCNSL study, results of which have been published previously [5]. A total of 22 patients were excluded from analysis due to lack of confirmed pathological diagnosis (n = 6), CNS involvement from systemic lymphoma (n = 4), infectious/inflammatory brain pathology (n = 4), brain metastases (n = 2) and non availability of CBC/LFT reports (n = 6) leaving 58 patients that constitute the present study cohort. Baseline characteristics of the study cohort (Table 1) did not show any significant differences in patients with PCNSL (n = 42) versus

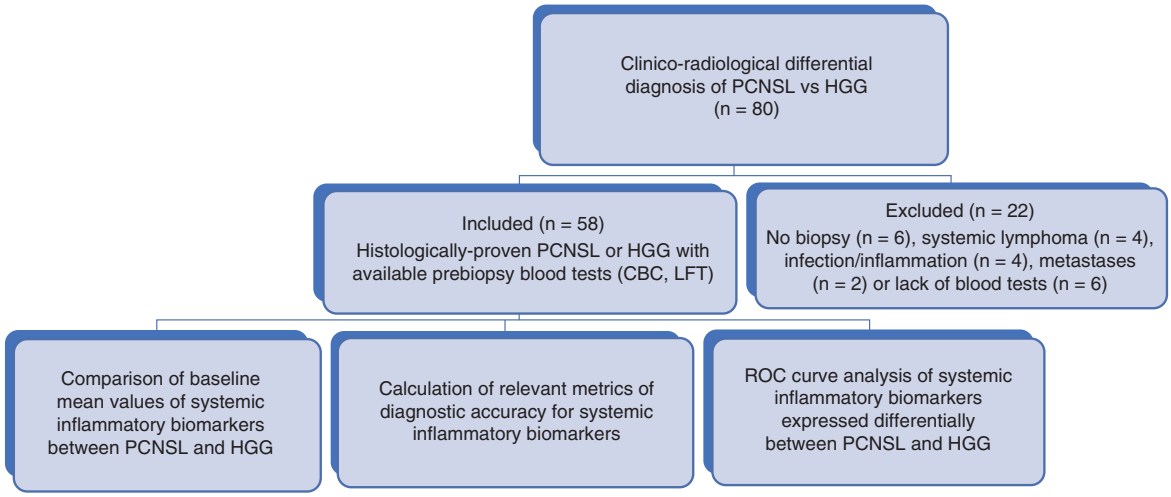

Figure 1. Flow-diagram showing flow of participants in the study.
CBC: Complete blood count; HGG: High-grade glioma; LFT: Liver function test; PCNSL: Primary central nervous system lymphoma; ROC: Receiver operating characteristics.

Table 1. Baseline characteristics of the study cohort (n = 58).

Characteristics	All patients (n = 58)	PCNSL (n = 42)	HGG (n = 16)	p-value†
Age in years				
Median age (range)	54.5 (18–72)	55 (18–72)	51 (18–69)	0.653
Gender				
Male	33 (56.9%)	22 (52.4%)	11 (68.8%)	0.261
Female	25 (43.1%)	20 (47.6%)	5 (31.2%)	
ECOG status				
PS = 0-1	25 (43.1%)	17 (40.5%)	8 (50%)	0.513
PS ≥2	33 (56.9%)	25 (59.5%)	8 (50%)	
Comorbidities				
Yes	23 (39.7%)	16 (38.1%)	7 (43.8%)	0.694
No	35 (60.3%)	26 (61.9%)	9 (56.2%)	
Focality				
Unifocal	28 (48.3%)	19 (45.2%)	9 (56.3%)	0.453
Multi-focal	30 (51.7%)	23 (54.8%)	7 (43.8%)	

†Reported p-values are based on χ^2 test for all characteristics excepting for comparison of median age which is based on unpaired student '*t*'-test.
ECOG: Eastern Co-operative Oncology Group; HGG: High-grade glioma; PCNSL: Primary central nervous system lymphoma; PS: Performance status.

HGG (n = 16). 12 of the 16 HGGs were glioblastoma (grade IV), while the remaining four were anaplastic astrocytoma (grade III). On comparing individual blood parameters between PCNSL and HGG, levels of two systemic inflammatory markers viz. ALC (Figure 2) and PNI (Figure 3) were found to be significantly different between these two diagnoses. The mean (±SD) ALC in PCNSL was 1.42 (±0.66) × 10^9 cells/dl which was significantly lower (p = 0.011) compared with 1.92 (±0.57) × 10^9 cells/dl in HGG (Table 2). Similarly, mean PNI of 46.27 (±6.7) in PCNSL was significantly lower (p = 0.013) than 50.27 (±4.29) seen in HGG (Table 2). ROC curve analysis (Figure 4) demonstrated an AUC of 0.70 and 0.72 for ALC and PNI respectively in the differential diagnosis of PCNSL from HGG. With a cut-off value of 1.87 × 10^9 cells/dl, ALC was associated with a sensitivity, specificity, PPV, NPV and diagnostic accuracy of 80.9% (95% CI: 65.9–91.4%), 56.2% (95% CI: 29.9–80.2%), 82.9% (95% CI: 73.2–89.6%), 52.9% (95% CI: 34.5–70.6%) and 74.1% (95% CI: 61–84.7%) respectively, Similar analysis for PNI identified a cut-off value of 45.29 to be associated with sensitivity, specificity, PPV, NPV and diagnostic accuracy of 47.6% (95% CI: 32–63.6%), 93.7% (95% CI: 69.8–99.8%), 95.2% (95% CI: 74.5–99.3%), 40.5% (95% CI: 33.2–48.3%) and 60.3% (95% CI: 46.6–72.9%) respectively. As was expected and reported previously also (5), SUVmax and T/N ratio derived from pretreatment FDG-PET/CT was significantly higher in patients with PCNSL (Table 2) allowing reliable discrimination from HGG with acceptably high diagnostic accuracy.

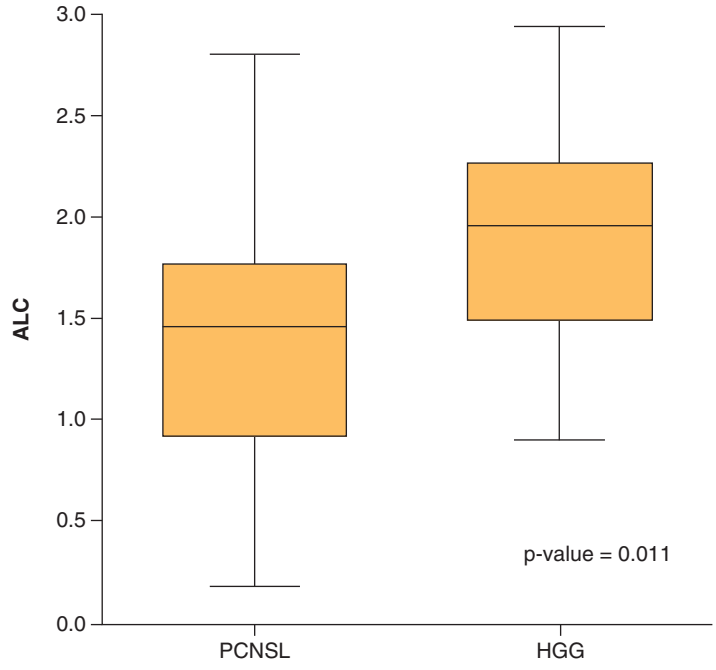

Figure 2. Boxplots (median with interquartile range) comparing absolute lymphocyte count in patients with biopsy-proven primary central nervous system lymphoma versus high-grade glioma. Note the significantly lower levels of ALC in PCNSL compared with HGG. ALC: Absolute lymphocyte count; HGG: High-grade glioma; PCNSL: Primary central nervous system lymphoma.

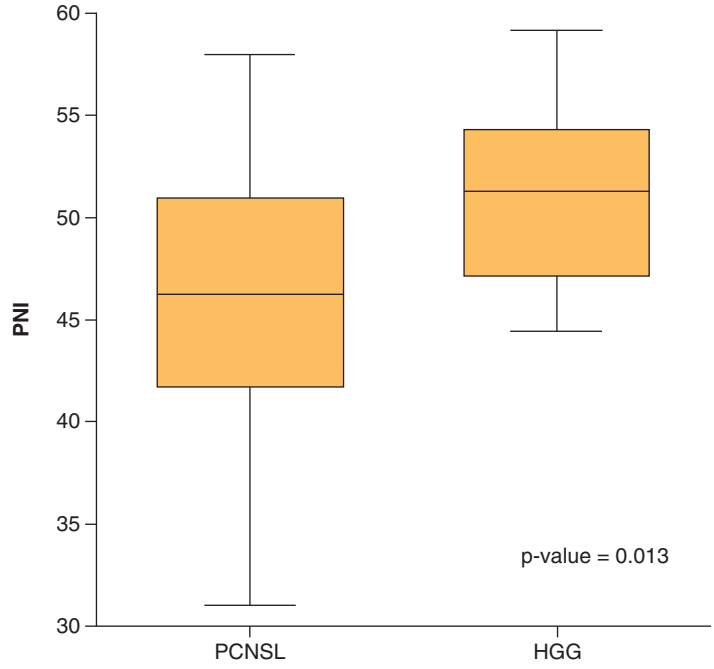

Figure 3. Boxplots (median with interquartile range) comparing prognostic nutritional index in patients with biopsy-proven primary central nervous system lymphoma versus high-grade glioma. Note the significantly lower value of PNI in PCNSL compared with HGG. HGG: High-grade glioma; PCNSL: Primary central nervous system lymphoma; PNI: Prognostic nutritional index.

Discussion

The interaction between inflammation and cancer has been an area of active research for decades [13,14]. It is widely hypothesized that the inflammatory response and host immune response is closely related to cancer occurrence, progression and disease biology [14]. The utility of systemic inflammatory biomarkers in the differential diagnosis of PCNSL from HGG with similar imaging morphology has not been studied or reported previously. This exploratory first-of-a kind study assessed the utility of systemic inflammatory biomarkers derived from routine blood investigations in a cohort of patients with suspected PCNSL to differentiate them reliably from HGG with similar morphologic imaging. The levels of ALC and PNI were found to be significantly lower in PCNSL compared with HGG. These markers complement established clinico radiological features and can be used to aid in the non-invasive differential diagnosis between PCNSL and HGG. Apart from having acceptably high accuracy, a good

Table 2. Comparison of systemic inflammatory markers and FDG-PET/CT-derived imaging biomarkers between primary central nervous system lymphoma and high-grade glioma.

Tested biomarker(s)	Mean value (+standard deviation)		p-value
	PCNSL (n = 42)	HGG (n = 16)	
Systemic inflammatory biomarkers			
Total platelet count	252.40 (±91.23)	287.75 (±79.52)	0.178†
Total leukocyte count	9.25 (±4.11)	10.72 (±3.05)	0.200†
Absolute neutrophil count	6.98 (±3.93)	7.81 (±2.63)	0.497
Absolute lymphocyte count	**1.42 (±0.66)**	**1.92 (±0.57)**	**0.011**†
Absolute monocyte count	0.57 (±0.30)	0.68 (±0.39)	0.269
Red-cell distribution width	14.46 (±2.02)	13.92 (±0.85)	0.682
Neutrophil-to-lymphocyte ratio	7.32 (±13.07)	4.50 (±2.57)	0.230
Platelet-to-lymphocyte ratio	242.12 (±231.42)	163.23 (±63.88)	0.175
Lymphocyte-to-monocyte ratio	3.03 (±1.75)	3.25 (±1.31)	0.497
Serum albumin	3.91 (±0.48)	4.13 (±0.39)	0.114†
Prognostic nutritional index	**46.27 (±6.70)**	**50.86 (±4.20)**	**0.013**†
FDG-PET/CT-derived imaging biomarkers‡			
Maximum standardized uptake value	28.71 (±13.05)	17.47 (±7.19)	0.002
Tumor/normal tissue ratio	2.36 (±0.76)	1.52 (±0.33)	<0.001

†p-values represent comparisons based on unpaired student 't'-test.
‡FDG-PET biomarkers were derived from slightly fewer patients than blood-based biomarkers.
HGG: High-grade glioma; PCNSL: Primary central nervous system lymphoma.

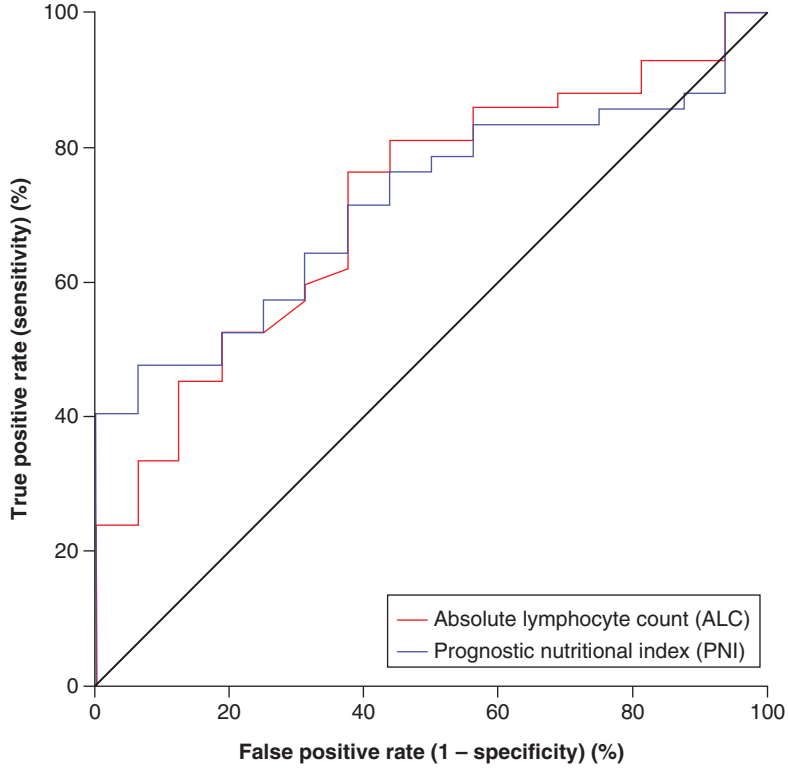

Figure 4. Receiver operating characteristics curves of absolute lymphocyte count and prognostic nutritional index in the differentiation of primary central nervous system lymphoma from high-grade glioma. Note that the upper left corner of the respective curves provides the most optimal cut-off value of ALC and PNI respectively in the noninvasive diagnosis of primary central nervous system lymphoma.
ALC: Absolute lymphocyte count; PNI: Prognostic nutritional index.

ancillary diagnostic test should be easy, simple, quick, reproducible and economical for widespread adoption and application in clinical practice. Systemic inflammatory biomarkers satisfy most of these desirable attributes leading to increasing interest in blood-based biomarkers for early diagnosis, response assessment, prognostication and disease surveillance in contemporary oncologic practice [24–26]. Several studies have focused on disease-specific cell-free DNA [27] or circulating tumor DNA [28], techniques which are difficult and challenging to implement in routine clinical practice due to logistic and resource-constraints. In contrast, systemic inflammatory indices, though non specific can be easily derived from simple blood tests done routinely in cancer patients.

Association of systematic inflammatory biomarkers with PCNSL is generally lacking with most studies focusing on adult diffuse glioma. A large prospective cohort study [29] tested the association of systemic inflammatory biomarkers such as CRP, TLC, NLR and IGF-1 with the risk of glioma. After adjustment for age, gender, race and education, 417 incident cases of glioma were identified among 428,537 biobank participants with 3,255,815 person-years of follow-up. Overall, weak non significant associations were observed with increasing level of biomarkers for the risk of glioma. There was no significant association of CRP and TLC with later risk of glioma. However, high IGF-1 and NLR showed positive association with risk of glioma in women, but not in men, warranting further studies. A large multicentric study [30] explored the diagnostic value of various systemic inflammatory biomarkers such as NLR, derived NLR (dNLR) defined as ratio of ([TLC minus ANC]/ALC), PLR, LMR and PNI in the differential diagnosis of diffuse gliomas (n = 750) from meningiomas (n = 271), acoustic neuromas (n = 44), non lesional epilepsy (n = 102) and healthy controls (n = 682). ROC curve analysis demonstrated higher values of NLR (AUC = 0.722), dNLR (AUC = 0.696), PLR (AUC = 0.760) and lower levels of LMR (AUC = 0.760) and PNI (AUC = 0.672) to be indicative of gliomas compared with other diagnosis. Another study [31] reported lower values of LMR (p = 0.004) and higher levels of PLR (p = 0.01) and NLR (p = 0.05) to correlate significantly with brain metastases (n = 70) compared with glioblastoma (n = 80) with an AUC of 0.61, 0.64 and 0.58 respectively suggesting moderately high diagnostic accuracy.

The prognostic impact of systemic inflammatory biomarkers has been demonstrated for various solid cancers and hematologic malignancies [32,33]. It has been demonstrated that higher values of NLR, PLR and RDW-CV (suggestive of higher levels of systemic inflammation); lower levels of LMR (indicative of decreased immune function); and lower levels of serum albumin and PNI (representing low nutritional state) correlate with worse outcomes pointing toward a complex interaction between systemic inflammation, immune-regulation and nutritional status. A recent meta-analysis of 18 studies [34] evaluating systemic inflammatory markers in 3261 patients of diffuse gliomas found NLR with hazard ratio (HR) of 1.38 (95% CI: 1.09–1.74; p = 0.008), RDW-CV (HR: 1.40; 95% CI: 1.13–1.74; p = 0.002) and PNI (HR: 0.57; 95% CI: 0.42–0.77; p = 0.0002) to be independent prognostic factors. The optimal cut-off of inflammatory biomarkers as prognostic factors in diffuse gliomas has been variable ranging from 4 to 7 for NLR and 44.4–52.5 for PNI in previously published reports [35–37].

Only two prior studies have reported the prognostic impact of systemic inflammatory biomarkers in PCNSL. In the first such retrospective cohort comprising of 62 patients with PCNSL, using a NLR cut-off value of 2, the high NLR group was associated with significantly worse 3-year progression-free survival (HR: 2.41, 95% CI: 1.07–5.42; p = 0.034) and overall survival (HR: 2.64, 95% CI: 1.06–6.60; p = 0.038) compared with the low NLR group [38]. The reported mean values of NLR and PLR in that study were 2.52 and 122.4 respectively which is substantially lower than the mean NLR of 7.32 and mean PLR of 242.12 seen in PCNSL patients in the present study. However, the mean levels of NLR (4.50) and PNI (50.82) observed in patients with HGG in the present study are in accordance with previously published data. More recently, another study has demonstrated the association of high levels of systemic inflammatory biomarkers such as NLR, PLR, systemic immune inflammation index and systemic inflammatory response index with shorter survival in a consecutive cohort of 73 patients with PCNSL [39]. The authors also reported optimal cut-off values for NLR, PLR, systemic immune inflammation and systemic inflammatory response index which were integrated into a composite 'CBC score' model that stratified patients into three distinct risk-groups (low, intermediate and high) with non overlapping survival curves [39]. On multivariate Cox regression analysis, PLR and CBC score emerged as significant and independent predictors of survival outcomes in PCSNL in addition to the well-established Memorial Sloan Kettering Cancer Centre (MSKCC) prognostic scoring system [40] that incorporates age and performance status in its model.

Strengths & limitations

Accuracy of systemic inflammatory biomarkers in PCNSL versus HGG was assessed against confirmed pathological diagnosis as reference standard which is a major strength of the current study. FDG-PET/CT imaging study was

designed and conducted in a prospective manner; however, the exploratory subset analysis of systemic inflammatory biomarkers to differentiate PCNSL from HGG is a post-hoc retrospective analysis with potential inherent biases and limitations. Despite the interesting results, small number of patients analyzed in the current report precludes robust and definitive conclusions. Multiple biomarkers were analyzed in the study; however, none of them retained statistical significance after Bonferroni correction for multiple testing which can be regarded as a methodological limitation. However, given exploratory nature of the analysis with sampling of convenience, such statistical adjustment although desirable may not be considered mandatory. This study utilized systemic inflammatory markers derived from routine blood work-up without assessing more robust biomarkers of systemic inflammation such as CRP, serum ferritin, plasma fibrinogen, erythrocyte sedimentation rate or pro-inflammatory cytokines such as interleukins and interferons. Similarly, the study did not use Glasgow prognostic score which has been shown to reflect the systemic inflammatory status more reliably than other composite indices. Lack of systematic documentation of steroid usage at the time of blood sampling could be another confounding factor; it is quite well recognized that steroids can profoundly influence the inflammatory milieu and immune function reflecting in alterations in the peripheral blood parameters. Nevertheless, given the strong clinico-radiological suspicion of PCNSL, every attempt was made to restrict steroid usage with most patients being taken off-steroids completely for at least 5–7 days prior to biopsy/surgery unless required clinically to maintain neurological stability. Although HIV itself is a risk factor for PCNSL, sero-positive patients were excluded from the index imaging study due to very different MRI characteristics of PCNSL in patients with and without HIV. It is possible that systemic inflammatory state is significantly altered in HIV patients with consequent reflection in the peripheral blood that might have potentially impacted upon results and inferences, had HIV sero-positive patients been included in the study. Finally, inflammation status in the tumor microenvironment was not studied on the biopsy specimens precluding its correlation with systemic inflammatory state.

Conclusion

Systemic inflammatory biomarkers can potentially complement established clinico-radiological features and aid in the differential diagnosis of PCNSL from HGG in patients with similar imaging morphology.

Summary points

- A complex interplay exists between cancer and inflammation that can manifest as increased levels of systemic inflammatory biomarkers in blood.
- The utility of systemic inflammatory biomarkers to help in noninvasive differential diagnosis of primary central nervous system lymphoma (PCNSL) from high-grade glioma (HGG) is lacking.
- Various systemic inflammatory biomarkers can be easily derived from routine pretreatment blood tests.
- Mean values of absolute lymphocyte count and prognostic nutritional index are significantly different between PCNSL and HGG.
- Systemic inflammatory biomarkers have fair accuracy in the noninvasive differential diagnosis of PCNSL from HGG.

Author contributions

Conception & design: T Gupta, M Gupta; administrative support: T Gupta, A Moiyadi, V Rangarajan; provision of study materials/patients: T Gupta, B Bagal, A Moiyadi; collection/assembly of data: N Purandare, S Epari, A Janu, T Gupta; data analysis & interpretation: P Nayak, Y Baviskar, A Chatterjee, GJ Sastri, T Gupta; manuscript writing: all authors; final approval of manuscript: all authors.

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Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

All procedures performed in the entire study (Project no. 145) were in accordance with the ethical standards of the Institutional Ethics Committee (IEC) of Tata Memorial Centre, India that functions in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All the patients provided written informed consent before participation in the study.

Data sharing statement

Data from this study will be shared upon reasonable request.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Rubenstein J, Ferreri AJM, Pittaluga S. Primary lymphoma of the central nervous system: epidemiology, pathology and current approaches to diagnosis, prognosis and treatment. *Leuk. Lymphoma* 49(Suppl. 1), 43–51 (2008).
2. Schaff LR, Grommes C. Primary central nervous system lymphoma. *Blood*doi:10.1182/blood.2020008377 (2021) (Epub ahead of print).
3. Tang YZ, Booth TC, Bhogal P, Malhotra A, Wilhelm T. Imaging of primary central nervous system lymphoma. *Clin. Radiol.* 66, 768–777 (2011).

•• **Describes and discusses imaging characteristics of primary central nervous system lymphoma (PCNSL).**

4. Malikova H, Koubska E, Weichet J *et al.* Can morphological MRI differentiate between primary central nervous system lymphoma and glioblastoma? *Cancer Imaging* 16, 40 (2016).
5. Gupta M, Gupta T, Purandare N *et al.* Utility of flouro-deoxy-glucose positron emission tomography/computed tomography in the diagnostic and staging evaluation of patients with primary CNS lymphoma. *CNS Oncol.* 8(4), CNS46 (2019).

• **Systematically assesses the role of pretreatment FDG-PET/CT in the diagnosis and staging of suspected PCNSL.**

6. Abrey LE, Batchelor TT, Ferreri AJM *et al.* Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. *J. Clin. Oncol.* 23, 5034–5043 (2005).
7. Barajas RF Jr, Politi LS, Anzalone N *et al.* Consensus recommendations for MRI and PET imaging of primary central nervous system lymphoma: guideline statement from the International Primary CNS Lymphoma Collaborative Group (IPCG). *Neuro. Oncol.* 23(7), 56–71 (2021).
8. Zou Y, Tong J, Leng H, Jiang J, Pan M, Chen Z. Diagnostic value of using 18F-FDG PET and PET/CT in immunocompetent patients with primary central nervous system lymphoma: a systematic review and meta-analysis. *Oncotarget* 8, 41518–41528 (2017).
9. Gupta T, Manjali JJ, Kannan S, Purandare N, Rangarajan V. Diagnostic performance of pre-treatment 18F-fluoro-deoxy-glucose positron emission tomography with or without computed tomography in patients with primary central nervous system lymphoma: updated systematic review and diagnostic test accuracy meta-analyses. *Clin. Lymphoma Myeloma Leuk.* 21(8), 497–507 (2021).
10. Gupta T, Manjali JJ, Kannan S, Purandare N, Rangarajan V. Diagnostic yield of extensive systemic staging including whole-body 18F-fluoro-deoxy-glucose positron emission tomography with or without computed tomography in patients with primary central nervous system lymphoma: systematic review and meta-analysis. *Clin. Lymphoma Myeloma Leuk.* 20, e836–e845 (2020).
11. Baraniskin A, Schroers R. Modern cerebrospinal fluid analyses for the diagnosis of diffuse large B-cell lymphoma of the CNS. *CNS Oncol.* 3(1), 77–85 (2014).
12. van Westrhenen A, Smidt LCA, Seute T *et al.* Diagnostic biomarkers for CNS lymphoma in blood and cerebrospinal fluid: a systematic review. *Br. J. Haematol.* 182(3), 384–403 (2018).
13. Coussens LM, Werb Z. Inflammation and cancer. *Nature* 420, 860–867 (2002).

•• **Summarizes the relationship between inflammation and cancer.**

14. Grivennikov SI, Greten FR, Karin M. Immunity, Inflammation, and Cancer. *Cell* 140, 883–889 (2010).

•• **Discusses the interplay between immunity, inflammation and cancer.**

15. McMillan DC. Systemic inflammation, nutritional status and survival in patients with cancer. *Curr. Opin. Clin. Nutr. Metab. Care* 12, 223–226 (2009).
16. Rochet NM, Markovic SN, Porrata LF. The role of complete blood cll count in rognosis-watch this space! *Oncol. Hematol. Rev.* 8, 76 (2012).
17. Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. *Nihon Geka Gakkai Zasshi* 85, 1001–1005 (1984).

18. Xishan Z, Ye Z, Feiyan M, Liang X, Shikai W. The role of prognostic nutritional index for clinical outcomes of gastric cancer after total gastrectomy. *Sci. Rep.* 10(1), 17373 (2020).
19. Hua X, Long Z-Q, Huang X *et al.* The value of prognostic nutritional index (PNI) in predicting survival and guiding radiotherapy of patients with T1-2N1 breast cancer. *Front. Oncol.* 9, 1562 (2020).
20. Deckert M, Brunn A, Montesinos-Rongen M, Siebert R. Absence of lymphatic vessels in PCNSL may contribute to confinement of tumor cells to the central nervous system. *J. Neuropathol. Exp. Neurol.* 75, 499–502 (2016).
21. Montesinos-Rongen M, Küppers R, Schlüter D *et al.* Primary central nervous system lymphomas are derived from germinal-center B cells and show a preferential usage of the V4-34 gene segment. *Am. J. Pathol.* 155, 2077–2086 (1999).
22. You H, Wei L, Kaminska B. Emerging insights into origin and pathobiology of primary central nervous system lymphoma. *Cancer Lett.* 509, 121–129 (2021).

•• **Provides newer insights into the origins of PCNSL.**

23. Chapuy B. Tropism of PCNSL: is it all about autoantigens? *Blood* 132, 2704–2706 (2018).
24. Cappelletti V, Appierto V, Tiberio P, Fina E, Callari M, Daidone MG. Circulating biomarkers for prediction of treatment response. *J. Natl Cancer Inst. Monogr.* 51, 60–63 (2015).
25. Xu-Welliver M, Carbone DP. Blood-based biomarkers in lung cancer: prognosis and treatment decisions. *Transl. Lung Cancer Res.* 6, 708–712 (2017).
26. Pierscianek D, Ahmadipour Y, Oppong MD *et al.* Blood-based biomarkers in high grade gliomas: a systematic review. *Mol. Neurobiol.* 56, 6071–6079 (2019).
27. Muluhngwi P, Valdes R Jr, Fernandez-Botran R, Burton E, Williams B, Linder MW. Cell-free DNA diagnostics: current and emerging applications in oncology. *Pharmacogenomics* 20, 357–380 (2019).
28. Cescon DW, Bratman SV, Chan SM, Siu LL. Circulating tumor DNA and liquid biopsy in oncology. *Nat. Cancer* 1, 276–290 (2020).
29. Cote DJ, Creed JH, Samanic CM *et al.* A prospective study of inflammatory biomarkers and growth factors and risk of glioma in a UK biobank. *Cancer Epidemiol.* 75, 102043 (2021).
30. Zheng SH, Huang JL, Chen M, Wang BL, Ou QS, Huang SY. Diagnostic value of preoperative inflammatory markers in patients with glioma: a multicenter cohort study. *J. Neurosurg.* 129, 583–592 (2018).

• **Reports diagnostic value of inflammatory biomarkers in diffuse glioma.**

31. Baran O, Kemerdere R, Korkmaz TS, Kayhan A, Tanriverdi T. Can preoperative neutrophil to lymphocyte, lymphocyte to monocyte, or platelet to lymphocyte ratios differentiate glioblastoma from brain metastasis? *Medicine (Baltimore)* 98(50), e18306 (2019).

• **Uses blood biomarkers to differentiate glioblastoma from brain metastases.**

32. Dolan RD, McSorley ST, Horgan PG, Laird B, McMillan DC. The role of the systemic inflammatory response in predicting outcomes in patients with advanced inoperable cancer: systematic review and meta-analysis. *Crit. Rev. Oncol. Hematol.* 116, 134–136 (2017).
33. Costa AFO, Menezes DL, Pinheiro LHS *et al.* Role of new Immunophenotypic markers on prognostic and overall survival of acute myeloid leukemia: a systematic review and meta-analysis. *Sci. Rep.* 7(1), 4138 (2017).
34. Wang D, Kang K, Lin Q, Hai J. Prognostic significance of preoperative systemic cellular inflammatory markers in gliomas: a systematic review and meta-analysis. *Clin. Transl. Sci.* 13, 179–188 (2020).
35. Zhou X, Dong H, Yang Y *et al.* Significance of the prognostic nutritional index in patients with glioblastoma: a retrospective study. *Clin. Neurol. Neurosurg.* 151, 86–91 (2016).
36. He Z-Q, Ke C, Al-Nahari F *et al.* Low preoperative prognostic nutritional index predicts poor survival in patients with newly diagnosed high-grade gliomas. *J. Neurooncol.* 132, 239–247 (2017).
37. Xu W-Z, Li F, Xu Z *et al.* Preoperative albumin-to-globulin ratio and prognostic nutrition index predict prognosis for glioblastoma. *Onco. Targets Ther.* 10, 725–733 (2017).
38. Jung J, Lee H, Yun T *et al.* Prognostic role of the neutrophil-to-lymphocyte ratio in patients with primary central nervous system lymphoma. *Oncotarget* 8, 74975–74986 (2017).

• **Explores the prognostic impact of systemic inflammatory biomarker (neutrophil-to-lymphocyte ratio) in PCNSL.**

39. Feng Y, Liu Y, Zhong M, Wang L. Complete blood count ccore model predicts inferior prognosis in primary central nervous system lymphoma. *Front. Oncol.* 11, 618694 (2021).
40. Abrey LE, Ben-Porat L, Panageas KS *et al.* Primary central nervous system lymphoma: the Memorial Sloan–Kettering Cancer Center prognostic model. *J. Clin. Oncol.* 24, 5711–5715 (2006).