

Full Length Article

Neurocognitive and neuropsychiatric presentation identifies a higher-risk clinical phenotype in IDH-wildtype glioblastoma: A retrospective cohort study

Flavio Donnini^{a,*}, Pierpaolo Pastina^a, Giuseppe Battaglia^a, Giovanni Rubino^a, Salvatore Chibbaro^b, Alfonso Cerase^c, Giuseppe Minniti^{d,e}, Paolo Tini^a

^a Unit of Radiation Oncology, Department of Medicine, Surgery and Neurosciences, University of Siena, Siena 53100, Italy

^b Unit of Neurosurgery, Department of Medicine, Surgery and Neurosciences, University of Siena, Siena 53100, Italy

^c Diagnostic and Therapeutic Neuroradiology Unit, University Hospital of Siena, Siena 53100, Italy

^d Radiation Oncology, Policlinico Umberto I, Department of Radiological, Oncological and Pathological Sciences, "Sapienza" University of Rome, Rome 00161, Italy

^e Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Neuromed, Pozzilli 86077, Italy

ARTICLE INFO

Keywords:

Glioblastoma
IDH-wildtype
Neurocognitive onset
Neuropsychiatric symptoms
Clinical phenotype
Prognosis
Progression-free survival
Brain networks

ABSTRACT

Objective: In IDH-wildtype glioblastoma, prognosis is conventionally interpreted through established molecular, clinical, surgical and anatomical factors, whereas the prognostic meaning of the mode of onset is less defined. We hypothesized that neurocognitive/neuropsychiatric presentation identifies an adverse clinical phenotype, potentially reflecting diagnostic delay and/or early disruption of distributed cerebral networks.

Methods: We retrospectively analyzed 165 patients with IDH-wildtype glioblastoma treated with standard chemoradiation at a single institution. The main presenting symptom was reviewed from clinical documentation and dichotomized as neurocognitive/neuropsychiatric versus all other presentations. The primary endpoint was progression-free survival (PFS), and overall survival (OS) was the secondary endpoint. Multivariable Cox models were adjusted for prespecified covariates: MGMT promoter methylation, extent of resection, baseline Karnofsky Performance Status, age, and subventricular zone contact.

Results: Thirty-one patients (18.8%) had a neurocognitive/neuropsychiatric onset. In unadjusted analysis, PFS showed a non-significant separation (log-rank $p = 0.175$), and OS curves did not differ (log-rank $p = 0.896$). After adjustment, neurocognitive/neuropsychiatric onset was associated with shorter PFS (HR 1.77, 95% CI 1.13–2.77; $p = 0.012$). The OS estimate was concordant and reached statistical significance in the secondary multivariable model (HR 1.71, 95% CI 1.02–2.87; $p = 0.041$). The PFS association was consistent across sensitivity analyses.

Conclusion: Neurocognitive/neuropsychiatric onset identified a higher-risk presentation phenotype associated with shorter PFS and, in secondary analyses, shorter OS after adjustment for established prognostic factors. These hypothesis-generating findings suggest that clinical mode of onset may capture prognostic information not fully reflected by conventional variables and warrant prospective multicenter validation.

1. Introduction

Glioblastoma is the most common and most aggressive primary malignant brain tumor in adults and carries a poor prognosis despite multimodal treatment [1]. Under the 2021 WHO classification, the diagnosis is restricted to IDH-wildtype tumors, the predominant and most therapy-resistant molecular subtype [2]. Standard care consists of maximal safe resection followed by conventionally fractionated

radiotherapy with concurrent and adjuvant temozolomide [1,3]. Within this framework, prognosis is conventionally interpreted through a small set of well-established factors, including MGMT promoter methylation status [4], age, performance status, extent of resection [5], and tumor location [6].

Beyond these variables, the clinical mode of presentation may itself carry prognostic information. Presenting symptoms may reflect how the tumor interacts with cerebral networks, how readily symptoms are

* Corresponding author.

E-mail address: flavio.donnini@student.unisi.it (F. Donnini).

<https://doi.org/10.1016/j.clineuro.2026.109602>

Received 9 July 2026; Accepted 28 July 2026

Available online 4 August 2026

0303-8467/© 2026 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

recognized, and whether diagnosis is delayed. Among presenting manifestations, seizures have been the most studied: a recent meta-analysis reported a potentially favorable prognostic impact of seizures at onset, although this effect was not retained in analyses restricted to IDH-wildtype tumors, underscoring the need for molecularly homogeneous cohorts [7].

At the opposite end of the clinical spectrum, neurocognitive and neuropsychiatric presentations are comparatively under-recognized. Cognitive dysfunction is common in adults with brain tumors, may be the earliest sign of disease, and has been associated with adverse outcome in glioma [8–10]. Unlike seizures, focal deficits, or raised intracranial pressure, cognitive, behavioral, affective, or psychiatric changes are clinically less specific and may be misattributed to functional, depressive, degenerative, or age-related conditions [11], potentially delaying diagnosis [12–14].

A complementary interpretation is biological and network-based. Contemporary connectomic neuro-oncology suggests that glioma-related symptoms may reflect disruption of large-scale functional networks rather than only focal anatomical damage. Neurocognitive and neuropsychiatric manifestations may therefore act as clinically visible markers of diffuse cortical-subcortical involvement, integrative network disruption, or greater occult tumor burden at diagnosis [15–18].

Despite these observations, most studies have treated presenting symptoms descriptively or focused on seizures. We therefore designed this study around the neurocognitive/neuropsychiatric subgroup, hypothesizing that such an onset identifies a prognostically distinct clinical phenotype independent of MGMT methylation, extent of resection, baseline performance status, age, and subventricular zone contact. PFS was the primary endpoint and OS the secondary endpoint.

2. Materials and methods

2.1. Study design and ethics

We conducted a retrospective, single-center, observational cohort study based on an institutional database of patients with IDH-wildtype glioblastoma treated at the Radiation Oncology Unit of the Azienda Ospedaliero-Universitaria Senese (University of Siena, Italy). The aim was not to provide a descriptive catalogue of presenting symptoms, but to test whether neurocognitive/neuropsychiatric presentation identifies

a clinically recognizable subgroup with distinct outcome. Clinical, molecular, radiological, and treatment data were retrieved from routinely maintained records. The study followed the Declaration of Helsinki and was approved by the local Ethics Committee (Area Vasta Sud-Est; protocol GLIOMARKERSOBS_2025-1; 6 May 2025). Informed consent was obtained from all subjects involved in the study. The study is reported in accordance with the STROBE guidelines for observational cohort studies [19].

2.2. Patient selection

Patients were eligible if they had histologically confirmed IDH-wildtype glioblastoma treated at our institution between January 2018 and December 2025. The database was locked for analysis on 30/05/2026. Inclusion required: (I) first-line surgical resection or biopsy followed by standard chemoradiation per the Stupp protocol; (II) available information on the main presenting symptom; and (III) available data on survival, progression status, and the principal covariates. Patients were excluded if they did not receive standard Stupp-based chemoradiation or if essential data on the presenting symptom or survival endpoints were missing. In this cohort, 203 patients were considered; 26 were excluded for non-Stupp treatment and 12 for missing or incomplete data, yielding an analytic cohort of 165 (Fig. 1).

2.3. Treatment

All patients underwent multidisciplinary evaluation. Surgery consisted of gross total resection, subtotal resection, or biopsy per neurosurgical judgement. Patients then received conventionally fractionated intensity-modulated radiotherapy to 59.4–60 Gy in 1.8–2 Gy fractions with concurrent and adjuvant temozolomide per the Stupp regimen [1]; target volumes followed current recommendations [20] and prior institutional practice [21,22].

2.4. Clinical, molecular, and radiological variables

Baseline variables included age, sex, baseline Karnofsky Performance Status (KPS), and baseline corticosteroid therapy. Extent of resection was classified, from neurosurgical documentation and postoperative contrast-enhanced MRI, as gross total resection (GTR, no residual

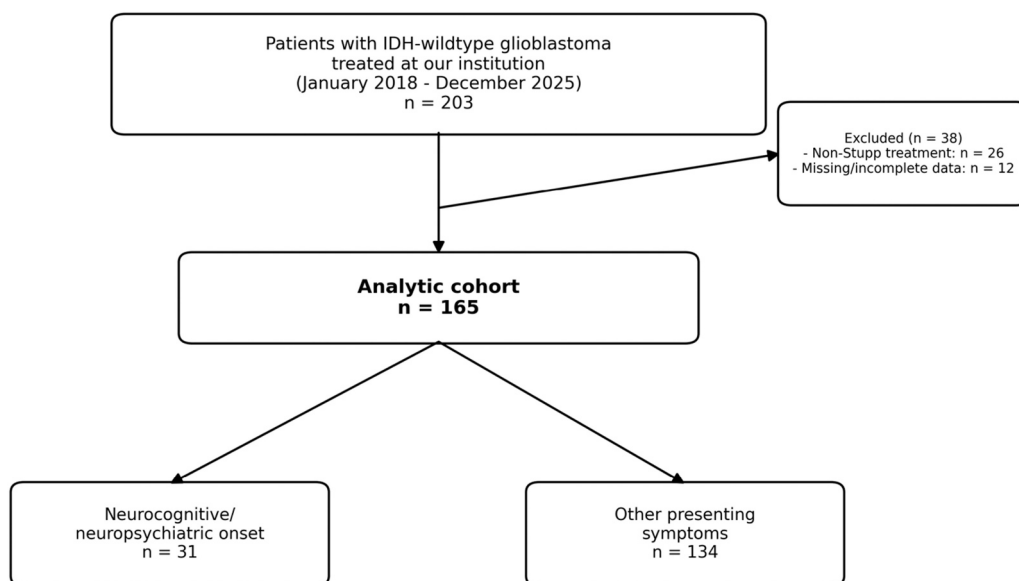


Fig. 1. Flowchart of cohort derivation. Of 203 patients considered in the institutional database, 26 were excluded for non-standard (non-Stupp) treatment and 12 for missing or incomplete data, yielding an analytic cohort of 165 patients. The analytic cohort included 31 patients with neurocognitive/neuropsychiatric onset and 134 patients with other presenting symptoms.

enhancement), subtotal resection (STR, residual enhancement after debulking), or biopsy. IDH-wildtype status was determined by immunohistochemistry and/or sequencing per WHO 2021 [2]. MGMT promoter methylation was assessed by methylation-specific PCR (10% threshold). The Ki-67/MIB-1 index was recorded from immunohistochemistry. Anatomical features on preoperative MRI included the principal involved lobe, laterality, focality, subventricular zone (SVZ) contact, corpus callosum involvement, and deep-structure involvement.

2.5. Primary exposure: mode of clinical onset

The main presenting symptom was classified by review of presentation documentation into four mutually exclusive, prespecified categories: seizure; headache/raised intracranial pressure; focal neurological deficit; and neurocognitive/neuropsychiatric presentation. The latter category included a disturbance of cognition or a behavioral, affective, personality, or psychiatric change as the leading manifestation, rather than a discrete epileptic, pressure-related, or focal neurological event. Examples included new memory or executive dysfunction, cognitive slowing, confusion not attributable to an acute metabolic cause, personality change, apathy, disinhibition, irritability, depressive or anxious symptoms, psychosis-like manifestations, or behavioral change prompting medical evaluation.

For the primary analysis, onset was operationalized as a binary exposure: neurocognitive/neuropsychiatric versus all other presentations combined. When multiple symptoms were documented, the earliest dominant symptom that prompted medical attention was selected. Symptoms occurring only as secondary consequences of a seizure, raised intracranial pressure, or focal neurological deficit were not coded as neurocognitive/neuropsychiatric onset unless explicitly described as the leading presentation. The retrospective nature of documentation prevented reliable severity grading; therefore, no ordinal neuropsychiatric onset score was entered into the main models. The original four-category variable was retained for secondary and descriptive analyses.

2.6. Endpoints

The primary endpoint was PFS, from histological diagnosis to radiologically documented progression or death from any cause, whichever occurred first, with progression assessed from follow-up imaging and clinical documentation referenced to Response Assessment in Neuro-Oncology (RANO) principles [23,24]. The secondary endpoint was OS, from diagnosis to death from any cause. Patients without an event were censored at last clinical contact.

2.7. Statistical analysis

Baseline characteristics were summarized for the whole cohort and by onset group. Continuous variables were compared with Student's *t*-test or the Mann-Whitney *U* test, as appropriate, and categorical variables with the chi-square or Fisher's exact test. These between-group *p*-values were considered descriptive. PFS and OS were estimated by the Kaplan-Meier method and compared with the log-rank test, with number-at-risk tables.

The principal analysis was a multivariable Cox proportional hazards model for PFS. Covariates were selected a priori on clinical and prognostic grounds: onset phenotype, MGMT promoter methylation, extent of resection, baseline KPS, age, and SVZ contact. An analogous model with the same covariates was fitted for OS. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. The proportional hazards assumption was assessed using scaled Schoenfeld residuals and showed no evidence of violation. Sensitivity analyses tested whether the association between onset phenotype and outcome remained stable after replacing SVZ contact with corpus callosum involvement, adding sex, adding Ki-67, and stratifying by age tertiles. All tests were two-sided,

with $p < 0.05$ considered statistically significant. Analyses used R version 4.5 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Cohort and baseline characteristics

A total of 165 patients met the eligibility criteria and formed the analytic cohort (Fig. 1). Mean age was 60.6 years (SD 10.1), 110 (66.7%) were male, and median baseline KPS was 90 (IQR 80–100). MGMT promoter methylation was present in 86 patients (52.1%). Resection was gross total in 79 patients (47.9%), subtotal in 62 (37.6%), and biopsy only in 24 (14.5%). The tumor contacted the SVZ in 68 patients (41.2%). Full baseline characteristics are summarized in Table 1.

The main presenting symptom was seizure in 41 patients (24.8%), headache/raised intracranial pressure in 50 (30.3%), focal deficit in 43 (26.1%), and neurocognitive/neuropsychiatric in 31 (18.8%). For the primary analysis, patients were grouped as neurocognitive/neuropsychiatric onset ($n = 31$) versus all other presentations ($n = 134$). The groups did not differ significantly in any measured baseline variable, including age, KPS, MGMT promoter methylation, extent of resection, SVZ contact, corpus callosum involvement, deep-structure involvement, baseline corticosteroid use, or Ki-67 (Table 1).

Median follow-up was 51.3 months (reverse Kaplan–Meier estimate). During follow-up, 141 patients (85.5%) had a PFS event and 123 (74.5%) had died. Event rates were similar between onset groups: PFS events occurred in 27 of 31 patients (87.1%) in the neurocognitive/neuropsychiatric group and in 114 of 134 patients (85.1%) in the other-

Table 1

Baseline characteristics of the whole cohort and by mode of onset. Continuous variables are mean (SD) or median [IQR]; categorical variables are *n* (%). Between-group *p*-values are descriptive.

Characteristic	Overall (<i>n</i> = 165)	Other onset (<i>n</i> = 134)	Neurocognitive/ neuropsychiatric onset (<i>n</i> = 31)	<i>p</i>
Age, years, mean (SD)	60.6 (10.1)	60.4 (10.5)	61.5 (8.2)	0.58
Male sex, <i>n</i> (%)	110 (66.7)	92 (68.7)	18 (58.1)	0.32
Baseline KPS, median [IQR]	90 [80, 100]	90 [80, 100]	90 [80, 90]	0.49
MGMT methylated, <i>n</i> (%)	86 (52.1)	68 (50.7)	18 (58.1)	0.55
Ki-67, %, median [IQR]	35 [25, 45]	35 [25, 45]	35 [30, 40]	0.64
Extent of resection, <i>n</i> (%)				0.21
Gross total resection	79 (47.9)	60 (44.8)	19 (61.3)	
Subtotal resection	62 (37.6)	51 (38.1)	11 (35.5)	
Biopsy	24 (14.5)	23 (17.2)	1 (3.2)	
Lobe, <i>n</i> (%)				0.96
Frontal	50 (30.3)	41 (30.6)	9 (29.0)	
Temporal	62 (37.6)	51 (38.1)	11 (35.5)	
Parietal	37 (22.4)	30 (22.4)	7 (22.6)	
Occipital	16 (9.7)	12 (9.0)	4 (12.9)	
Left laterality, <i>n</i> (%)	90 (54.5)	72 (53.7)	18 (58.1)	0.69
SVZ contact, <i>n</i> (%)	68 (41.2)	56 (41.8)	12 (38.7)	0.84
Corpus callosum involvement, <i>n</i> (%)	35 (21.2)	30 (22.4)	5 (16.1)	0.62
Deep-structure involvement, <i>n</i> (%)	38 (23.0)	34 (25.4)	4 (12.9)	0.23
Baseline corticosteroids, <i>n</i> (%)	135 (81.8)	108 (80.6)	27 (87.1)	0.59
Deaths (OS events), <i>n</i> (%)	123 (74.5)	101 (75.4)	22 (71.0)	0.66
PFS events, <i>n</i> (%)	141 (85.5)	114 (85.1)	27 (87.1)	1.00

onset group; OS events occurred in 22 of 31 patients (71.0%) and 101 of 134 patients (75.4%), respectively.

3.2. Progression-free survival (PFS)

In unadjusted Kaplan-Meier analysis, PFS showed a numerical separation between onset groups, but the difference did not reach statistical significance (log-rank $p = 0.175$; Fig. 2A). Median PFS was 9.4 months in the neurocognitive/neuropsychiatric group and 11.1 months in the other-onset group.

In the prespecified multivariable Cox model, neurocognitive/neuropsychiatric onset was independently associated with shorter PFS (HR 1.77, 95% CI 1.13–2.77; $p = 0.012$), after adjustment for MGMT promoter methylation, extent of resection, baseline KPS, age, and SVZ contact (Table 2). MGMT methylation was associated with longer PFS, whereas subtotal resection, biopsy, and lower KPS were associated with shorter PFS. Age and SVZ contact were not independently associated with PFS in this model.

3.3. Overall survival (OS)

In unadjusted Kaplan-Meier analysis, OS did not differ significantly between onset groups (log-rank $p = 0.896$; Fig. 2B). Median OS was 18.5 months in the neurocognitive/neuropsychiatric group and 20.5 months in the other-onset group.

In the multivariable Cox model for the secondary endpoint, neurocognitive/neuropsychiatric onset was associated with shorter OS (HR 1.71, 95% CI 1.02–2.87; $p = 0.041$; Table 3). MGMT methylation, extent of resection, baseline KPS, and SVZ contact were also independently associated with OS, whereas age was not.

3.4. Sensitivity analyses and four-category onset

The association between neurocognitive/neuropsychiatric onset and

Table 2
Multivariable Cox proportional hazards model for progression-free survival (n = 165; 141 events).

Covariate	HR (95% CI)	p
Neurocognitive/neuropsychiatric onset (vs other)	1.77 (1.13–2.77)	0.012
MGMT methylated (vs unmethylated)	0.42 (0.29–0.60)	< 0.001
Subtotal resection (vs GTR)	2.50 (1.70–3.67)	< 0.001
Biopsy (vs GTR)	2.15 (1.26–3.66)	0.005
Baseline KPS (per point)	0.96 (0.94–0.98)	< 0.001
Age (per year)	0.99 (0.97–1.01)	0.12
SVZ contact (vs no)	1.29 (0.89–1.86)	0.18

Table 3
Multivariable Cox proportional hazards model for overall survival (n = 165; 123 events).

Covariate	HR (95% CI)	p
Neurocognitive/neuropsychiatric onset (vs other)	1.71 (1.02–2.87)	0.041
MGMT methylated (vs unmethylated)	0.43 (0.29–0.63)	< 0.001
Subtotal resection (vs GTR)	1.92 (1.26–2.93)	0.002
Biopsy (vs GTR)	2.73 (1.58–4.72)	< 0.001
Baseline KPS (per point)	0.97 (0.95–0.99)	0.002
Age (per year)	1.00 (0.98–1.02)	0.82
SVZ contact (vs no)	1.47 (1.07–2.16)	0.042

shorter PFS was stable across sensitivity analyses (Table 4). The adjusted HR remained similar when SVZ contact was replaced by corpus callosum involvement, when sex or Ki-67 was added to the model, and when the model was stratified by age tertiles. For OS, adding sex or stratifying by age tertiles yielded estimates similar to the primary OS model.

In an exploratory four-category model using seizure as the reference group, headache/raised intracranial pressure and focal neurological deficit showed hazards close to the reference category. The neurocognitive/neuropsychiatric category showed the highest adjusted hazard for PFS (HR 1.72, 95% CI 1.04–2.85; $p = 0.035$), supporting the binary grouping used in the primary analysis.

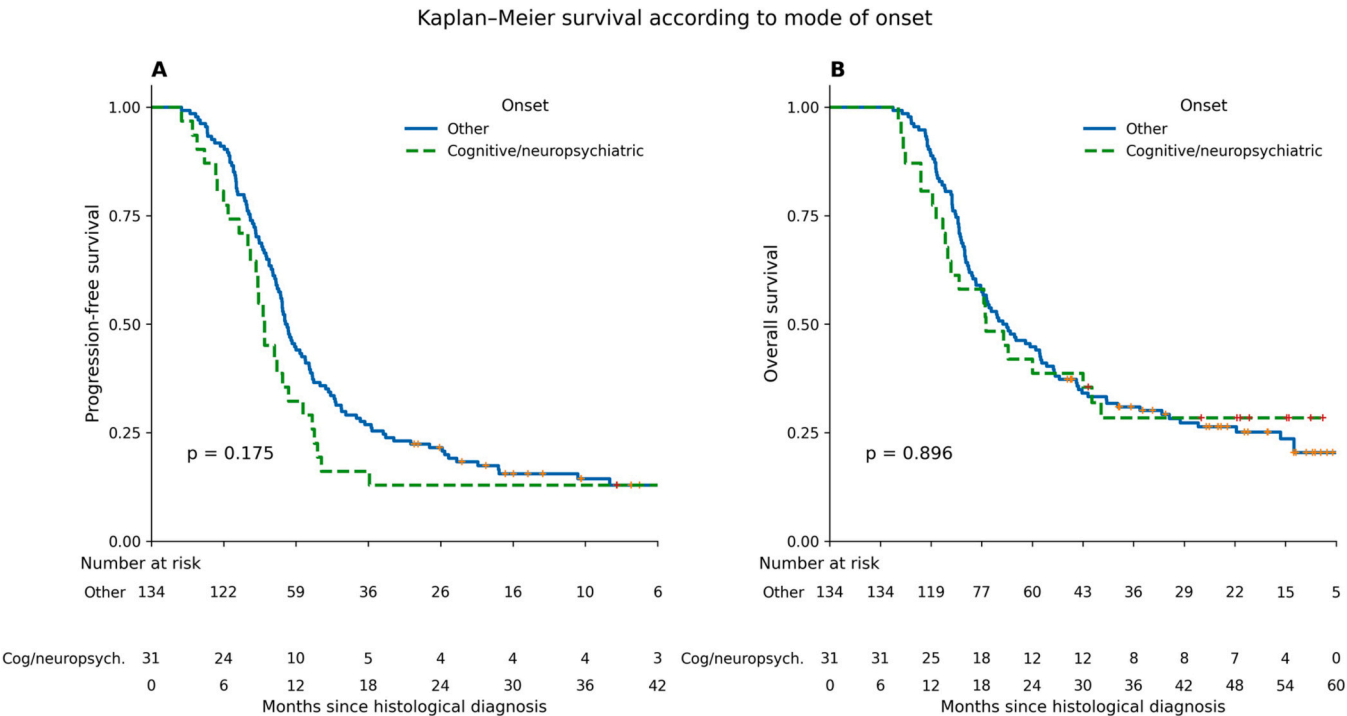


Fig. 2. Kaplan-Meier survival curves according to mode of onset. Patients with neurocognitive/neuropsychiatric onset were compared with patients presenting with all other symptoms. (A) Progression-free survival: median PFS was 9.4 months in the neurocognitive/neuropsychiatric group and 11.1 months in the other-onset group (log-rank $p = 0.175$). (B) Overall survival: median OS was 18.5 months in the neurocognitive/neuropsychiatric group and 20.5 months in the other-onset group (log-rank $p = 0.896$). Number-at-risk tables are shown below each curve.

Table 4

Sensitivity analyses for the association between neurocognitive/neuropsychiatric onset and survival. Each row reports the adjusted HR for neurocognitive/neuropsychiatric onset versus all other presentations from a separate Cox model.

Endpoint/model specification	Adjusted HR for onset (95% CI)	p
PFS - primary model	1.77 (1.13–2.77)	0.012
PFS - corpus callosum involvement replacing SVZ contact	1.93 (1.25–2.98)	0.003
PFS - primary model + sex	1.74 (1.11–2.73)	0.015
PFS - primary model + Ki-67	1.76 (1.12–2.75)	0.014
PFS - stratified by age tertiles	1.79 (1.15–2.79)	0.010
OS - primary model	1.71 (1.02–2.87)	0.041
OS - primary model + sex	1.69 (1.00–2.84)	0.049
OS - stratified by age tertiles	1.70 (1.00–2.88)	0.050

4. Discussion

In this cohort of 165 patients with IDH-wildtype glioblastoma treated with standard chemoradiation, neurocognitive/neuropsychiatric onset identified a higher-risk clinical presentation phenotype. After adjustment for established prognostic factors, this phenotype was independently associated with shorter PFS and, in secondary analyses, shorter OS. Importantly, the neurocognitive/neuropsychiatric group was not characterized by a worse baseline distribution of recognized adverse prognostic variables. Age, KPS, MGMT promoter methylation, extent of resection, SVZ contact, corpus callosum involvement, deep-structure involvement, corticosteroid use, and Ki-67 were similar between groups.

The unadjusted Kaplan-Meier curves and the adjusted Cox models answer different clinical questions. The Kaplan-Meier curves compare the two onset groups without accounting for other prognostic variables and therefore provide a useful descriptive view of the data. In this analysis, the PFS curves showed a numerical separation but did not reach statistical significance, and the OS curves were not significantly different. The multivariable Cox model instead asks whether onset phenotype adds prognostic information after accounting for major determinants such as MGMT status, surgery, KPS, age, and SVZ contact. In that adjusted comparison, neurocognitive/neuropsychiatric onset was associated with earlier progression and shorter survival. The direction of this discordance is informative. In the present cohort the neurocognitive/neuropsychiatric group did not carry an excess of adverse baseline factors; if anything, it showed a more favorable profile, with a higher proportion of gross total resection (61.3% vs 44.8%) and of MGMT promoter methylation (58.1% vs 50.7%). In the unadjusted analysis these protective features partially offset, and thereby masked, the adverse prognostic effect of the onset phenotype, so that no significant separation emerged on the log-rank test. Multivariable adjustment removes this imbalance and unmasks an independent association. Such suppression is the expected behavior when an exposure is positively associated with protective covariates, and it argues against the adjusted association being a spurious artifact of modeling rather than a genuine prognostic signal. Overall, this suggests that the onset phenotype may carry prognostic information that is not captured by conventional clinical, molecular, surgical, or anatomical variables.

Several mechanisms may explain this association. First, neurocognitive and neuropsychiatric symptoms are often subtle and non-specific. They may be attributed to depression, anxiety, stress, aging, neurodegenerative disease, or functional complaints, potentially delaying neuroimaging and diagnosis. A longer interval before diagnosis could allow greater occult tumor burden or more advanced network involvement by the time treatment starts. Second, the association may reflect tumor-brain biology. Cognitive and behavioral functions depend on distributed cortical-subcortical networks; therefore, a neurocognitive/neuropsychiatric presentation may be a clinical marker of diffuse infiltration, involvement of integrative network hubs, or more disruptive tumor-network interaction [15]. These mechanisms are not

mutually exclusive and cannot be separated in the present dataset.

These findings also complement the literature on seizures at presentation. Seizures have often been associated with more favorable outcome in glioblastoma, although this effect is less clear in IDH-wildtype cohorts [7]. In the exploratory four-category analysis, seizure, headache/raised intracranial pressure, and focal deficit behaved similarly, whereas the neurocognitive/neuropsychiatric category showed the highest adjusted hazard. This supports the idea that the prognostic signal is driven by the neurocognitive/neuropsychiatric phenotype rather than by presenting symptoms in general.

Clinically, the result should be interpreted as hypothesis-generating. Neurocognitive/neuropsychiatric onset is inexpensive, immediately available from clinical history, and may help identify patients who warrant particular attention after standard chemoradiation. It should not currently be used to intensify treatment or change standard management. Rather, it supports careful documentation of presenting symptoms, early neuroimaging when unexplained cognitive or behavioral changes occur, and closer prospective evaluation of this phenotype in multicenter cohorts.

4.1. Limitations

This study has several limitations. The retrospective single-center design is susceptible to selection bias and residual confounding. Although measured baseline variables were well balanced, unmeasured factors may still have contributed to the observed association.

Onset was classified retrospectively from clinical documentation rather than by standardized neuropsychological or psychiatric assessment. The neurocognitive/neuropsychiatric category is heterogeneous, and symptom severity could not be graded reliably. We also lacked systematic data on diagnostic interval, preoperative contrast-enhancing tumor volume, edema/FLAIR volume, lesion-network mapping, and connectomic metrics. Therefore, the relative contributions of diagnostic delay, tumor burden, and intrinsic network involvement cannot be determined.

Finally, PFS was assessed retrospectively according to RANO-referenced clinical documentation without centralized blinded imaging review, and pseudoprogression may have influenced some progression calls. The findings should therefore be considered exploratory and require prospective validation.

5. Conclusion

In a homogeneous single-center cohort of IDH-wildtype glioblastoma treated with standard chemoradiation, neurocognitive/neuropsychiatric onset identified a candidate higher-risk clinical phenotype independently associated with shorter PFS and, in secondary analyses, shorter OS. Clinical mode of presentation may therefore provide prognostic information beyond established molecular, clinical, surgical, and anatomical factors. Prospective multicenter validation should incorporate standardized neuropsychological assessment, diagnostic-interval data, volumetric imaging, and tumor-network metrics.

CRedit authorship contribution statement

PAOLO TINI: Conceptualization, Methodology, Validation, Writing – review & editing, Supervision, Project administration. **GIUSEPPE MINNITI:** Methodology, Validation, Writing – review & editing, Supervision. **GIOVANNI RUBINO:** Investigation, Data curation, Writing – review & editing. **GIUSEPPE BATTAGLIA:** Investigation, Data curation, Writing – review & editing. **ALFONSO CERASE:** Investigation, Data curation, Resources, Writing – review & editing. **SALVATORE CHIBBARO:** Investigation, Resources, Writing – review & editing. **PIER-PAOLO PASTINA:** Investigation, Data curation, Writing – review & editing. **FLAVIO DONNINI:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Visualization, Writing –

review & editing, Investigation.

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Azienda Ospedaliero-Universitaria Senese, Area Vasta Sud-Est (protocol code GLIOMARKERSOBS_2025-1; approval date 6 May 2025).

Consent to participate

Informed consent was obtained from all subjects involved in the study.

Consent for publication

All authors approved the submitted version for publication. The manuscript contains no individually identifiable data.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used Claude (Anthropic) in order to improve the English language of the manuscript text and to assist with formatting of the reference list. After using this tool, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the published article.

Funding

This research received no external funding.

Declaration of Competing Interest

The authors declare that they have no competing financial interests or personal relationships that could be perceived to have influenced the work reported in this paper.

Acknowledgements

Not applicable.

Data availability

The data presented in this study are not publicly available due to privacy and institutional restrictions. De-identified data may be available from the corresponding author on reasonable request and subject to approval by the local Ethics Committee and institutional policies.

References

- [1] R. Stupp, W.P. Mason, M.J. van den Bent, et al., Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma, *N. Engl. J. Med.* 352 (2005) 987–996, <https://doi.org/10.1056/NEJMoa043330>.
- [2] D.N. Louis, A. Perry, P. Wesseling, et al., The 2021 WHO classification of tumors of the central nervous system: a summary, *Neuro Oncol.* 23 (2021) 1231–1251, <https://doi.org/10.1093/neuonc/noab106>.
- [3] M. Weller, M. van den Bent, M. Preusser, et al., EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood, *Nat. Rev. Clin. Oncol.* 18 (2021) 170–186, <https://doi.org/10.1038/s41571-020-00447-z>.
- [4] M.E. Hegi, A.C. Diserens, T. Gorlia, et al., MGMT gene silencing and benefit from temozolomide in glioblastoma, *N. Engl. J. Med.* 352 (2005) 997–1003, <https://doi.org/10.1056/NEJMoa043331>.
- [5] T.J. Brown, M.C. Brennan, M. Li, et al., Association of the extent of resection with survival in glioblastoma: a systematic review and meta-analysis, *JAMA Oncol.* 2 (2016) 1460–1469, <https://doi.org/10.1001/jamaoncol.2016.1373>.
- [6] A.M. Mistry, A.T. Hale, L.B. Chambliss, K.D. Weaver, R.C. Thompson, R.A. Ihrle, Influence of glioblastoma contact with the lateral ventricle on survival: a meta-analysis, *J. Neurooncol.* 131 (2016) 125–133, <https://doi.org/10.1007/s11060-016-2278-7>.
- [7] J. Rossi, F. Cavalleri, M.C. Bassi, et al., To be or not to be: the dilemma over the prognostic role of epilepsy at presentation in patients with glioblastoma – a systematic review and meta-analysis, *BMC Cancer* 24 (2024) 1488, <https://doi.org/10.1186/s12885-024-13249-8>.
- [8] M.J.B. Taphoorn, M. Klein, Cognitive deficits in adult patients with brain tumours, *Lancet Neurol.* 3 (2004) 159–168, [https://doi.org/10.1016/S1474-4422\(04\)00680-5](https://doi.org/10.1016/S1474-4422(04)00680-5).
- [9] C.A. Meyers, K.R. Hess, W.K. Yung, V.A. Levin, Cognitive function as a predictor of survival in patients with recurrent malignant glioma, *J. Clin. Oncol.* 18 (2000) 646–650, <https://doi.org/10.1200/JCO.2000.18.3.646>.
- [10] D.R. Johnson, A.M. Sawyer, C.A. Meyers, B.P. O'Neill, J.S. Wefel, Early measures of cognitive function predict survival in patients with newly diagnosed glioblastoma, *Neuro Oncol.* 14 (2012) 808–816, <https://doi.org/10.1093/neuonc/nos082>.
- [11] S. Madhusoodanan, M.B. Ting, T. Farah, U. Ugur, Psychiatric aspects of brain tumors: a review, *World J. Psychiatry* 5 (2015) 273–285, <https://doi.org/10.5498/wjp.v5.i3.273>.
- [12] H. Bruhn, I. Blystad, P. Milos, et al., Initial cognitive impairment predicts shorter survival of patients with glioblastoma, *Acta Neurol. Scand.* 145 (2022) 94–101, <https://doi.org/10.1111/ane.13529>.
- [13] H. Bruhn, B. Tavelin, L. Rosenlund, R. Henriksson, Do presenting symptoms predict treatment decisions and survival in glioblastoma? Real-world data from 1458 patients in the Swedish brain tumor registry, *Neurooncol. Pract.* 11 (2024) 652–659, <https://doi.org/10.1093/nop/npae036>.
- [14] F. Ghandour, A. Squassina, R. Karaky, M. Diab-Assaf, P. Fadda, C. Pisanu, Presenting psychiatric and neurological symptoms and signs of brain tumors before diagnosis: a systematic review, *Brain Sci.* 11 (2021) 301, <https://doi.org/10.3390/brainsci11030301>.
- [15] J. Derks, A.R. Dirkson, P.C. de Witt Hamer, et al., Connectomic profile and clinical phenotype in newly diagnosed glioma patients, *Neuroimage Clin.* 14 (2017) 87–96, <https://doi.org/10.1016/j.nicl.2017.01.007>.
- [16] J. Derks, S. Kulik, P. Wesseling, et al., Understanding cognitive functioning in glioma patients: the relevance of IDH-mutation status and functional connectivity, *Brain Behav.* 9 (2019) e01204, <https://doi.org/10.1002/brb3.1204>.
- [17] V.M. Stoecklein, S. Stoecklein, F. Galie, et al., Resting-state fMRI detects alterations in whole brain connectivity related to tumor biology in glioma patients, *Neuro Oncol.* 22 (2020) 1388–1398, <https://doi.org/10.1093/neuonc/noaa044>.
- [18] M.G. Hart, R. Romero-Garcia, S.J. Price, J. Suckling, Global effects of focal brain tumors on functional complexity and network robustness: a prospective cohort study, *Neurosurgery* 84 (2019) 1201–1213, <https://doi.org/10.1093/neuros/nyy378>.
- [19] E. von Elm, D.G. Altman, M. Egger, S.J. Pocock, P.C. Gøtzsche, J. P. Vandenbroucke, The strengthening of reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies, *Lancet* 370 (2007) 1453–1457, [https://doi.org/10.1016/S0140-6736\(07\)61602-X](https://doi.org/10.1016/S0140-6736(07)61602-X).
- [20] M. Niyazi, N. Andratschke, M. Bendszus, et al., ESTRO-EANO guideline on target delineation and radiotherapy details for glioblastoma, *Radiother. Oncol.* 184 (2023) 109663, <https://doi.org/10.1016/j.radonc.2023.109663>.
- [21] P. Tini, F. Donnini, F. Marampon, et al., Biomolecular predictors of recurrence patterns and survival in IDH-wild-type glioblastoma: a retrospective analysis of patients treated with radiotherapy and temozolomide, *Brain Sci.* 15 (2025) 713, <https://doi.org/10.3390/brainsci15070713>.
- [22] F. Donnini, G. Minniti, S. Chibbaro, et al., Reduced clinical target volume margins in glioblastoma: exploratory evidence supporting further margin reduction independent of MGMT status, *Brain Sci.* 16 (2026) 458, <https://doi.org/10.3390/brainsci16050458>.
- [23] P.Y. Wen, D.R. Macdonald, D.A. Reardon, et al., Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group, *J. Clin. Oncol.* 28 (2010) 1963–1972, <https://doi.org/10.1200/JCO.2009.26.3541>.
- [24] P.Y. Wen, M. van den Bent, G. Youssef, et al., RANO 2.0: update to the response assessment in neuro-oncology criteria for high- and low-grade gliomas in adults, *J. Clin. Oncol.* 41 (2023) 5187–5199, <https://doi.org/10.1200/JCO.23.01059>.