BMC Cancer

SYSTEMATIC REVIEW Open Access

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

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Abstract

Despite some evidence of a possible link between epileptogenesis and tumorigenesis in glioblastoma, the prognostic value of epilepsy at presentation has been debated over the years. We performed a systematic review and meta-analysis to summarize all published data evaluating the prognostic significance of seizures as a presenting manifestation of glioblastoma. A comprehensive search of five databases from inception to December 2023 was conducted. Included studies underwent meta-analysis, with subgroup analyses performed to identify sources of heterogeneity. Fifteen studies were included in the analysis. Seizures were considered a favorable prognostic factor in seven studies, while eight studies found no differences in overall survival between patients with seizures and those with other presenting symptoms. Eleven studies were included in the meta-analysis. The overall pooled analysis indicated a potentially favorable prognostic impact of seizures at the clinical onset of glioblastoma (HR 0.73; 95% CI 0.61–0.87). However, subgroup analysis within studies focusing on IDH-wild type cases showed no discernible impact from preoperative seizures. Retrospective design, poor quality in reporting results, and heterogeneity in tumor characteristics and therapies are the main limitations of included studies.

Future prospective studies on large, homogeneous cohorts of patients with IDH-wild type glioblastoma are warranted. Overall, these findings suggest that while seizures may hold some prognostic value, further research is essential to clarify their role. Understanding the true prognostic role of seizures at clinical onset may enhance our ability to predict patient outcomes and guide clinical decision-making.

Keywords Epilepsy, Glioma, Glioblastoma, Seizures, Glutamate, Survival, Tumor

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Introduction

Glioblastoma (GBM) is the most frequent malignant tumor of the central nervous system in the adult population and is characterized by an aggressive course and poor prognosis [1]. The addition of concurrent oral temozolomide (TMZ) to standard radiotherapy (RT) after surgery (Stupp protocol) followed by maintenance of TMZ are the current standards of care [2]. Despite multimodality treatment efforts, recurrence is inevitable.

The prognosis of GBM patients depends on patient-, tumor- and treatment-related variables. Among patient-related prognostic factors, age over 69 years is associated with worse survival [3], and this is mostly attributed to comorbidities that make patients more susceptible to insults caused by the tumor itself, surgery, and adjuvant therapies. For the same reason, preoperative performance status has an important effect on the prognosis.

In the context of tumor-related variables, molecular factors have become increasingly important in this context. The O(6)-methylguanine-DNA methyltransferase (MGMT) promoter methylation has a prognostic and predictive significance, as it is associated with prolonged overall survival and a better response to combined treatment [3]. Unfavorable prognostic factors are observed with Epidermal Growth Factor Receptor (EGFR) amplification, Telomerase Reverse Transcriptase Promoter (TERTp) mutation, combined whole chromosome 7 gain and whole chromosome 10 loss (+7/−10) [4, 5].

Finally, the extent of surgical intervention has an important role, with significant survival advantage for complete resection than subtotal resection [3]. Furthermore, the addition of concomitant chemo-radiotherapy and adjuvant therapy with temozolomide provide an additional gain in survival [2].

Seizures occur in 30–62% of patients with glioblastoma during the disease course and can be the presenting symptom in 25–30% of individuals [6]. It is common knowledge that epileptogenesis is a dynamic process that continues after seizure onset and it takes place in the peri-tumoral brain tissue as opposed to the tumor itself [7, 8]. This area appears to play an increasingly important role not only in epileptogenesis but also in tumor progression/recurrence [9]. Furthermore, a growing body of evidence emphasizes that the molecular mechanisms of epileptogenesis and tumorigenesis are closely linked [6, 8]. However, epilepsy at presentation has been associated with longer survival in some studies, although the prognostic value of this finding remains controversial.

We conducted a systematic review and meta-analysis to investigate the impact of epilepsy at presentation on glioblastoma prognosis based on existing literature. The primary objective of this review was to elucidate disparities in months of Overall Survival (OS) between GBM patients presenting with seizures and patients with other presenting symptoms (e.g., headache, focal neurologic deficit, cognitive deficit). The secondary objective aimed to evaluate potential differences in progression-free survival (PFS) between these two patient groups.

Materials and methods

This systematic review adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We followed the PRISMA 2020 Checklist, as reported in Table S1. Notably, no review protocol was registered before the start of the review process.

Search strategy

A systematic search was independently performed by M.B. and J. R. for all articles published until December 2023, on "MEDLINE, EMBASE, CINAHL, SCOPUS, WEB OF SCIENCE".

We used the following keywords: "Epilepsy", "epilep*", "Seizures", "seizure", "Glioblastoma", "astrocytoma", "glioblastoma", "Survival Analysis", "Survivors", "Disease-Free Survival", "surviv*" (Table S2).

Study selection and data extraction

A preliminary evaluation of findings involved screening titles and abstracts. Both prospective observational and retrospective studies were considered. Subsequently, the search was refined to encompass studies with full-text availability in the English language. We included both prospective and retrospective observational studies that presented data on OS in patients with epilepsy compared to those without epilepsy at the time of clinical presentation. Single case reports, review articles, and conference abstracts were excluded. Additionally, we omitted articles that focused on outcomes other than the prognostic significance of seizures at clinical onset on survival in GBM patients, as well as studies that included gliomas of varying grades or tumors with differing histological characteristics. Furthermore, we excluded studies that lacked specific information regarding epilepsy, GBM therapy, or the natural history of the tumor. Article selection and review were conducted by two authors (F.C. and J.R.). Upon identification of pertinent studies, data were independently extracted from each article. Any discrepancies in study inclusion were resolved through discussion involving a third investigator (F.V.) to reach a consensus decision.

The extracted relevant data from the included articles following full-text review encompassed: study design; sample size; demographic characteristics of patients (sex and age); performance status at diagnosis; tumor side and volume; tumor histology; IDH mutation and MGMT gene methylation status; type of surgery (biopsy, gross-total resection, or subtotal resection); adjuvant

Table 1 Demographic and clinical characteristics of the patients included in this review

First Author (year)	Study design	*N* of patients	Age (years)	Sex	Performance status	Molecular profile	Tumor volume	Type of surgery	Adjuvant therapies	*N* of patients with seizures as a presenting symptom	Age in patients with seizures (years)	Duration of symptoms (from onset to diagnosis) in patients with seizures	*N* of patients without seizures	Age in patients without seizures (years)	Duration of symptoms (from onset to diagnosis) in patients without seizures
Ozbek, 2004 [10]	OBSTU	76	median: 55; range: 19–86	M:54 (71%) F:22 (29%)	KPS ≥ 70: 45 (59.2%); KPS < 70: 31 (40.8%)	NA	NA	Biopsy: 1 (1.3%); STR: 57 (75%); GTR: 18 (23.7%)	RT: 76 (100%)	11 (14.5%)	NA	Mean: 57.5 days; SD: 63.78 days	65 (85.5%)	NA	Mean: 78.9 days; SD: 76.14 days
Toledo,2015 [11]	OBSTU	134	mean: 56; SD: 14.7; range: 14–78	M: 88 (66%); F: 46 (34%)	NA	De novo GBM: 113 (84%); "secondary"GBM: 21 (16%)	NA	GTR: 89 (66.4%)	RT: 103 (76.9%) CT: 98 (73.1%)	37 (27.6%)	NA	8.9 months	97 (72.4%)	NA	NA
Berendsen, 2016 [17]	OBSTU	647	mean: 61.5; SD: 12.3	M 387 (59.8%); F 260 (40.2%)	KPS ≥ 70: 461 (71.3%); KPS < 70: 182 (28.1%)	IDH1 R132H mutation: 8/136 patients (5.9%) in the epilepsy group vs. 13/224 (5.8%) in patients without epilepsy	Epilepsy group: median 17.8 cm^3, range 0.1–201.6 cm^3; Patients without epilepsy: median 40.7 cm^3, range 0.4–204.2 cm^3	Biopsy: 223 (34.5%); debulking: 424 (65.5%)	None: 147 (22.7%); monotherapy RT or TMZ: 163 (25.2%); RT+TMZ: 332 (51.3%); Missing: 5 (0.8%)	212 (32.9%)	mean: 59.3; SD: 12.8	NA	435 (67.1%)	mean: 62.5; SD:11.9	NA
Flanigan, 2017 [12]	OBSTU	443	mean: 60.2; SD: 12.4	M: 266 (60%); F: 177 (40%)	NA	NA	mean: 4.7 cm^3; SD: 1.5	GTR: 219 (49%)	RT: 382 (95%); TMZ: 363 (91%); adjuvant therapy (e.g., Bevacizumab): 182 (46%);	63 (14.2%)	Age ≥ 65 years: 9 (20%) in seizure-only group, 5 (28%) in symptoms post-seizure group	NA	374 (84.4%)	NA	NA
Toledo, 2017 [18]	OBSTU prospective	56	mean: 57; SD: 13.4; range: 30–77	M: 32 (57%); F: 24 (43%)	median KPS: 80	IDH1 R132H mutation: 5/56 (8.9%)	NA	GTR: 33 (58.9%)	RT: 49 (87.5%); CT: 47 (83.9%)	15 (26.8%)	NA	NA	41 (73.2%)	NA	NA
Lorimer, 2017 [13]	OBSTU	339	median: 75; range 70–90	M: 192 (57%); F: 147 (43%)	ECOG = 0: 23 (7%); ECOG = 1: 105 (32%); ECOG = 2: 97 (30%); ECOG = 3: 75 (23%); ECOG = 4: 27 (8%)	NA	NA	biopsy: 68 (20%); STR: 71 (21%); GTR: 37 (11%)	BSC: 202 (60%); palliative RT: 91 (27%); radical RT: 6 (2%); TMZ: 21 (6%); RT + TMZ: 18 (5%); lomustine alone: 1 (< 1%)	94 (27.7%)	NA	NA	245 (72.3%)	NA	NA
Rigamonti, 2017 [19]	OBSTU	151	mean: 72.4 years; range 65–83	M: 91 (60.3%); F: 60 (39.7%)	KPS ≥ 70: 117 (77.5%); KPS < 70: 34 (22.5%)	IDH1 R132H mutation: 2/36 (5%)	NA	GTR: 101 (66.8%); STR: 24 (15.9%); biopsy: 26 (17,3%)	RT + CT: 93 (61.6%); RT: 21 (13.9%); CT: 4 (2.6%); none: 33 (21.9%)	32 (21.1%)	NA	NA	119 (78.8%)	NA	NA
Dobran, 2018 [14]	OBSTU	139	mean: 62 years; range: 25–86	M: 85 (61.2%); F: 54 (38.8%)	KPS > 70: 102 (73.4%); KPS < 70: 37 (26.6%)	NA	NA	GTR: 62 (44.6%); STR + partial + biopsy: 77 (55.4%)	RT+TMZ: 85 (61%); RT: 13 (9%); CT:16 (12%); no adjuvant therapy: 25 (18%)	50 (35.9%)	< 65 years: 36 (72%); >65 years: 14 (28%)	NA	89 (64.1%)	< 65 years: 33 (23.9%); >65 years: 56 (40.6%)	NA

Table 1 (continued)

First Author (year)	Study design	*N* of patients	Age (years)	Sex	Performance status	Molecular profile	Tumor volume	Type of surgery	Adjuvant therapies	*N* of patients with seizures as a presenting symptom	Age in patients with seizures (years)	Duration of symptoms (from onset to diagnosis) in patients with seizures	*N* of patients without seizures	Age in patients without seizures (years)	Duration of symptoms (from onset to diagnosis) in patients without seizures
Dührsen, 2019 [21]	OBSTU	107	Epilepsy group: mean 62.3 years, SD 11.6; patients without epilepsy: mean 65.0 years, SD 10.7	M: 57 (53%); F: 50 (47%)	NA	IDH-wild type: 107 (100%)	Epilepsy group: mean 24.81cm^3; SD 4.32 $cm^{3;}$ patients without epilepsy: mean 44.43 cm^3; SD 3.29 cm^3	NA	RT+TMZ: 87 (81%); RT: 9 (8%); TMZ: 6 (6%); no adjuvant therapy: 5 (5%)	23 (21.5%)	mean: 62.3; SD: 11.6	NA	84 (78.5%)	mean: 65.0; SD: 10.7	NA
Henker, 2019 [22]	OBSTU	224	mean: 65.8 years; SD 10.6 (range 31-92)	M:123 (54.9%); F: 101 (45.1%)	mean KPS: 73.8; SD: 18.11	IDH-wild type: 224 (100%); MGMT unmethylated: 68/109 (62.4%)	Mean: 32.1 $cm^{3;}$ SD: 26.73 cm^3	GTR: 99 (45%)	NA	74 (33%)	NA	NA	150 (67%)	NA	NA
Ahmadipour, 2021 [20]	OBSTU	867	mean: 63.83; SD: 11.51	M: 501 (57.8%); F: 366 (42.2%)	KPS 90–100: 338 (39.7%); KPS 70–80: 414 (48.6%); KPS ≤ 60%: 100 (11.7%)	IDH1 mutation: 17 (3.1%); missing IDH1 mutation status: 311 (35.9%); MGMT promoter methylation: 310 (41.6%); missing MGMT promoter methylation status.: 121 (14%)	NA	biopsy: 247 (28.5%)	NA	236 (27.2%)	NA	NA	631 (72.8%)	NA	NA
Mrowczynski, 2021 [15]	OBSTU	218	median: 64; range: 5–88	M: 110 (51%); F: 108 (49%)	NA	NA	NA	NA	RT: 148 (67.9%); TMZ 152 (69.7%)	21 (9.6%)	NA	NA	197 (90.4%)	NA	NA
Zhao, 2021 [23]	OBSTU	194	median: 55; range: 19–80	M: 115 (59.3%); F: 79 (40.7%)	KPS: ≥70: 194 (100%)	IDH-wild type: 194 (100%)	≤5 cm: 123(63.4%); >5: 71(36.6%)	GTR: 194 (100%)	concurrent RT+CT: 194 (100%); adjuvant CT: 194 (100%)	22 (11.4%)	NA	NA	172 (88.6%)	NA	NA

Table 1 (continued)

First Author (year)	Study design	*N* of patients	Age (years)	Sex	Performance status	Molecular profile	Tumor volume	Type of surgery	Adjuvant therapies	*N* of patients with seizures as a presenting symptom	Age in patients with seizures (years)	Duration of symptoms (from onset to diagnosis) in patients with seizures	*N* of patients without seizures	Age in patients without seizures (years)	Duration of symptoms (from onset to diagnosis) in patients without seizures
Jilla, 2022 [16]	OBSTU	46	median 51; range 21–76 years	M: 26 (56.5%); F: 20 (43.5%)	ECOG 1,2: 21 (45,7%); ECOG 3, 4: 25 (54,3%)	NA	NA	GTR: 17 (37%); STR: 29 (63%)	concurrent TMZ: 31 (67.4%); ≥ 6 cycles of adjuvant TMZ: 15 (32.6%); <6 cycles of adjuvant TMZ: 31 (67.4%)	14 (30%)	NA	NA	32 (70%)	NA	NA
Pesce, 2022 [24]	OBSTU	177	Epilepsy group: mean 57.3 years, SD 13.31; patients without epilepsy: mean 62.3 years, SD 12.31	M: 97 (54.8%); F: 80 (45.2%)	KPS ≥ 80: Patients with seizures *N* = 37/49 (75.5%); Patients without seizures *N* = 90/128 (70.31%); KPS < 80: Patients with seizures *N* = 12 (24.5%); Patients without seizures *N* = 38 (29.69%)	Patients with seizures: MGMT methylation in 11/18 cases (61.1%); patients without seizures: MGMTmethylation in 14/32 cases (43.75%)	patients with seizures: mean 18.97 cm^3, SD 16.6 cm^3; patients without seizures: mean 22.85 cm^3; SD 18.63 cm^3	Patients with seizures: GTR 46/49 (93.8%); STR 3/49 (6.2%); patients without seizures: GTR 104/128 (81.25%); STR 24/128 (18.75%)	RT+TMZ: 177 (100%)	49 (27.7%)	mean: 57.3; SD:13.31	NA	128 (72.3%)	mean: 62.3; SD:12.31	NA

Abbreviations: Observational Study (OBSTU); male (M); female (F); Karnofsky Performance Status (KPS); Eastern Cooperative Oncology Group (ECOG); not available (NA); isocitrate dehydrogenase (IDH); Gross total resection (GTR); subtotal resection (STR); radiotherapy (RT); Temozolomide (TMZ); chemotherapy (CT); standard deviation (SD)

treatments (e.g., chemotherapy and/or radiotherapy, palliative care); the proportion of patients experiencing epilepsy as the presenting manifestation; the average time between the onset of symptoms and the histological diagnosis (when available). Overall survival and PFS in patients with epilepsy compared to patients without epilepsy at clinical presentation, as well as hazard ratio (HR) data were presented. Missing summary data was not included in the analysis. No sensitivity analysis was planned.

Risk of bias assessment of included studies

We conducted a Risk of Bias assessment for each included study utilizing the Newcastle-Ottawa Scale (NOS) tool. This tool uses a 'star system' in which a study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively. Two authors (J.R. and F.Ve.) performed the quality assessment independently. Any discrepancy was resolved by discussion.

The certainty of evidence assessment was not planned.

Meta-analysis

We conducted a meta-analysis of included studies reporting the effect size as HR on OS. We obtained estimates of log hazard ratios and standard errors from results of multivariate Cox proportional hazards regression models. We also included estimates from univariate Cox proportional hazards regression, when adjusted estimates were not available. Log hazard ratios and standard errors were combined using a random effects model with restricted maximum likelihood (REML), while heterogeneity was assessed using the I2 statistics. We also undertook subgroup analyses to explore and identify potential sources of heterogeneity among the included studies. Meta-analysis was performed using STATA 16.1 IC (Stata Corporation, Texas, TX). The publication bias was assessed visually using the funnel plot.

Results

Literature search

Following an initial search, a total of 2804 publications were screened. Among these, 977 duplicates were identified and subsequently removed. The eligibility of the remaining 1827 papers was assessed, leading to the exclusion of 1781 irrelevant articles who focused on other topics, based on criteria including title, article type, and abstract content. Consequently, 46 articles underwent full-text review. Among these, two were review articles; five studies investigated different outcomes and did not specifically examine the prognostic significance of seizures at clinical onset on survival in GBM patients; eight studies involved gliomas of varying grades or tumors with different histological characteristics, and eight studies lacked specific information regarding epilepsy, GBM therapy, or the natural history of the tumor. Additionally, 8 conference abstracts were not included. The flow diagram of the study selection process is reported in Figure S1.

Fifteen studies met the inclusion criteria and were consequently incorporated into the review process.

Characteristics and results of included studies

Tables 1 and 2 summarize demographic and clinical data, as well as survival data of patients included in the selected studies.

Exploring GBM patients regardless of IDH Mutation Status

We identified seven studies wherein no data regarding the biomolecular characterization of GBM were reported [10–16], and four studies that included both IDH-wild type and IDH-mutated tumors in survival analysis [17–20]. In these studies, a spectrum of 46 to 867 patients diagnosed with GBM was examined. The mean age varied between 56 and 72 years, while the percentage of GBM patients manifesting seizures spanned from 9.6 to 36%. Regarding survival analysis, only one study included IDH mutation status in the multivariate analysis [20]. Seizures at clinical onset were considered a favorable prognostic factor in six studies [10, 11, 13, 17, 18, 20]. Among these studies, one highlighted that seizures at the time of diagnosis were the sole predictor of extended survival among patients aged 60 years and below, while for patients over 60 years, neither seizures nor other factors were linked to prolonged survival [18]. Five studies did not find any differences in terms of overall survival between patients with seizures and patients with other presenting symptoms [12, 14–16, 19]. Specifically, Flanigan and colleagues did not identify significant differences in survival among patients with preoperative seizures. However, they observed that patients exclusively experiencing seizures in the presurgical phase survived more than twice as long as those who developed other symptoms after seizure onset (26.8 vs. 10.1 months, HR=0.21 [0.11–0.43], $P<0.001$), as well as patients without preoperative seizures (26.8 vs. 13.1 months, HR=0.50 [0.35–0.70], $P<0.001$) [12]. Only two studies reported results by seizure semiology with inconsistent results. The first reported a trend toward better prognosis in cases with secondary generalized seizures [20], while the second reported a lower median OS in patients with focal evolving to bilateral convulsive seizure, compared to patients presenting focal seizures with or without impairment of consciousness [14].

Table 2 Analysis of survival in the studies included in this review

First Author (year)	OS_seizure group	OS_non-seizure group	PFS_seizure group	PFS_non-seizure group
Ozbek, 2004 [10]	13 months	9 months	NA	NA
Toledo, 2015 [11]	1 year: 85.5%; 2 years: 48.7%; 5 years: 25.6%	1 year: 37.7%; 2 years: 12.9%; 5 years: 6.2%	NA	NA
Berendsen, 2016 [17]	Median: 13.2 months (95% CI: 11.4–14.9)	median 8.4 months (95% CI: 7.4–9.5)	NA	NA
Flanigan, 2017 [12]	Seizure-only at clinical onset: median 26.8 months, range 18.2–34.2; other symptoms post-seizures: 10.2 months, range 6.7–16.6	Median 14.3 months, range 13.1–15.6	NA	NA
Toledo, 2017 [18]	OS at 20 months in patients ≤ 60 years: 100%; OS at 20 months in patients > 60 years: 0%	OS at 20 months in patients ≤ 60 years: 58.3%; OS at 20 months in patients > 60 years: 19.5%	NA	NA
Lorimer, 2017 [13]	Presenting with seizures: HR 0.62; CI 0.481–0.795; $p < 0.001$; multivariate analysis: HR 0.632; CI 0.478–0.834; $p = 0.001$	NA	NA	NA
Rigamonti, 2017 [19]	Presenting with seizures: HR 0.8; $p = 0.67$		NA	NA
Dobran, 2018 [14]	mean: 10 months; SD: 2.3	mean: 7 months; SD: 1.6	NA	NA
Dührsen, 2019 [21]	Cox regression analysis: HR: 1.4 (CI: 0.777–2.523); $p = 0.26248$.	NA	NA	NA
Henker, 2019 [22]	Presenting with seizures, univariate analysis: HR 1.22; CI 0.801–1.85; $p = 0.357$	NA	NA	NA
Ahmadipour, 2021 [20]	median: 12.4 months (interquartile range: 6.2–21.2); $p < 0.0001$	median: 8.0 months (interquartile range: 3.1–14.9)	NA	NA
Mrowczynski, 2021 [15]	Presenting with seizures: HR 0.717; CI 0.427–1.201; $p = 0.206$	NA	NA	NA
Zhao, 2021 [23]	NA	- Presenting with non-seizures symptom, univariate analysis: HR 4.356 (95% CI: 1.053–18.027; $p = 0.042$) - Presenting with non-seizures symptom, multivariate analysis: HR 3.847 (95% CI: 0.918–16.120 $p = 0.065$)	NA	NA
Jilla, 2022 [16]	13.21 months	9.38 months	7.50 months	7.53 months
Pesce, 2022 [24]	mean: 20.20 months; SD: 17.11 months	mean: 16.44 months; SD: 13.73 months	mean: 9.71; SD: 10.84	mean: 9.35 months; SD: 12.9 months

Abbreviations: Overall survival (OS); Progression-free survival (PFS); Confidence interval (CI); Hazard ratio

Exploring IDH-wild type glioblastomas

Among the included studies, four were conducted specifically on IDH-wild type glioblastomas [21–24]. In these studies, a cohort ranging from 107 to 224 patients diagnosed with GBM was evaluated. The mean age ranged from 60 to 66 years, while the proportion of GBM patients experiencing seizures ranged from 11 to 33%. Regarding survival analysis, one study considered the extent of resection (but not the type of adjuvant treatment) in multivariate analysis [21]. Another study excluded subtotal resections with extensive residual disease, biopsies, and absence of adjuvant therapies (RT+CT) following surgery from the survival analysis [22]. Finally, two studies included only patients who underwent total or subtotal resection of the lesions, followed by a standard Stupp protocol from 30 to 35 days after surgery [23, 24]. None of the four included studies identified any difference in overall survival between patients presenting with seizures and those with alternative presenting symptoms.

Meta-analysis

Eleven studies reported the effect size of preoperative seizure on OS as HR (of which 9 reporting adjusted HR and 2 reporting unadjusted HR only), and were therefore included in the meta-analysis [10–13, 15, 17, 19–23]. The total sample size was of 3269 patients of which 774 (23.7%) with preoperative seizures. Three studies included only cases with IDH-wild type GBM [21–23], other three studies reported proportion of IDH-mutated cases ranging from 3 to 6% [17, 19, 20], while five studies reported no information on IDH mutation status [10–13, 15]. The overall pooled estimate was HR 0.73 (95% CI 0.61–0.87) as reported in Fig. 1. Despite this, the forest plot and the I2=56.8% suggested underling heterogeneity among studies.

Subgroup analysis was conducted based on the proportion of IDH-mutated cases, which included studies reporting no data on this variable, studies encompassing only IDH-wild type cases, and studies with mixed populations. The results of this analysis are presented in Fig. 2. Additionally, Fig. 2 illustrates the proportion of IDH-mutated cases for studies with mixed populations, along with the Risk of Bias assessed through the number

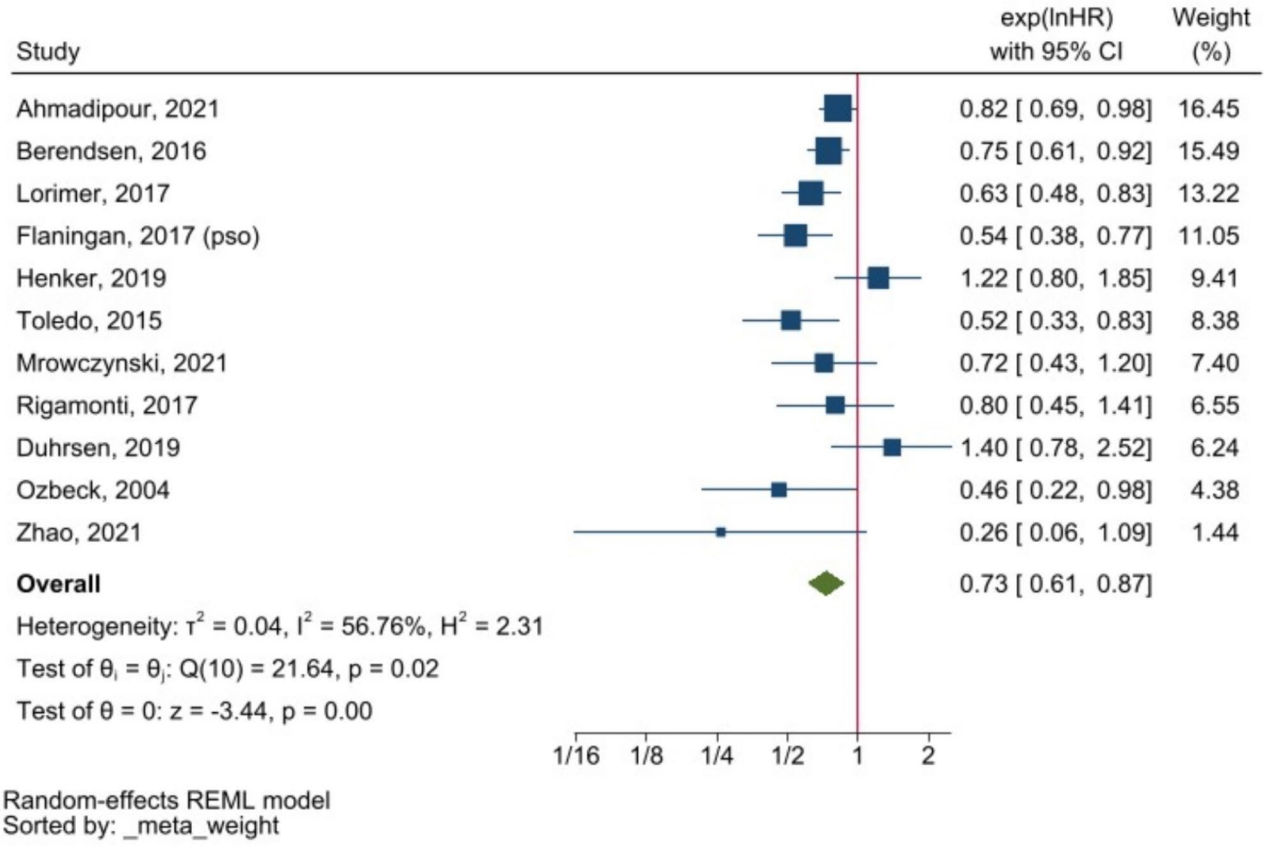

Fig. 1 Forest plot analysis of pooled Hazard Ratios characterizing the relationship between positive seizure history at initial presentation and mortality in patients with glioblastoma

Abbreviations: pre-operative seizure only (pso)

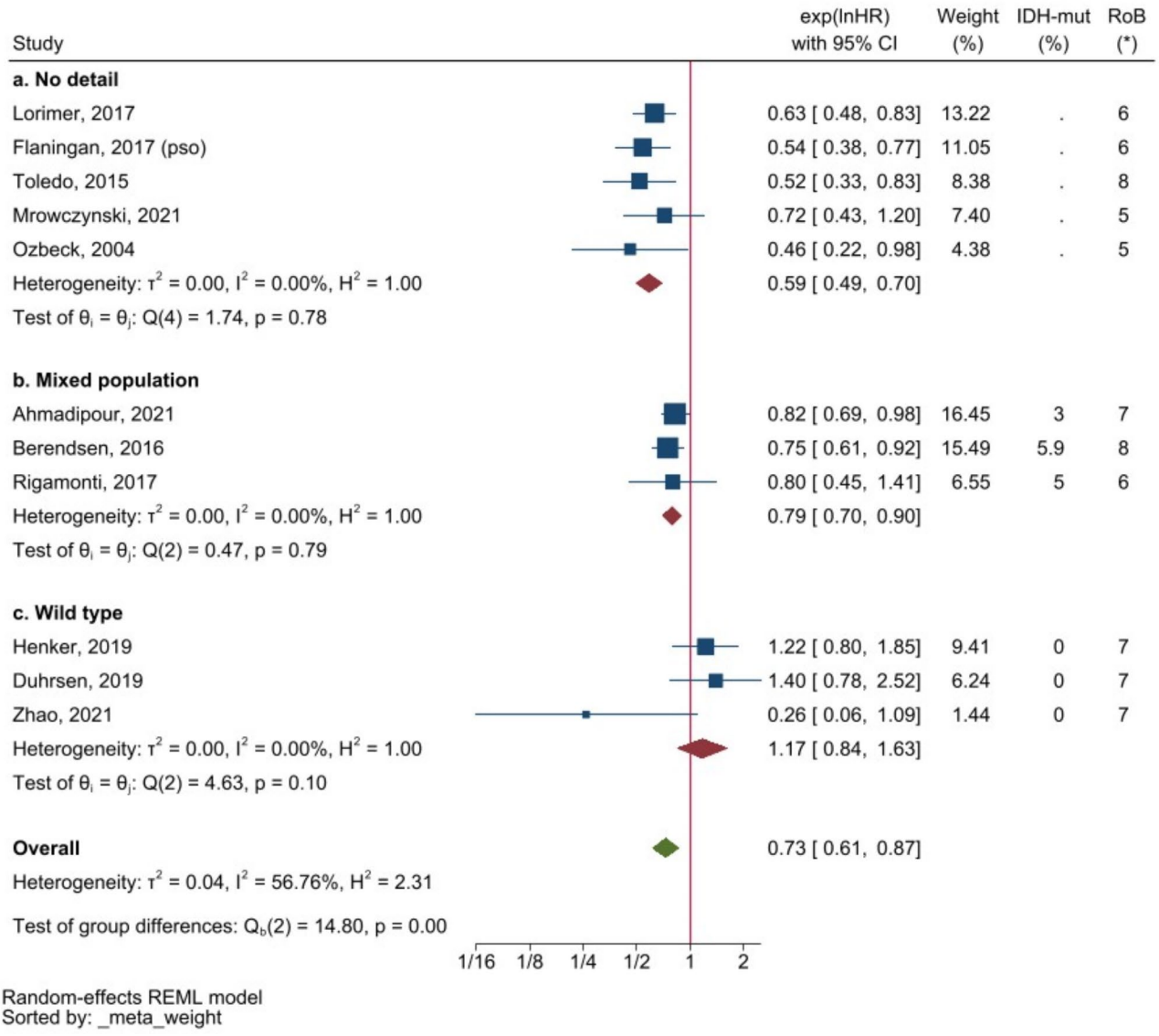

Fig. 2 Forest plot of subgroup analysis according to proportion of IDH-mutated cases
Abbreviations: pre-operative seizure only (pso)

of stars according to the Newcastle-Ottawa Scale (NOS), as outlined in Table 3 and S3. The subgroup analysis suggested no effect of preoperatory seizures in studies including only IDH-wild type cases, while the HR showed a decreasing trend with the increase of the proportion of IDH-mutated cases. It must be noted that IDH mutation status was not included in the multivariate analysis except for the study of Ahmadipour et al. 2021 [20], in which, however, IDH 1–2 mutation status was not available for 311 (35.9%) patients (Table 3 and S3). Given the positive association between IDH mutation, the presence of preoperatory seizures, and the better prognosis of IDH-mutated cases compared to IDH-wild type cases, a residual confounding may exist.

The funnel plot analysis suggested no relevant publication bias (Figure S2). A subgroup analysis excluding the two studies reporting unadjusted HR only was performed [15, 22], with no differences on pooled estimates (Figure S3).

Discussion

In this systematic review, 15 articles focusing on the role of epilepsy at clinical presentation in the prognosis of patients with GBM in terms of PFS and OS were analyzed. The sample size ranged from 46 to 867 adult patients. The percentage of patients with seizures at onset ranged from 9 to 36%. Only six studies reported information on seizure semiology [11, 12, 14, 18, 20, 24], and only two reported results by seizures type with inconsistent

Table 3 Risk of bias assessment reported as number of stars according to the newcastle-ottawa scale (NOS)

Study	Selection	Comparability	Outcome
Ozbek et al., 2004	**	*	**
Toledo e al., 2015	****	*	***
Berendsen et al., 2016	****	*	***
Toledo et al., 2017	****	*	***
Lorimer et al., 2017	***	*	**
Ahmadipour et al., 2021	****	*	**
Flanigan et al., 2017	***	*	***
Rigamonti, 2017	***	*	**
Dobran et al., 2018	***	*	**
Dührsen et al., 2019	***	**	**
Henker et al., 2019	****	*	**
Mrowczynski et al., 2021	**		***
Zhao et al., 2021	**	**	***
Jilla et al., 2022	***	*	**
Pesce et al., 2022	***	*	**

results [14, 20]. Seven studies did not reported any data regarding the biomolecular characterization of GBM [10–16], whereas four studies included both IDH-wild type and IDH-mutated tumors in survival analysis [17–20]. Among these, IDH mutation status was not included in the multivariate analysis except for the study conducted by Ahmadipour et al. in 2021 [20]. Nevertheless, in this particular study, the IDH 1–2 mutation status was unavailable for 311 out of 867 patients (35.9%). Finally, four studies specifically focused on IDH-wild type glioblastomas [21–24].

Seizures at clinical onset were considered a favorable prognostic factor in six studies [10, 11, 13, 17, 18, 20], whereas 8 studies did not find any differences in terms of overall survival between patients with seizures and patients with other presenting symptoms [14–16, 19, 21–24]. One study found a favorable prognostic role of seizures at onset, which was lost if other symptoms developed after epileptic onset [12]. This underscores that when there is a delay between the clinical onset of seizures and surgical intervention, the prognostic advantage of pre-operative seizures appears to diminish significantly.

It is notable that there is a paucity of reporting of subgroup analysis by combination of seizures and other presenting symptoms, as well as by type of seizures, which constrains the possibility of exploring the causal pathway linking pre-operative seizures with early diagnosis and prognosis.

Seizures are the presenting symptom of GBM in approximately 25–30% of patients [6]. Epileptogenesis in GBM is a dynamic process occurring within the peritumoral cortex. Here, the establishment of a microenvironment abundant in cytokines, chemokines, and growth factors plays a pivotal role, contributing not only to epileptogenesis but also to tumor proliferation and invasiveness [8, 25]. Moreover, specific molecular alterations in tumor cells can have a crucial impact on both tumor growth and seizure risk [6]. For instance, several mutations in genes that determine aberrant glutamate release by glioblastoma cells, and an excess of glutamatergic activity in the tumor environment, may favor epileptogenesis as well as tumor growth and invasiveness [8]. Indeed, several anti-glutamatergic drugs, such as the selective non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist perampanel, have demonstrated robust anti-epileptic activity, but also a potential anti-tumor effect according to several preclinical in vitro studies [26].

Therefore, it would be expected that the development of epilepsy in the pre-surgical phase should be associated with a higher rate of tumor growth and invasiveness. However, most of the studies conducted until 2018 demonstrated a favorable prognostic role of seizures at clinical onset in terms of overall survival. These studies presented some confounding factors, such as the inclusion of participants with differences in terms of tumor volume and location (lobar and midline or subtentorial tumors, the latter often linked to a poorer prognosis and infrequently associated with epilepsy), extent of tumor resection, and adjuvant therapies. Most importantly, most studies conducted until 2018 included both IDH wild-type and IDH-mutated glioblastomas.

It is widely recognized that mutations in the IDH gene are associated with an elevated risk of seizures both before and after surgery. Specifically, the R132H mutation of the IDH1 gene leads to a gain of gene function, resulting in the accumulation of D-2-hydroxyglutarate (D-2-HG), a compound structurally analogous to glutamate [27]. Furthermore, the IDH1-2 mutation is linked to a more favorable prognosis, evidenced by a median overall survival of 32 months compared to 23 months for GBM with MGMT gene promoter methylation and 12 months for unmethylated GBM [28]. Other patient-related and tumor-related factors are associated with both early seizures and better survival. For instance, early seizures in GBM are often associated with younger age and small cortical lesions, more often located in temporal or frontal lobe, which are more easily attacked by surgery and therefore more susceptible to complete excision [29].

With the advent of the new 2021 classification of primary tumors of the central nervous system, mutation of the IDH gene has become an exclusion factor for the diagnosis of glioblastoma [5], and most studies from 2021 onwards excluded IDH mutated tumors from survival analyses. At the same time, these studies found no differences in survival between patients with seizures at onset and seizure-free patients.

In the context of the meta-analysis, despite the comprehensive pooled analysis suggesting a potential beneficial prognostic influence linked to seizures at the onset of glioblastoma, the subgroup examination reveals an absence of identifiable impact from preoperative seizures within studies confined to wild-type cases. Notably, the hazard ratio demonstrates a diminishing trend in association with an increasing prevalence of IDH-mutated cases. According to the subgroup analysis, an effect modification of IDH-mutation status could also not be excluded. Moreover, studies such as that by Toledo et al. have reported that seizures at the time of diagnosis were the sole predictor of extended survival among patients aged 60 years and below. In contrast, for patients over 60 years, neither seizures nor other factors were linked to prolonged survival [18]. Given that IDH mutations are more commonly found in younger patients, it is possible that the potential inclusion of some IDH-mutant cases could have contributed to the survival differences observed, particularly in younger patients with seizures.

Therefore, studies with more reliable data on IDH mutation status are needed to disentangle the prognostic value of peri-operatory seizures.

Furthermore, additional limitations are evident, particularly regarding the heterogeneity in the extent of surgery and adjuvant treatments administered to participants across various studies. Notably, only the investigations conducted by Zhao et al. [23] and Pesce et al. [24] exclusively enrolled patients who underwent total or subtotal resection of lesions, followed by a standard Stupp protocol.

Moreover, potential limitations encompass the retrospective design (except for the study conducted by Toledo and coworkers [18]), and the absence of PFS as a survival outcome (with the exception of the studies by Jilla et al. [16] and Pesce et al. [24]). Using PFS as a prognostic marker would provide more specific insights into the role of epilepsy in tumor progression, as OS may be influenced by diverse factors such as initial performance status, post-therapeutic complications, or the superimposition of other diseases during the clinical course.

Therefore, prospective studies involving homogeneous cohorts of IDH-wild type GBM patients are imperative to delineate more accurately the role of seizures at clinical onset in glioblastoma patients, focusing on both OS and PFS. A limitation of the review process is the lack of a review protocol registered before the start of the review process given by an oversight during the project initiation phase. Despite this, no deviations from the intended protocol occurred.

Conclusion

Although emerging evidence indicates a possible link between epileptogenesis and tumorigenesis in glioblastoma, our findings underscore the ongoing uncertainty regarding the prognostic significance of seizures at onset. Confounding factors, such as molecular heterogeneity, surgical extent, and variations in adjuvant therapies, continue to obscure clear conclusions in existing studies. To resolve this, future prospective research on large, well-defined cohorts of IDH-wild-type GBM patients is crucial, with a focus on minimizing bias and providing more definitive insights into the role of seizures in prognosis.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-13249-8.

Supplementary Material 1

Supplementary Material 2

Author contributions

Conceptualization: J.R., F.C., and F.V.; methodology: M.C.B., J.R., F.C.; software: M.C.B., G.T., G.D.R.; validation: F.Ve., G.B., C.L., B.D., A.C., A.N., R.R., M.R., M.B., C.I., G.P., P.G.R., A.P., and F.V.; formal analysis: F.C., G.T., F.Ve., G.D.R., P.G.R.; investigation: J.R., F.C., M.C.B., F.Ve., P.G.R.; resources: M.C.B.; data curation: J.R., F.C., M.C.B., F.Ve., G.B., C.L., B.D., P.G.R., A.C., F.V.; writing original draft preparation: J.R.; writing—review and editing: F.C., G.B., C.L., F.Ve., P.G.R., B.D., A.P., F.V.; visualization: J.R., F.C., M.C.B., F.Ve., G.T., G.D.R., G.B., C.L., B.D., A.C., A.N., R.R., M.R., M.B., C.I., G.P, P.G.R., A.P., F.V.; supervision: G.B., and F.V.; project administration: F.V.; funding acquisition: G.B., F.V. All authors have read and agreed to the published version of the manuscript.

Funding

This study was partially supported by Italian Ministry of Health – Ricerca Corrente Annual Program 2023; European Innovative Research&Technological Development Projects in Nanomedicine, ERA-NET EuroNanoMed III, project "Silk-fibroin interventional nano-trap for the treatment of glioblastoma" (EURONANOMED2019-75/GLIOSILK), to F.V.; the University of Modena and Reggio Emilia; FAR2021 Mission Oriented "Nano-Immuno Targeting for the Treatment of Glioblastoma Multiforme", to G.B., C.I., G.P.

Data availability

All data generated or analysed during this study are included in this published article.

Declarations

Ethics approval

Not applicable (systematic review).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Consent to participate

Not applicable, as this study did not involve humans.

Human ethics and consent to participate declarations

Not applicable.

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Received: 12 May 2024 / Accepted: 26 November 2024
Published online: 03 December 2024

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