ANNALS of Clinical and Translational Neurology
Open Access
AMERICAN NEUROLOGICAL ASSOCIATION

BRIEF COMMUNICATION

Plasma β-synuclein, GFAP, and neurofilaments in patients with malignant gliomas undergoing surgical and adjuvant therapy

Samir Abu-Rumeileh[1], Lorenzo Barba[1], Matthias Bache[2], Steffen Halbgebauer[3,4], Patrick Oeckl[3,4], Petra Steinacker[1], Antje Güttler[2], Jacqueline Keßler[2], Jörg Illert[5], Christian Strauss[5], Dirk Vordermark[2] & Markus Otto[1]

[1]Department of Neurology, Martin-Luther-University Halle-Wittenberg, Halle (Saale), 06120, Germany
[2]Department of Radiotherapy, Martin-Luther-University Halle-Wittenberg, Halle (Saale), 06120, Germany
[3]Department of Neurology, Ulm University Hospital, Ulm, Germany
[4]German Center for Neurodegenerative Diseases Ulm (DZNE e. V.), Ulm, Germany
[5]Department of Neurosurgery, Martin-Luther-University Halle-Wittenberg, Halle (Saale), 06120, Germany

Correspondence
Markus Otto, Department of Neurology, Martin-Luther-University Halle-Wittenberg, Halle (Saale) 06120, Germany. Tel: +49 345 557 2858; Fax: +49 345 557 2860; E-mail: markus.otto@uk-halle.de

Received: 6 June 2023; Revised: 17 July 2023; Accepted: 5 August 2023

***Annals of Clinical and Translational Neurology* 2023; 10(10): 1924–1930**

doi: 10.1002/acn3.51878

Abstract

We analyzed the longitudinal concentrations and prognostic roles of plasma β-synuclein (β-syn), glial fibrillary acidic protein (GFAP), and neurofilament proteins (NfL and NfH) in 33 patients with malignant gliomas, who underwent surgical and adjuvant therapy. GFAP and NfL levels were increased in patients with glioblastoma compared to cases with other tumors. β-syn, NfL and NfH increased after surgery, whereas GFAP decreased at long-term follow-up. β-syn and neurofilament concentrations were influenced by surgery and/or radiotherapy regimens. GFAP and neurofilament levels were significantly associated with survival. Plasma neuronal and astrocytic biomarkers are differentially altered in malignant glioma types and displayed distinct trajectories after surgical and adjuvant therapy.

Introduction

Malignant gliomas are the most common and aggressive primary tumors of the central nervous system in adult patients.[1,2] Biofluid markers are urgently needed to optimize the prognostic assessment and monitor treatment responsiveness as well as tumor recurrence. Blood neurofilament light (NfL) and heavy (NfH) chain proteins, and glial fibrillary acidic protein (GFAP) are well-established neuronal and astrocytic biomarkers, respectively[3,4]; however, their potential application in malignant gliomas has not been fully explored.[4-8] Furthermore, β-synuclein (β-syn) is emerging as a promising synaptic marker in several neurological diseases,[9-12] and might be of interest in the neuro-oncological field, given its high expression in glioma tissues.[13]

In this study, we investigated the longitudinal concentrations and prognostic value of plasma β-syn, GFAP, NfL, and NfH proteins in a cohort of patients with malignant gliomas, who underwent surgical and adjuvant therapy.

Methods

Selection criteria

We retrospectively analyzed 105 blood samples obtained from 33 patients with malignant gliomas, recruited from 2008 to 2010 at the Department of Neurosurgery, Martin-Luther-University Halle-Wittenberg (Halle, Germany). Patient demographical and clinical characteristics as well as diagnostic and treatment data are reported in the supplementary methods and elsewhere.[14] Briefly, preoperative neuroimaging data were collected for each patient.[14] Complete and incomplete resection were performed in 16 and 17 patients, respectively.[14] Histological analysis revealed a glioblastoma or other malignant gliomas in 21 and 12 patients, respectively.[14,15] Thirty-one of the 33 patients underwent radiotherapy (mean total dose 54 Gy, total dose ≤54 Gy $n = 11$, > 54 Gy $n = 20$).[14] We calculated the overall survival as the time (in months) from the first blood collection to death or date of the last follow-up information (September 2011).[14] The study

was carried out in compliance with the Helsinki Declaration and was approved by the Ethics Committee of the Medical Faculty of the Martin-Luther-University Halle-Wittenberg (/2008).

Biomarker analyses

EDTA plasma samples were collected at scheduled timepoints and processed according to standard procedures. Timepoints were the following: before surgery (t0) (n = 28), after surgery and before starting radiotherapy (t1) (n = 30), at the end of radiotherapy (t2) (n = 28), and at the first post-treatment follow-up 4–8 weeks after the end of radiotherapy (t3) (n = 19).[14] Mean interval times are reported in the supplementary methods. Plasma β-syn, GFAP, NfL, and NfH were analyzed according to previously reported protocols (details in the supplementary methods).[10,11,16,17]

Statistical analyses

We used the Mann–Whitney U-test and Kruskal–Wallis test (followed by Dunn-Bonferroni post hoc test) to compare continuous variables, depending on the number of the groups. Spearman's correlations and multivariable linear regression analyses were used to test the possible associations between variables. Kaplan–Meier analyses as well as univariate and multivariate Cox regressions investigated the associations between survival, each blood biomarker and/or known prognostic factors[18] in malignant gliomas (details in the supplementary methods).

Results

Associations between plasma biomarkers and clinical variables

At t0, both plasma GFAP and NfL were moderately to strongly correlated with preoperative tumor volume (GFAP: r = 0.617, p = 0.002; NfL: r = 0.479, p = 0.018) and necrotic volume (GFAP: r = 0.757, p < 0.001; NfL: r = 0.604, p = 0.004), whereas β-syn was moderately associated with necrotic volume (r = 0.439, p = 0.047). NfH did not correlate with any neuroradiological variable.

Patients with glioblastoma had increased GFAP (t0: p < 0.001, t1: p = 0.004; t2: p = 0.001; t3: p = 0.014) and NfL (t0: p < 0.001, t1: p = 0.003; t2: p = 0.001; t3: p = 0.007) levels compared to those with other tumors, whereas β-syn and NfH values did not differ between the two groups (Fig. 1A). Given the higher mean preoperative tumor volume in glioblastomas compared to other tumors (p = 0.038, supplementary methods), we performed the comparisons at t0 after adjustment for tumor volume and confirmed the same results (GFAP: β = 0.637, p < 0.001; NfL: β = 0.599, p = 0.003). Associations between biomarkers and demographical variables are reported in the supplementary results.

Time course of plasma biomarkers and effect of therapeutic regimens on biomarker levels

In the entire cohort, β-syn, NfL and NfH levels increased after surgery (β-syn: t1–t0: 2.4-fold, p = 0.004; t2–t0: p = 0.034; NfL: t1–t0: 2.9-fold, p = 0.003; t2–t0: p = 0.047; NfH: t1–t0: 2.5-fold, p = 0.006; t2–t0, p = 0.040) and showed a nonsignificant decreasing trend at follow-up (Tables 1 and 2 and Fig. 1B). Conversely, GFAP levels did not increase significantly after surgery, but decreased significantly at long-term follow-up (t3–t1: p = 0.007) (Fig. 1B).

The type of surgery influenced both β-syn and neurofilament (NfL and NfH) but not GFAP levels (Tables 1 and 2). Specifically, β-syn increased after both complete and incomplete resection (t1–t0: complete: 1.9-fold, p = 0.022; subtotal: 4.8-fold, p = 0.027) but remained significantly high only after incomplete resection (t2–t0: p = 0.031) before reducing at follow-up, whereas the concentrations decreased early after complete resection (t3–t1: 2.5-fold, p = 0.025) (Fig. 1C). Generally, incomplete resection was associated with significantly higher β-syn values at t2 (p = 0.002) and t3 (p = 0.028) compared to complete

Figure 1. (A) Distribution of plasma β-syn, GFAP, NfH, and NfL levels in patients with glioblastoma and in those with other malignant gliomas. Groups were compared by Kruskal–Wallis test and Dunn's post hoc test. Data are shown as medians and IQRs. (B) Time course of plasma β-syn, GFAP, NfH, and NfL in the entire cohort at different timepoints [preoperative phase (t0), after surgery and before adjuvant therapy (t1) and after adjuvant therapy (t2 and t3)]. As plasma concentrations of GFAP differed by several orders of magnitude from other biomarkers, units were adjusted to align all time courses in one graph. β-syn, NfH, and NfL are presented as log(pg/mL), whereas GFAP values as log(ng/mL). Data are shown as medians and IQRs. (C) Time course of plasma β-syn in patients undergoing complete or incomplete resection. β-syn is presented as log (pg/mL). Data are shown as medians and IQRs. (D) Time course of plasma NfL and NfH in patients undergoing complete or incomplete resection. NfH and NfL are presented as log(pg/mL). Data are shown as medians and IQRs. (E) Time course of plasma β-syn in patients undergoing radiotherapy at high (>54 Gy) or low total dose (≤54 Gy). β-syn is presented as log(pg/mL). Data are shown as medians and IQRs. (F–H) Survival curves in the entire cohort according to the values of significantly prognostic blood biomarkers: GFAP (F), NfL (G), NfH (H). Biomarker levels have been stratified in low and high levels with respect to their median values (GFAP: 2403 pg/mL, NfL: 114 pg/mL, NfH: 868 pg/mL). The cumulative time-dependent probability of survival was calculated by the Kaplan–Meier estimate. The reported p-values refer to the log rank test.

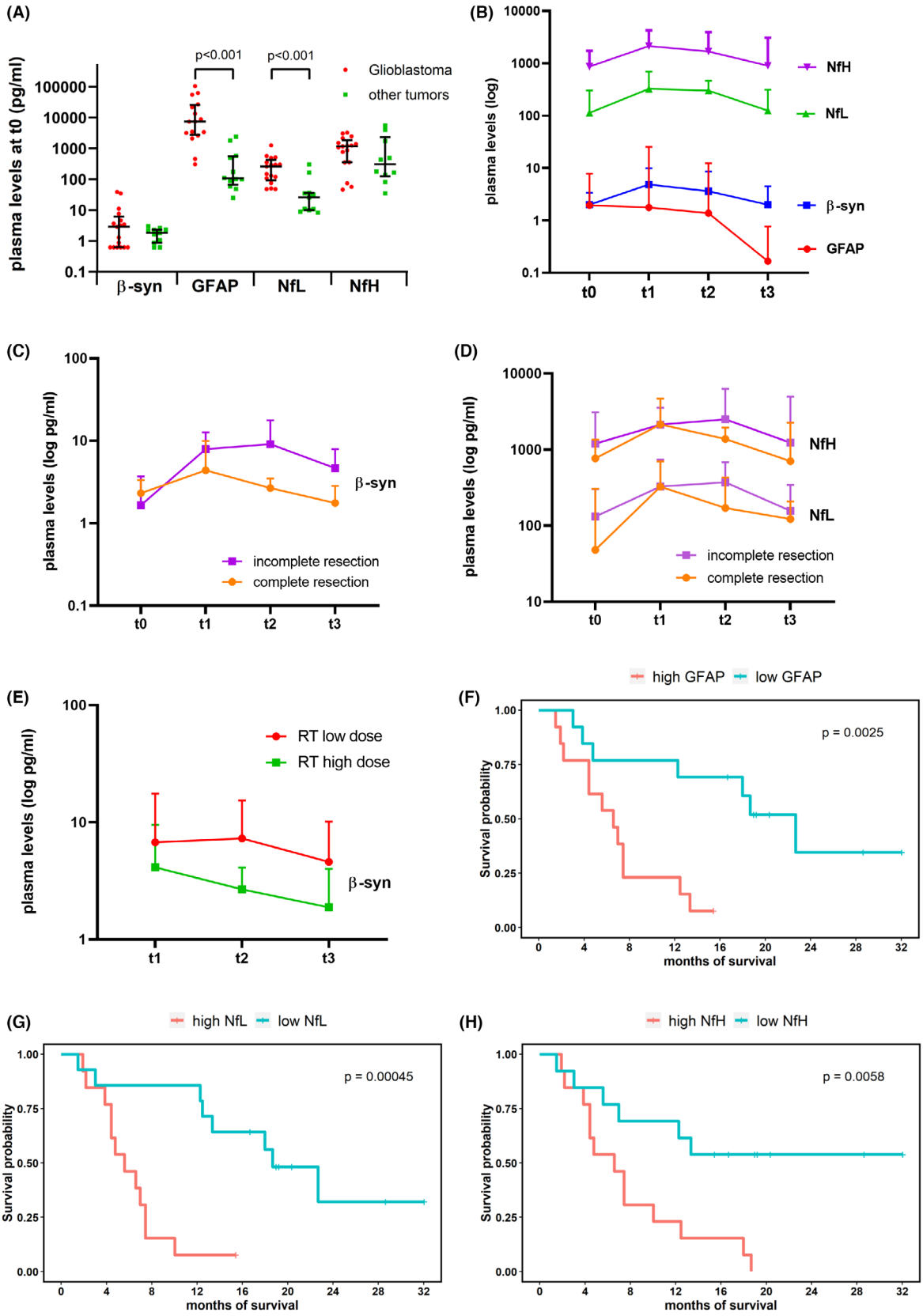

Table 1. Time course of plasma β-syn and GFAP in patients with malignant gliomas.

β-syn	Subgroup	Baseline t0 (pg/mL)	After surgery t1 (pg/mL)	End of radiotherapy t2 (pg/mL)	Post-radiotherapy follow-up t3 (pg/mL)
Entire cohort		2.01 (0.63–3.40)	4.86 (2.68–10.11)	3.47 (2.32–7.92)	2.00 (1.32–4.50)
Type of tumor	Glioblastoma (n = 21)	2.89 (0.63–6.14)	9.08 (3.49–10.59)	3.83 (2.93–8.17)	3.11 (1.00–4.31)
	Other tumors (n = 12)	1.84 (0.88–2.31)	2.85 (2.12–6.75)	2.14 (1.61–11.13)	1.89 (1.45–5.64)
Type of surgery	Complete resection (n = 16)	2.31 (0.75–3.33)	4.38 (2.17–9.97)	2.68 (2.03–3.49)	1.76 (1.24–2.83)
	Incomplete resection (n = 17)	1.66 (0.63–3.69)	7.91 (2.84–12.67)	9.11 (4.10–17.76)	4.67 (2.67–7.90)
Radiotherapy total dose	≤54 Gy (n = 11)	–	6.75 (1.19–17.51)	7.28 (3.68–15.34)	4.59 (3.46–4.83)
	>54 Gy (n = 20)	–	4.12 (2.80–9.52)	2.68 (1.94–4.10)	1.88 (1.22–3.99)

GFAP	Subgroup	Baseline t0 (pg/mL)	After surgery t1 (pg/mL)	End of radiotherapy t2 (pg/mL)	Post-radiotherapy follow-up t3 (pg/mL)
Entire cohort		2403 (111–8727)	2495 (781–25962)	1242 (323–6548)	471 (173–1220)
Type of tumor	Glioblastoma (n = 21)	7452 (2766–25507)	13241 (1887–55960)	2278 (1042–17548)	931 (598–2609)
	Other tumors (n = 12)	102 (59–572)	858 (170–2153)	271 (130–740)	223 (155–399)
Type of surgery	Complete resection (n = 16)	2624 (101–8104)	2803 (645–13597)	1054 (323–2079)	531 (221–1135)
	Incomplete resection (n = 17)	2105 (274–34006)	2153 (781–63176)	1233 (350–2861)	335 (137–1421)
Radiotherapy total dose	≤54 Gy (n = 11)	–	13954 (1199–55045)	4042 (1942–26998)	701 (221–2118)
	>54 Gy (n = 20)	–	1774 (395–13372)	742 (260–1330)	335 (173–1220)

Values are given in median and interquartile range.
β-syn, beta-synuclein protein; GFAP, glial fibrillary acidic protein; Gy, grays.

Table 2. Time course of plasma neurofilament proteins (NfL and NfH) in patients with malignant gliomas.

NfL	Subgroup	Baseline t0 (pg/mL)	After surgery t1 (pg/mL)	End of radiotherapy t2 (pg/mL)	Post-radiotherapy follow-up t3 (pg/mL)
Entire cohort		113.5 (32.7–301.5)	326.5 (155.0–691.3)	301.5 (111.3–465.8)	125.0 (55.2–313.0)
Type of tumor	Glioblastoma (n = 21)	259.0 (91.2–425.0)	535.0 (250.0–922.0)	400.0 (169.9–627.0)	192.0 (141.0–383.5)
	Other tumors (n = 12)	26.1 (10.0–36.4)	131.0 (57.9–276.0)	98.8 (50.2–223.5)	69.7 (52.1–143.5)
Type of surgery	Complete resection (n = 16)	48.1 (11.0–307.0)	326.5 (188.0–702.3)	171.5 (111.3–430.8)	122.5 (87.7–208.5)
	Incomplete resection (n = 17)	132.0 (36.4–302.0)	328.4 (103.0–740.0)	372.0 (95.7–684.3)	157.0 (53.3–343.0)
Radiotherapy total dose	≤54 Gy (n = 11)	–	535.0 (250.0–1096.0)	429.5 (355.8–780.8)	252.5 (88.0–410.5)
	>54 Gy (n = 20)	–	209.0 (104.0–551.0)	163.5 (68.5–341.3)	120.0 (55.2–214.0)

NfH	Subgroup	Baseline t0 (pg/mL)	After surgery t1 (pg/mL)	End of radiotherapy t2 (pg/mL)	Post-radiotherapy follow-up t3 (pg/mL)
Entire cohort		868 (165–1729)	2144 (1020–4267)	1686 (426–3938)	901 (225–3087)
Type of tumor	Glioblastoma (n = 21)	1160 (356–1826)	2205 (1554–45761)	1950 (1439–4282)	1350 (634–3730)
	Other tumors (n = 12)	305 (124–2300)	1519 (489–3693)	422 (218–2389)	480 (214–1811)
Type of surgery	Complete resection (n = 16)	769 (78–1353)	2145 (1148–4692)	1382 (298–1955)	707 (248–2262)
	incomplete resection (n = 17)	1201 (306–3116)	2144 (877–3544)	2514 (921–6315)	1234 (225–4961)
Radiotherapy total dose	≤54 Gy (n = 11)	–	1554 (489–2972)	3296 (1698–6256)	2065 (430–4052)
	>54 Gy (n = 20)	–	268 (80–1364)	709 (247–2147)	567 (224–2566)

Values are given in median and interquartile range.
Gy, grays; NfH, neurofilament heavy chain protein; NfL, neurofilament light chain protein.

resection (Fig. 1C). Moreover, NfL and NfH showed a similar time course to that of β-syn after complete and incomplete resections, but the postoperative increase was statistically significant only after complete surgery (NfL: t1–t0: 6.8-fold, $p = 0.009$; t2–t0: $p = 0.042$; NfH: t1–t0: 2.8-fold, $p = 0.008$) (Fig. 1D).

A radiotherapy total dose >54 Gy was associated with a significant reduction in β-syn concentrations (t3–t1: 2.2-fold, $p = 0.008$). Indeed, patients receiving a total dose ≤54 Gy demonstrated significantly higher β-syn levels at t2 ($p = 0.003$) and t3 ($p = 0.046$) compared to the other subgroup (Fig. 1E). In both subgroups receiving a total dose ≤ or >54 Gy, GFAP levels displayed a tendency toward decreasing values (t1–t3: $p = 0.037$ and $p = 0.027$, respectively, after multiple comparison correction both not significant). No effect of radiotherapy total dose was seen on NfL and NfH levels.

The same analyses in the group of patients with glioblastoma are reported in the supplementary results.

Associations between plasma biomarkers and survival

Following univariate Cox regression analysis, significant associations with survival were found in the entire cohort for plasma GFAP (hazard ratio and 95% confidence interval, HR (95%CI): 1.629 (1.237–2.143), $p < 0.001$), NfL (HR: 2.573 (1.561–4.239), $p < 0.001$) and NfH (HR: 1.652 (1.107–2.465), $p = 0.014$) (Table S1). Similarly, patients with higher levels of all three biomarkers had shorter survival times at Kaplan–Meier survival analyses (Fig. 1F–H). Multivariate analyses and sub-analyses in glioblastoma patients are reported in the supplementary results and in Tables S1–S5.

Discussion

In this study, we described the temporal pattern and prognostic value of plasma β-syn, GFAP, and neurofilament proteins (NfL and NfH) in patients with malignant gliomas who underwent surgical and adjuvant therapy.

First, we found a postinterventional increase in plasma β-syn values irrespective of the extent of surgery. In this regard, the acute synaptic disruption following a surgical traumatic injury might be responsible for the release of β-syn from the pre-synaptic terminals and for its acute raise in blood in the postoperative phase. Similarly, we previously reported elevated blood β-syn levels in patients with traumatic brain injury.[11] However, we found sustained high β-syn levels after an incomplete resection but an early decline at follow-up following a complete resection. Here, we could speculate that the presence of residual tumor might lead to persistent structural damage or, alternatively, to chronic protein release/leakage[13] or both. In accordance with the latter hypothesis, we found a significant decrease of β-syn in patients treated with a high radiotherapy total dose, suggesting the possible effect of the adjuvant regimen in mitigating β-syn release.

As previously reported,[4–6] we found higher GFAP levels in glioblastoma compared to other tumors and strong associations between the biomarker levels and preoperative tumor or necrosis volume. Considering the latter finding,[4–6] the correlations between GFAP blood levels and expression in tumor tissue[6] and the decline of plasma GFAP in our cohort at long-term follow-up, the marker might be potentially used to measure the efficacy of treatment and/or residual disease.

Moreover, we observed increased NfL levels in glioblastoma patients and temporal patterns of both NfL and NfH similar to that of β-syn after the two types of surgery (see above), providing further evidence for the high sensitivity of plasma neurofilaments to track acute neuroaxonal damage after neurosurgical procedures.[19]

Although, we cannot exclude the normal physiological kinetics of the biomarkers contributing to our findings. Specifically, given their long half-life and slow turn-over inside neurons, neurofilaments can accumulate over a period of weeks after neuronal damage and gradually decrease.[3,20] In contrast, serum GFAP peaks at 20 hours following brain injury, and declines over 72 hours with an estimated half-life of 24–72 hours.[4,21] These data may, thus, partially explain the relatively steady levels of neurofilaments after surgery compared to the rapid decline of GFAP at follow-up in our cohort.

Concerning the prognostic value of blood biomarkers, further studies are needed to better investigate this issue, given that, in our cohort, baseline GFAP, NfL, and NfH demonstrated a moderate association with survival only with univariate Cox regression analysis. Similarly, their performance should be compared to that of other candidate prognostic biomarkers (i.e., galectin-1, long noncoding RNAs, pyroptosis-related genes).[22–24]

Overall, the major strengths of our study comprise its longitudinal nature and the exploitation of immunoassays with higher sensitivity and readout resolution compared to those used in previous studies.[4] Nevertheless, potential limitations include the small sample size, and the lack of longitudinal volumetric data, as well as the absence of healthy or tumor control groups not undergoing surgical and/or adjuvant therapy. Furthermore, although our cases were diagnosed according to the past WHO classification of tumors of the central nervous system (due to the lack of molecular characterization at the time of patient recruitment),[14,15] the biomarker distribution in the comparison of glioblastoma with other tumors may maintain its validity even according to the new 2021 classification.[25]

In conclusion, plasma β-syn, GFAP, and neurofilaments are differentially altered according to the subtype of malignant glioma and showed distinct trajectories after surgical and adjuvant therapy. Studies on larger cohorts might better clarify the relative contribution of surgical and adjuvant therapies to blood biomarker dynamics.

Author Contributions

Conception and design of the study: SAR, MB, DV, and MO; sample collection, acquisition, and analysis of data: SAR, LB, MB, SH, PO, PS, AG, JK, JI, CS, DV, and MO; drafting of the manuscript: SAR and MO; critical revision and final approval of the manuscript: SAR, LB, MB, SH, PO, PS, AG, JK, JI, CS, DV, and MO.

Acknowledgments

The authors wish to thank Katrin Schulz for her valuable technical assistance and Dr. Jamie Alexander King for the English language editing. M.O. was supported by grants from the German Federal Ministry of Education and Research (projects: FTLDc 01GI1007A), the EU Joint Programme-Neurodegenerative Diseases (JPND) network, the EU Moodmarker program (01EW2008), Roux program of the Martin Luther University Halle-Wittenberg, the Foundation of the State Baden-Württemberg (D.3830), GenfiProx (01ED2008A), the German Research Foundation/DFG (SFB1279), the Boehringer Ingelheim Ulm University BioCenter (D.5009), and the Thierry Latran foundation (D.2468). S.A.R. received research support from the Medical Faculty of the Martin-Luther-University Halle-Wittenberg (Clinician Scientist Program No. CS22/06). Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interest

M.O. gave scientific advice to Axon, Biogen Idec, Fujirebio and Roche, all unrelated to the work presented in this paper. The foundation of the state Baden-Wuerttemberg handed in a patent for the measurement of β-synuclein in neurological diseases. Relevant authors are M.O., S.H., and P.O. The other authors report no conflicts of interest.

References

1. Omuro A, DeAngelis LM. Glioblastoma and other malignant gliomas: a clinical review. JAMA. 2013;310:1842-1850. doi:10.1001/jama.2013.280319
2. Weller M, van den Bent M, Preusser M, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. Nat Rev Clin Oncol. 2021;18:170-186. doi:10.1038/s41571-020-00447-z
3. Abu-Rumeileh S, Abdelhak A, Foschi M, et al. The multifaceted role of neurofilament light chain protein in non-primary neurological diseases. Brain. 2023;146:421-437. doi:10.1093/brain/awac328
4. Abdelhak A, Foschi M, Abu-Rumeileh S, et al. Blood GFAP as an emerging biomarker in brain and spinal cord disorders. Nat Rev Neurol. 2022;18:158-172. doi:10.1038/s41582-021-00616-3
5. Gállego Pérez-Larraya J, Paris S, Idbaih A, et al. Diagnostic and prognostic value of preoperative combined GFAP, IGFBP-2, and YKL-40 plasma levels in patients with glioblastoma. Cancer. 2014;120:3972-3980. doi:10.1002/cncr.28949
6. Tichy J, Spechtmeyer S, Mittelbronn M, et al. Prospective evaluation of serum glial fibrillary acidic protein (GFAP) as a diagnostic marker for glioblastoma. J Neurooncol. 2016;126:361-369. doi:10.1007/s11060-015-1978-8
7. Hepner A, Porter J, Hare F, et al. Serum Neurofilament light, glial fibrillary acidic protein and tau are possible serum biomarkers for activity of brain metastases and gliomas. World J Oncol. 2019;10:169-175. doi:10.14740/wjon1228
8. Ali H, Harting R, de Vries R, Ali M, Wurdinger T, Best MG. Blood-based biomarkers for glioma in the context of Gliomagenesis: a systematic review. Front Oncol. 2021;11:665235. doi:10.3389/fonc.2021.665235
9. Oeckl P, Halbgebauer S, Anderl-Straub S, et al. Targeted mass spectrometry suggests Beta-Synuclein as synaptic blood marker in Alzheimer's disease. J Proteome Res. 2020;19:1310-1318. doi:10.1021/acs.jproteome.9b00824
10. Halbgebauer S, Abu-Rumeileh S, Oeckl P, et al. Blood β-Synuclein and Neurofilament light chain during the course of prion disease. Neurology. 2022;98:e1434-e1445. doi:10.1212/WNL.0000000000200002
11. Halbgebauer R, Halbgebauer S, Oeckl P, et al. Neurochemical monitoring of traumatic brain injury by the combined analysis of plasma Beta-Synuclein, NfL, and GFAP in Polytraumatized patients. Int J Mol Sci. 2022;23:9639. doi:10.3390/ijms23179639
12. Barba L, Abu Rumeileh S, Bellomo G, et al. Cerebrospinal fluid β-synuclein as a synaptic biomarker for preclinical Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2023;94:83-86. doi:10.1136/jnnp-2022-329124
13. The human protein atlas. Synuclein beta. 2022 https://www.proteinatlas.org/ENSG00000074317-SNCB/pathology
14. Güttler A, Giebler M, Cuno P, et al. Osteopontin and splice variant expression level in human malignant glioma: radiobiologic effects and prognosis after radiotherapy. Radiother Oncol. 2013;108:535-540. doi:10.1016/j.radonc.2013.06.036
15. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol. 2007;114:97-109. doi:10.1007/s00401-007-0243-4

16. Oeckl P, Anderl-Straub S, von Arnim C, et al. Serum GFAP differentiates Alzheimer's disease from frontotemporal dementia and predicts MCI-to-dementia conversion. J Neurol Neurosurg Psychiatry. 2022;93:659-667. doi:10.1136/jnnp-2021-328547
17. Halbgebauer S, Steinacker P, Verde F, et al. Comparison of CSF and serum neurofilament light and heavy chain as differential diagnostic biomarkers for ALS. J Neurol Neurosurg Psychiatry. 2022;93:68-74. doi:10.1136/jnnp-2021-327129
18. Holst CB, Christensen IJ, Skjøth-Rasmussen J, Hamerlik P, Poulsen HS, Johansen JS. Systemic immune modulation in gliomas: prognostic value of plasma IL-6, YKL-40, and genetic variation in YKL-40. Front Oncol. 2020;10:478. doi:10.3389/fonc.2020.00478
19. Bergman J, Dring A, Zetterberg H, et al. Neurofilament light in CSF and serum is a sensitive marker for axonal white matter injury in MS. Neurol Neuroimmunol Neuroinflamm. 2016;3:e271. doi:10.1212/NXI.0000000000000271
20. Fisse AL, Pitarokoili K, Leppert D, et al. Serum neurofilament light chain as outcome marker for intensive care unit patients. J Neurol. 2021;268:1323-1329. doi:10.1007/s00415-020-10277-9
21. Papa L, Brophy GM, Welch RD, et al. Time course and diagnostic accuracy of glial and neuronal blood biomarkers GFAP and UCH-L1 in a large cohort of trauma patients with and without mild traumatic brain injury. JAMA Neurol. 2016;73:551-560. doi:10.1001/jamaneurol.2016.0039
22. Chen Q, Han B, Meng X, et al. Immunogenomic analysis reveals LGALS1 contributes to the immune heterogeneity and immunosuppression in glioma. Int J Cancer. 2019;145:517-530. doi:10.1002/ijc.32102
23. Qin J, Jiang C, Cai J, Meng X. Roles of long noncoding RNAs in conferring glioma progression and treatment. Front Oncol. 2021;11:688027. doi:10.3389/fonc.2021.688027
24. Sun P, Wang X, Zhong J, et al. Development and validation of a pyroptosis-related genes signature for risk stratification in gliomas. Front Genet. 2023;14:1087563. doi:10.3389/fgene.2023.1087563
25. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro Oncol. 2021;23:1231-1251. doi:10.1093/neuonc/noab106

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supporting Information