Clinical and Translational Oncology
https://doi.org/10.1007/s12094-024-03656-5

RESEARCH ARTICLE

Assessing the prognostic role of panimmune inflammation in high-grade gliomas

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Received: 3 July 2024 / Accepted: 29 July 2024

Abstract

Objective High-grade gliomas are aggressive brain tumors with poor prognoses. Understanding the factors that influence their progression is crucial for improving treatment outcomes. This study investigates the prognostic significance of panimmune inflammation in patients diagnosed with high-grade gliomas.

Materials–Methods Data from 89 high-grade glioma patients were analysed retrospectively. The Panimmune inflammation Value (PIV) of each patient meeting the eligibility criteria was calculated on the basis of platelet, monocyte, neutrophil, and lymphocyte counts obtained from peripheral blood samples taken on the first day of treatment. PIV is calculated using the following formula: $PIV = T \times M \times N \div L$. A receiver operating characteristic (ROC) analysis was employed to identify the optimal cut-off value for PIV about progression-free survival (PFS) and overall survival (OS) outcomes. The primary and secondary endpoints were the differences in OS and PFS between the PIV groups. The Kaplan−Meier method was used for survival analyses.

Results The ROC analysis indicated that the optimal PIV threshold was 545.5, which exhibited a significant interaction with PFS and OS outcomes. Patients were subsequently divided into two groups based on their PIV levels: a low PIV (L-PIV) group comprising 45 patients and a high PIV (H-PIV) group comprising 44 patients. A comparative analysis of survival rates indicated that patients with elevated PIV had a shorter median PFS of 4.0 months compared to 8.0 months in the low PIV group ($P = 0.797$), as well as a reduced median OS of 19.0 months versus not available (NA) in the low PIV group ($P = 0.215$).

Conclusion Our study results did not reveal a statistically significant association between H-PIV measurements and reduced PFS or OS. However, PIV effectively stratified newly diagnosed high-grade glioma patients into two distinct groups with significantly different PFS and OS outcomes.

Keywords High-grade gliomas · Panimmune inflammation · Progression-free survival · Overall survival

Introduction

High-grade gliomas (HGGs) are malignant primary central nervous system tumors (PCNST) that typically exhibit rapid progression. The most prevalent high-grade gliomas (HGGs) in adults are isocitrate dehydrogenase wild-type glioblastoma (grade 4), grade 3 and 4 IDH-mutant astrocytoma, and grade 3 IDH-mutant, 1p/19q-codeleted oligodendroglioma [1]. The median age of onset for HGG is 60–65 years, with a median survival period of 15–20 months and a 5-year survival rate of 5–10% [2, 3].

The most important prognostic variables in patients treated with standard CRT regimens are pathological diagnosis, extent of surgery, ECOG performance status, and age. [4]. As these parameters, other than pathology, are susceptible to subjective conditions, there remains a need for more objective classification methods.

A substantial body of evidence suggests that systemic inflammation plays a pivotal role in the pathogenesis of gliomas, disease progression, and the prognosis of patients undergoing similar therapeutic modalities [5]. Several blood-based indicators of systemic inflammation have been investigated for their potential to predict outcomes in patients with PCNST. The results of these studies have demonstrated a significant correlation between the survival of patients and the levels of these biomarkers, either individually or in combination [6–9]. In contrast to the aforementioned studies,

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Published online: 14 August 2024

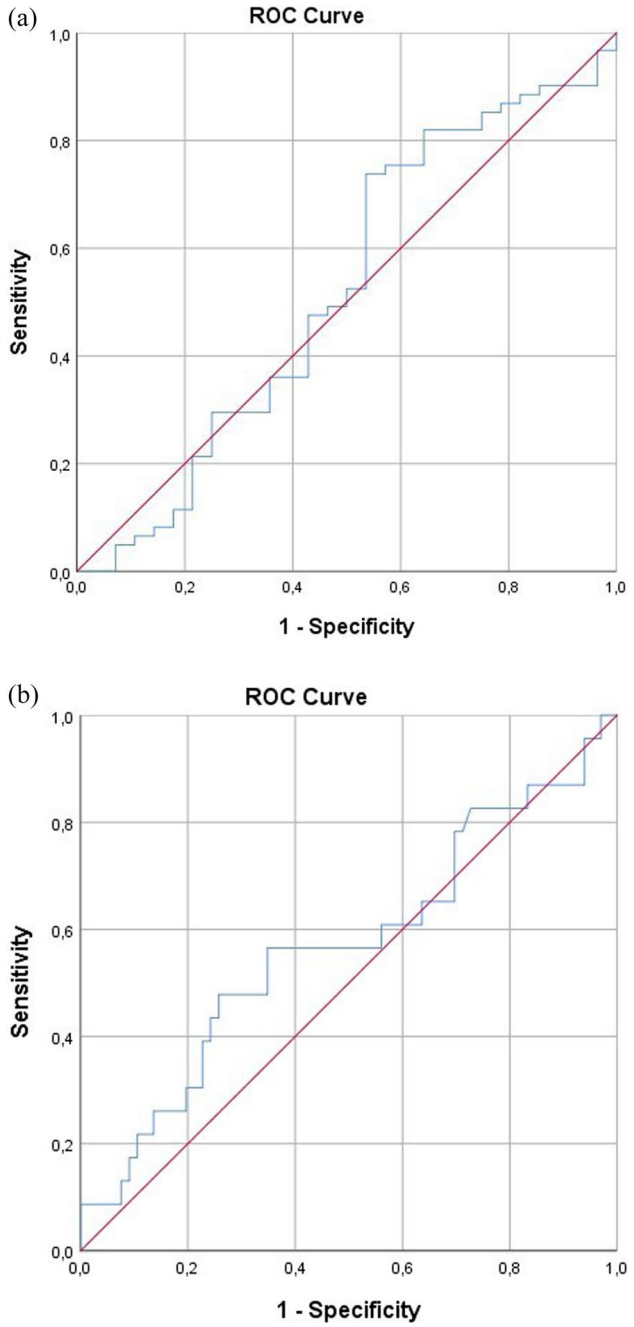


Fig. 1 The results of the receiver operating characteristic curve analyses are presented herewith. **a** Progression-free survival **b** Overall survival

several significant studies have demonstrated that HGGs can skew tumor-associated macrophage and microglia function toward the M2 phenotype. This has been shown to play an important role in immune suppression and the promotion of tumour progression in glioma tissue [10–13]. Both perspectives can be considered valid in their own right.

Previously published reports have demonstrated a robust correlation between Panimmune Inflammation Value (PIV) and progression-free survival (PFS) and overall survival (OS) in patients with advanced colorectal cancer, advanced breast cancer, oesophageal cancer, small cell and non-small cell lung cancers, irrespective of whether they are undergoing surgery and/or systemic therapy [14–18]. One study highlighted the prognostic significance of PIV, particularly in the context of glioblastoma [19].

In light of the dearth of research on HGGs, we undertook a retrospective cohort study to ascertain the potential prognostic utility of PIV in this patient population and to contribute to two distinct hypotheses.

Materials and methods

A retrospective review of the medical records of newly diagnosed patients with HGG was conducted at the Department of Medical Oncology at Etlik City Hospital between September 2022 and December 2023. The eligibility criteria were as follows: patients aged between 18 and 90 years, histologically confirmed glioblastoma according to the WHO classification, IDH-wild type, astrocytoma-IDH-mutant grade 3 or 4, oligodendroglioma-IDH-mutant and 1p/19q codeletion, and grade 3 with no prior chemotherapy or radiotherapy. The study included patients who had undergone preoperative and postoperative gadolinium-enhanced magnetic resonance imaging (MRI) scans, chemotherapy and radiotherapy treatment plans, and pretreatment complete blood count and biochemistry tests. Patients who did not fulfil the requisite criteria were excluded, including those with direct evidence of active infection or a previous history of immunosuppressive disease.

PIV Measurement and statistical analysis

The PIV is calculated by multiplying the recorded numbers of neutrophils, platelets and monocytes at the time of diagnosis and then dividing this product by the number of lymphocytes. The resulting value is expressed as follows: neutrophil count (10^3/MMC) × platelet count (10^3/MMC) × monocyte count (10^3/MMC) ÷ lymphocyte count (10^3/MMC) [20].

A receiver operating characteristic (ROC) analysis was employed to ascertain the optimal cut-off values for the classification of patients as low PIV (L-PIV) or high PIV (H-PIV). A value below the cut-off point is defined as low PIV (L-PIV), while a value above the cut-off point is defined as high PIV (H-PIV). The sensitivity and specificity of the prognosis prediction of the PIV were evaluated using a time-dependent ROC curve.

The primary endpoint, OS, was defined as the interval between the commencement of treatment and the date of death or the last visit. The secondary endpoint, PFS, was

Table 1 Demographic and Clinical Characteristics of the Patients

	Whole cohort (n = 89)	L-PIV < 545.5 (n = 45)	H-PIV > 545.5 (n = 44)	P
Median Age _year	58(25–86)	58(25–86)	59(26–84)	0.75*
Age groups_n (%)				
< 65 years	62(49.5)	30(66.7)	32(72.7)	0.53
≥ 65 years	27(50.5)	15(33.3)	12(27.3)	
Gender, n (%)				
Female	43(48.3)	20(44.4)	23(52.3)	0.46
Male	46(51.7)	25(55.6)	22(47.7)	
Comorbidity_n (%)				
Yes	48(53.9)	25(55.6)	23(52.3)	0.75
No	41(46.1)	20(44.4)	21(47.7)	
Pathological Diagnosis, n(%)				
Glioblastoma	72(80.8)	34(75.6)	38(86.4)	0.19
Astrocytoma	10(11.2)	7(15.6)	3(6.8)	
Oligodendroglioma	7(7.9)	4(8.9)	3(6.8)	
ECOG_n (%)				
0–1	58(65.1)	32(71.1)	26(59.1)	0.44
2	20(22.4)	10(22.2)	11(25.0)	
3	10(11.2)	3(6.7)	6(13.6)	
4	1(1.1)	0(0.0)	1(2.3)	
Multifocal_n (%)				
Yes	11(12.3)	6(13.3)	5(11.4)	0.77
No	78(87.7)	39(86.7)	39(88.6)	
Tumor Volume_n (%) < 200cm^3				
200–400cm^3	3(3.3)	1(2.2)	2(4.5)	0.57
> 400cm^3	43(48.3)	24(53.3)	19(43.2)	
	43(48.3)	19(44.4)	24(52.3)	
Diagnosis _n (%)				
Resection (total + parsial)	83(92.2)	43(95.6)	40(90.9)	0.38
Biopsy	6(6.8)	2(4.4)	4(9.1)	
Resection_n (%)				
Total	57(92.2)	31(72.1)	26(65.0)	0.48
Parsial	26(6.8)	12(27.9)	14(35.0)	
IDH_n (%)				
Mutant	19(21.3)	12(26.7)	7(15.9)	0.21
Wild	70(78.7)	32(73.3)	38(84.1)	

Pearson χ^2 test

ECOG Eastern cooperative oncology group performance status, *IDH* isocitrate dehydrogenase

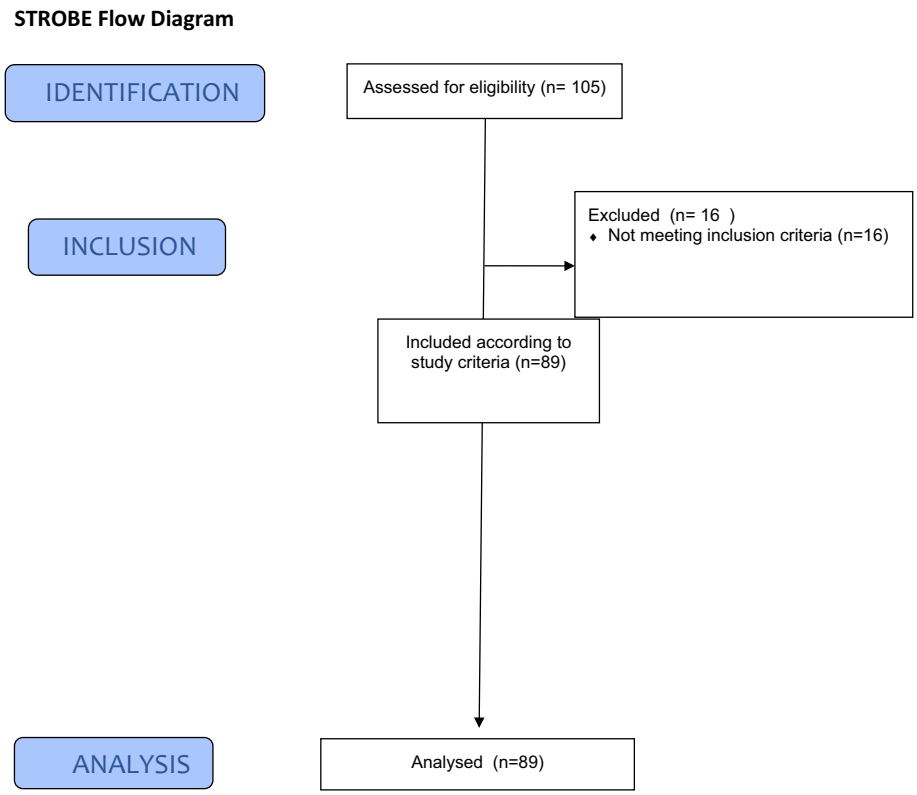
*Mann–Whitney U Test

defined as the interval between the commencement of treatment and the date of the initial observation of relapse or death/last visit.

Quantitative variables were expressed as mean and range, while categorical variables were defined in terms of percentage frequency distributions. The chi-square test and the Mann–Whitney U test were employed to analyse the association between PIV groups and other clinicopathological characteristics.

Kaplan–Meier survival curves were employed to estimate survival outcomes, and log-rank test analyses were conducted for intergroup comparisons. Cox proportional hazard models were employed to derive estimates of hazard ratios (HRs) in univariable models. A two-tailed p-value of less than 0.05 was considered to indicate statistical significance. The statistical analyses were conducted using the SPSS version 25 software.

Results



The median age of the patients included in the study was 58 years (range: 25–86 years). Of the patients included in the study, 46 (51.7%) were male and 43 (48.3%) were female. The primary diagnoses of the patients are as follows: The majority of patients (72, 80.8%) had been diagnosed with glioblastoma, while a smaller proportion (10, 11.2%) had been diagnosed with astrocytoma and a further 7 (7.9%) with oligodendroglioma. With regard to the performance status at the time of diagnosis, 58 patients (65.1%) exhibited an ECOG PS of 0–1. A total of 83 patients (92.2%) were diagnosed through total or partial resection, while 6 patients (6.8%) were diagnosed through biopsy. The optimal PIV limits, as determined by ROC curve analysis, were 545.5 (area under the curve [AUC]), with a sensitivity of 53.5% and a specificity of 54% (Fig. 1). No statistically significant differences were observed in the demographic or clinical characteristics between the L-PIV and H-PIV groups. Table 1 presents a summary of the demographic and clinical characteristics of the 89 patients who participated in the study.

A total of 81 patients (91.0%) received standard TMZ concurrent with RT treatment after diagnosis, as determined through an evaluation of the treatment characteristics and clinical outcomes. Due to the age of the patients, the presence of comorbidities, and their performance status, four patients (4.5%) received only RT as adjuvant treatment, while four patients (4.5%) did not receive any treatment. A total of 72 (79.7%) of the entire cohort received maintenance TMZ following chemoradiotherapy (CRT), while 34 (38.2%) of the patients received treatment for a minimum of six months. Of the 28 patients who experienced relapse, 14 were in the L-PIV cohort and 14 were in the H-PIV cohort. A total of 66 patients (74.2%) were still alive at the time of the analysis, and 60 patients (67.4%) remained progression-free after a median follow-up period of 10.85 months (range = 0–104). A summary of the treatment characteristics and clinical outcomes is provided in Table 2.

The median estimated PFS of the cohort was 6.0 months (95% confidence interval (CI): 3.08–8.91 months), while the median PFS in the L-PIV cohort was 8.0 months (95% confidence interval (CI): 1.5–12.5 months), and that in the H-PIV cohort was 4.0 months (95% confidence interval (CI): 0.46–7.53 months). No significant differences were observed between the cohorts. ($p = 0.797$) (Fig. 2).

Table 2 Patients Treatment characteristics and clinical outcomes

	Whole cohort (n = 89)	L-PIV < 545.5 (n = 45)	H-PIV > 545.5 (n = 44)	P
CRT_n (%)				
Yes	81(91.0)	42(93.3)	39(88.6)	0.57
RT only	4(4.5)	2(4.4)	2(4.5)	
No	4(4.5)	1(2.2)	3(6.8)	
Maintenance TMZ _n (%)	72(79.7)	40(88.9)	32(72.7)	0.05
Duration of TMZ n (%)				
1–6 months	38(42.6)	19(47.5)	19(59.4)	0.31
7–12 months	34(38.2)	21(52.5)	13(40.6)	
Recurrence, n(%)				
Yes	28(31.4)	14(31.1)	14(32.6)	0.88
No	60(67.4)	31(68.9)	29(62.9)	
Recurrence, n(%)				
Local	25(89.2)	13(92.9)	12(85.7)	0.54
Multifocal	3(3.3)	1(7.1)	2(14.3)	
Resurgery n (%)				
Yes	19(67.8)	10(71.4)	9(64.3)	0.68
No	9 (32.1)	4(28.6)	5(35.7)	
After recurrence_n (%)				
Did not receive	11(39.2)	6(46.2)	5(35.7)	0.21
TMZ	7(25)	5(38.5)	2(14.3)	
BEVA	2(7.1)	1(7.1)	1(7.2)	
BEVIRI	4(14.2)	0(0.0)	4(28.5)	
Karmustin	2(7.1)	1(7.1)	1(7.2)	
IMRT	2(7.1)	1(7.1)	0(0.0)	
Ex_n(%)	23(25.8)	10(22.2)	13(29.5)	0.43
Alive_n(%)	66(74.2)	35(77.8)	31(70.5)	
PFS(months)	6.0	8.0	4.0	0.78*
OS(months)	31.0	NA	19	0.21*

OS overal survival, *PFS* progression free survival, *TMZ* temozolamide, *CRT* chemo-radiotherapy

*Log-rank(%95 confidence interval)

The estimated median OS in the study cohort was 31 months (95% CI: 12.2–54.9 months). Median OS was not reached in the L-PIV cohort (95% CI: 19.0-NA months) and was 19.0 months in the H-PIV cohort (95% CI: 11.9–26.0 months). No significant difference was observed between the cohorts (p = 0.215) (Fig. 3).

The results of the univariate analyses indicated that patients aged 65 years or older (p = 0.02), patients with a pathological diagnosis of glioblastoma (p = 0.003) and patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or higher (p < 0.001) were significantly associated with significantly worse OS, however, the same statistical significance was not observed in the PIV groups (Table 3).

Discussion

The objective of this retrospective cohort study was to assess the prognostic value of PIV in patients with newly diagnosed HGG. The findings of this study did not demonstrate a notable correlation between patients' adverse immune-inflammatory status and unfavourable clinical outcomes. Specifically, a higher PIV (≥ 545) was not found to be significantly associated with worse PFS or OS outcomes, independent of other prognostic variables, namely, well-known tumour resection type, age and performance status.

The current gold standard treatment for high-grade gliomas (HGGs), particularly glioblastoma, is maximal safe resection followed by adjuvant therapy. This comprises temozolomide (TMZ) concurrent chemoradiotherapy (cCRT) and six months of maintenance TMZ [21]. The Stupp protocol, which is also referred to as such, comprises the administration of radiotherapy in conjunction with 75 mg/m^2/day TMZ concurrently with 2 Gy fractions, resulting in a total dose of 60 Gy. This is followed by six cycles of TMZ monotherapy. This treatment approach has been observed to enhance overall survival in patients under the age of 70 with a favourable performance status [22]. In elderly patients and/or patients with a very poor performance status, supportive care may be deemed an appropriate approach [23]. In the course of our study, the majority of patients completed the CRT programme, with nearly 80% subsequently undergoing maintenance TMZ treatment.

The therapeutic modalities endorsed in the literature on disease progression have been demonstrated to enhance disease survival and are endorsed by international guidelines [24–26]. In the course of our study, 19 of the 28 patients who exhibited signs of disease progression underwent reoperation, with approximately 60% of these patients receiving sequential treatment. The longer estimated overall survival (OS) in the short-term follow-up period may be attributed to the efficacy of the administered treatment. Indeed, although not included in the guidelines, a case-based study demonstrated that durable complete remission could be achieved through the combined use of anti-VEGF and anti-EGFR in HGG [27].

A review of the literature reveals a paucity of studies evaluating the prognostic significance of PIV for HGG patients, with findings that are inconclusive and contradictory. Similarly, Chaichana et al. proposed that age and comorbidities are not reliable predictors of survival, a conclusion that aligns with our own findings [28]. Conversely, a recent study demonstrated that PIV has robust and independent prognostic value in glioblastoma patients. Patients with PIV ≥ 385 exhibited significantly shorter median

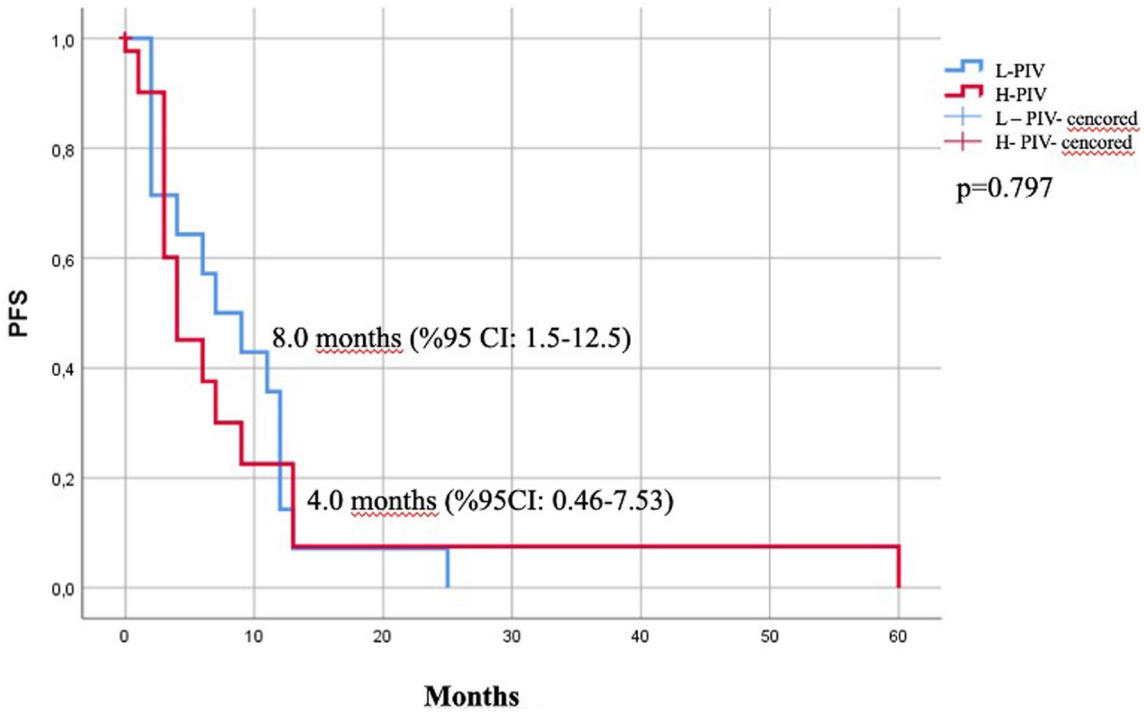


Fig. 2 Kaplan–Meier Estimates of Progression-Free Survival According to PIV

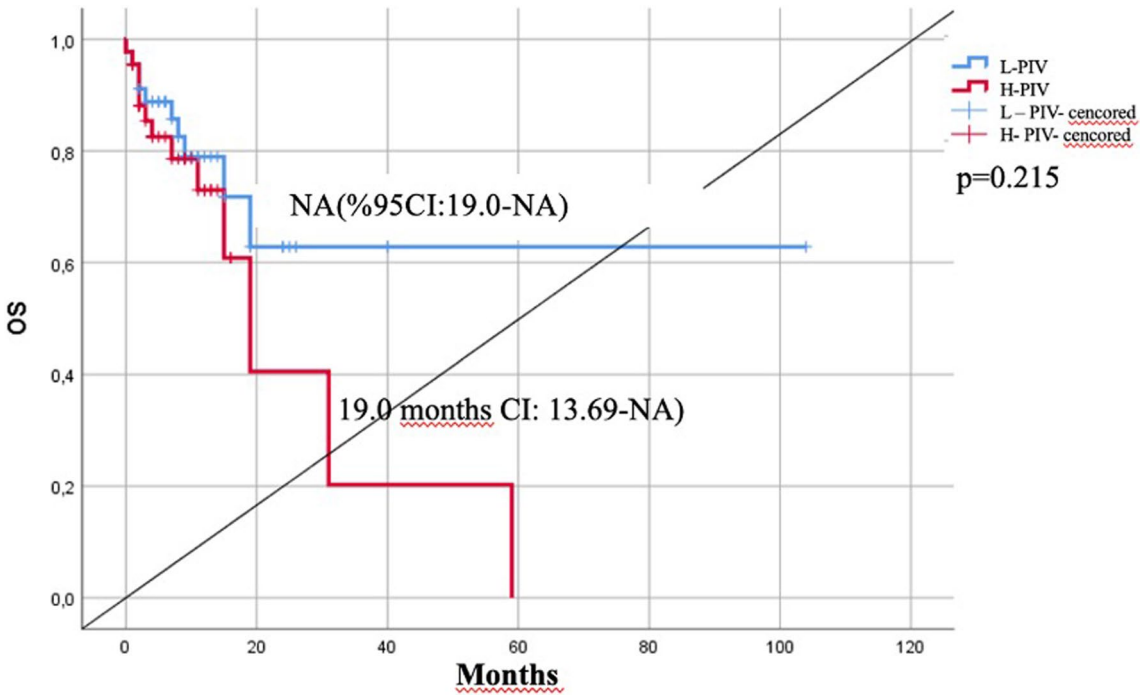


Fig. 3 Kaplan–Meier Estimates of Overall Survival According to PIV

Table 3 Univariate analysis results

Characteristic	Patients	Median PFS (months)	P	Median OS (months)	P
Age groups					
< 65 years	62	10.5	0.48	31.0	**0.02**
≥ 65 years	27	4.0		15.0	
Gender					
Woman	43	7.0	0.59	31.0	0.14
Male	46	6.0		19.0	
Comorbidity					
Yes	48	7.0	0.84	19.0	0.26
No	41	4.0		59.0	
Pathological Diagnosis					
Glioblastoma	72	4.0	**0.04**	19.0	**0.003**
Other	17	12.0		59.0	
ECOG					
0–1	58	4.0		31.0	**< 0.001**
2	21	8.0	0.73	19.0	
3	9	NA		2.0	
4	1	NA		NA	
Multifocal					
Yes	11	4.0	0.68	31.0	0.96
No	78	7.0		59.0	
TumorVolume					
$< 200cm^3$	3	NA		NA	0.54
200–400	43	7.0	0.92	31.0	
$> 400cm^3$	43	5.0		NA	
Diagnosis					
Resection	83	6.0		31.0	0.90
Biopsy	6	3.0	0.35	NA	
Resection					
Total	57	4.0		31.0	0.16
Parsial	26	11.5	0.10	NA	
PIV groups					
L-PIV	45	8.0	0.78	NA	0.21
H-PIV	44	4.0		19.0	

Bold values are statistically significant

OS (12.2 vs. 22.9 months; $P < 0.001$) and PFS (10.3 vs. 16.2 months; $P < 0.001$) than those with PIV < 385[19]. Despite a numerical difference in PFS and OS between the low and high PIV groups, no statistically significant correlation was identified.

A systematic review and meta-analysis of the relationship between PIV and cancer prognosis was conducted, encompassing 15 studies with a total of 4942 patients. The findings indicated that high PIV was a significant contributor to the risk of death and progression (HR: 2.00, 95% CI: 1.51–2.64, $p < 0.001$ and HR: 1.80, 95% CI: 1.39–2.32, $p < 0.001$, respectively) [29].

Despite the demonstrated efficacy and success of immune checkpoint inhibitors in the treatment of other cancers, clinical trials on PCNSTs, particularly glioblastoma, utilising these drugs have not yielded improvements in the efficacy or prognosis of patients receiving immune checkpoint inhibitors [30]. The findings of this study, in alignment with those of the preceding studies, indicate that PIV may possess prognostic significance in cancers where treatment options are directly proportional to tumour immunogenicity. However, this may not be accepted as a prognostic factor in primary central nervous system tumours where immunotherapy, also known as immune desert, is not effective. The findings of our study lend support to this hypothesis.

The current study is constrained by a number of factors. It is important to note that this study is a single-centre retrospective cohort analysis, lacking a validation cohort. Consequently, the findings are subject to the limitations inherent to such studies, including the potential for selection bias. Secondly, a PIV group-specific analysis of genetic markers was not feasible due to the absence of patient identification and categorisation by MGMT methylation, isocitrate dehydrogenase-1 (IDH-1), and IDH-2, PDGF, PTEN, EGFR, p53, ATRX, and TERT status. Thirdly, while individual or simultaneous wide variations in the counts of PIV components may significantly alter the optimal cut-off value during RT plus TMZ and maintenance TMZ periods, it should be noted that our PIV measurements and associated cut-off values reflect the results of only a single timepoint snapshot. It is therefore recommended that our findings be treated with caution and considered as hypothesis-generating rather than definitive guidelines until the results of appropriately designed large-scale investigations become available.

Notwithstanding the aforementioned limitations, it is hypothesised that the findings will prove useful in the prognostic stratification of such patients. This will facilitate the prediction of patient prognosis and, with the advent of more effective drugs, will inform the selection of optimal treatment options.

Conclusion

Further research is required to substantiate the findings of the current study; however, they indicate that PIV, a cost-effective, non-invasive, readily accessible, straightforward to calculate and reproducible biomarker, was capable of independently categorising newly diagnosed HGGs into two groups with significantly disparate PFS and OS outcomes, although this distinction lacked statistical significance.

Data availability The datasets generated and examined in the present study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors affirm that they do not have any conflicts of interest related to the publication of this article.

Ethical approval Prior to the commencement of data collection, the study design was approved by the Etlik City Hospital review board.

Informed consent We confirm that written informed consent has been obtained from the involved patient(s) or if appropriate from the parent, guardian, or power of attorney of the involved patient(s); and, they have approved for this information to be published in this case report (series). Complete written informed consent was obtained from the patient for the publication of this study and accompanying images.

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