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ORIGINAL COMMUNICATION

Prediagnosis epilepsy and survival in patients with glioma: a nationwide population-based cohort study from 2009 to 2018

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Abstract

Objective Considering that epilepsy is common, and knowledge is lacking on its role especially for the prognosis of high-grade gliomas, the objective of this study was to investigate the association between epilepsy prior to glioma diagnosis and survival among glioma patients.

Methods In a nationwide population-based cohort study, we included 3763 adult glioma patients diagnosed between 2009 and 2018 according to the Danish Neuro-Oncology Registry. Information on epilepsy was redeemed through Danish Neuro-Oncology Registry, National Patient Registry, and National Prescription Registry. Cox proportional hazard models with 95% confidence intervals (CIs) were applied to examine hazard ratios (HRs) for the association between epilepsy (< 1 year prior to glioma including epilepsy at onset; 1–10 years prior to glioma; no prior epilepsy) and risk of death, and whether it differed according to tumor grade and size, performance status, and treatment modalities.

Results A 32% decreased risk of death in patients with epilepsy within 1 year prior to glioma compared to no prior epilepsy was found (HR = 0.68; CI 0.63–0.75). A favorable prognosis was seen for epilepsy in all glioma grades: II (HR = 0.55; CI 0.39–0.77), III (HR = 0.59; CI 0.48–0.73), and IV (HR = 0.85; CI 0.77–0.94).

Conclusions Patients with epilepsy within 1 year prior to glioma diagnosis had significant survival benefits compared to patients with no prior epilepsy. This association was significant for both low-grade gliomas (grade II) and high-grade gliomas (grade III and IV). Survival benefits in glioma patients with epilepsy at onset are possibly primarily attributable to tumor-specific histopathology, molecular biomarkers, and early diagnosis.

Keywords Epilepsy · Preoperative · Survival · Glioma · Grade

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Introduction

Epilepsy could play a role in glioma survival, especially as an onset symptom of glioma [1]; however, knowledge is lacking regarding this association in high-grade gliomas (HGGs). Epileptic seizures may occur at any time during the disease course, years before glioma presentation (mostly pre-magnetic resonance imaging (MRI) era), at onset, or they may develop later on in the course of glioma [2]. Incidence of coexisting epilepsy and glioma varies according to tumor grade: from 58–90% in low-grade gliomas (LGGs, World Health Organization (WHO) grade II) [3, 4] where around 85% of the patients experience it at glioma onset [4], to 30–60% in HGGs (WHO grade III-IV) [3, 4] where approximately 42% of the patients experience it at onset [1]. Mechanisms of glioma-related epilepsy are not completely understood, and different factors have been suggested to play a role according to tumor grades. On one hand, LGGs may be more epileptogenic due to their slow-growing nature [5] and the presence of specific molecular biomarkers [6, 7]. On the other hand, the lower epileptogenicity of HGGs may be due to their rapid-growing nature mechanically compressing the brain tissue, resulting in other dominating neurological symptoms rather than epileptic seizures [5].

Previous studies on LGGs [8–16], HGGs [1, 17–24], and across tumor grades [25, 26] have found conflicting results regarding the impact of epilepsy on survival. A number of studies found that epilepsy has a positive effect on glioma survival [1, 8–14, 17, 19, 21, 23, 25, 26], particularly when epileptic seizures are the presenting symptom of glioma [1, 10, 11, 13, 17, 23, 25, 26], while others did not find such survival benefit [15, 16, 18, 20, 22, 24, 25], especially when adjusting for various clinical and paraclinical characteristics [15, 18, 20, 22, 24].

The majority of the former studies are limited by small populations ($N = 19$–172) [8–10, 13, 18, 19, 21–23], only two studies have investigated differences in survival benefit between LGG versus HGG patients [25, 26], and knowledge on potential survival benefits according to timing of epilepsy onset prior to glioma diagnosis or according to clinical and paraclinical characteristics remains largely unexplored.

Investigating the effect of prior epilepsy on survival among glioma patients might help identify a potential subgroup of glioma patients with prior epilepsy who exhibit a unique disease course and have common biological features that require a targeted treatment towards both the seizures and the tumor.

Using a large nationwide population-based cohort study, our primary aim was to examine the association between epilepsy prior to glioma diagnosis and survival among patients with gliomas, considering the duration of prediagnosis epilepsy and adjusting for the prognostic effect of other clinical and paraclinical characteristics.

Materials and methods

Study design

A nationwide population-based cohort study including all 3763 patients with histologically verified gliomas grade II, III, and IV diagnosed across Denmark between 2009 and 2018 merging data from three Danish health registries by applying the unique personal identification numbers assigned to all Danish citizens in the Danish Civil Registration System since 1st of April 1968 [27].

Data sources

The Danish Neuro-Oncology Registry (DNOR) is a nationwide clinical database including all patients aged ≥ 18 years, diagnosed with histologically confirmed glioma since 2009 [28]. To obtain the most homogeneous adult case population, we have excluded WHO grade I gliomas. Data on tumor type and grade were obtained by the contemporary WHO classifications from 2007 [29] and 2016 [30]. Moreover, clinical and paraclinical characteristics including: age at diagnosis, sex (male; female), WHO grade (II; III; IV), onset symptoms [focal symptoms (yes; no), cognitive change (yes; no), headache (yes; no), epilepsy (yes; no)], contrast enhancement (yes; no), unifocality (yes; no), midline crossing (yes; no), localization (frontal; temporal; parietal; occipital; other), tumor size (i.e., longest tumor diameter; < = 45 mm; > 45 mm), Eastern Cooperative Oncology Group (ECOG) performance status prior to surgery[31](0–2; 3–4), type of surgery (biopsy; partial resection; macrototal resection), radiotherapy (yes; no), and chemotherapy (yes; no) were obtained. Furthermore, information on comorbidities at glioma diagnosis according to Charlson's comorbidity index [32] was obtained and the calculated Charlson's comorbidity index had three values: score 0 (no comorbidity), 1–2 (medium comorbidity), and 3 + (high comorbidity).

The Danish National Patient Registry (DNPR) includes information on inpatient department contacts since 1977 and outpatient contacts since 1995 [33]. Information on epilepsy diagnosis between January 1st 2005 and December 31st 2017 according to the International Classification of Diseases, Tenth Revision (ICD-10): DG40, DG41, DZ033A, DR568, DR568C, DR568D, DR568E, DR568F, DR568G was obtained.

The Danish National Prescription Registry (DNPrR) includes information on all medications prescribed since 1995[34]. Information on antiepileptic medication

prescribed between January 1st 1999 and December 31st 2018 using the Anatomical Therapeutic Chemical (ATC) codes was obtained: N03AA, N03AB, N03AC, N03AD, N03AE, N03AF, N03AG, and N03AX.

When seizure history, which in the DNOR has been obtained by a physician at glioma diagnosis, was negative or undefined, epilepsy was operationalized as having either a hospitalization diagnosis with epilepsy according to the DNPR or being prescribed antiepileptic medication before glioma diagnosis according to the DNPrR. The duration of epilepsy was categorized as: < 1 year prior to glioma diagnosis (including epilepsy at onset); 1–10 years prior to glioma diagnosis; no prior epilepsy. Categorization into further time periods was not possible due to sample size.

Study population

We identified 3922 patients aged ≥ 18 years diagnosed with histologically verified glioma WHO grades II, III, and IV between January 1st 2009 and December 31st 2018, and following exclusion of persons with missing date of histological diagnosis ($N = 136$) and unspecified glioma grades ($N = 23$), we analyzed 3763 cases with complete information according to the analysis protocol.

Statistical analyses

Descriptive analyses were performed to compare glioma patients' clinical and paraclinical characteristics and treatment data according to the epilepsy status (< 1 year prior to glioma diagnosis; 1–10 years prior to glioma diagnosis; no prior epilepsy) using the Chi-square test for categorical and t test for continuous variables. p values < 0.05 were considered statistically significant. Survival data were evaluated by Kaplan–Meier plots, and the differences were estimated with the log-rank test.

Cox proportional model with hazard ratios (HRs) and 95% confidence intervals (CIs) were used to assess the association between epilepsy (< 1 year prior to glioma diagnosis; 1–10 years prior to glioma diagnosis; no prior epilepsy as reference) and risk of death. Time since diagnosis was used as the underlying time scale, and patients were followed until date of death, date of emigration, or 31st December 2018, whichever came first. To meet the proportionality assumption, we stratified by both age and comorbidities, i.e., we allowed for different baseline hazards in each stratum. To address potential confounding effects, all models were adjusted for age and comorbidities. To explore potentially vulnerable subgroups, we examined effect measure modification according to tumor grade, tumor size, ECOG performance status prior to surgery, and treatment modalities. Due to missingness in some of the variables, we furthermore performed multiple imputation, with the assumption that data were missing at random as a sensitivity analysis supplementing the complete case analyses. We used the substantive-model compatible fully conditional specification [35], to impute missing values for the covariates tumor size ($N = 389$) and performance status prior to surgery ($N = 330$), using data from tumor grade, type of surgery, and radio- and chemotherapy as auxiliary variables. For each missing variable, we created 20 imputed datasets with 15 iterations and pooled the results according to Rubin's rule. Analyses were performed using the statistical program R version 3.6.3[36].

Data protection and ethics

This study was approved by the Danish Cancer Society (No. 2018-DCRC-0054). The Danish legislation allows use of administrative registry data without approval from the Ethics Board or the collection of informed consent when no patients are contacted to conduct a scientific study.

Data availability statement

Conforming to Danish legislature and the EU General Data Protection Regulation, as data included in the study are obtained from Danish health registries, it cannot be publicly accessed.

Results

Clinical and paraclinical characteristics and epilepsy status of patients with gliomas

Around one-third (36%) of glioma patients had prior epilepsy: 31% of patients had epilepsy < 1 year prior to glioma diagnosis while only 5% had epilepsy 1–10 years prior to glioma diagnosis. Among patients with epilepsy < 1 year prior to glioma diagnosis, around 21% of them had grade II gliomas, 22% had grade III, while 57% of them had grade IV gliomas (Table 1).

In comparison to patients with epilepsy 1–10 years prior to glioma diagnosis and patients with no prior epilepsy, patients with epilepsy < 1 year prior to glioma diagnosis were characterized by being younger and male. In terms of clinical characteristics, patients with epilepsy < 1 year prior to glioma had a higher proportion with no comorbidity, and they showed less frequent prior focal symptoms, cognitive change, or headache. Moreover, the majority of these patients were characterized by having tumors that showed no contrast enhancement, unifocal, and that mainly did not cross midline, with primarily frontal and temporal localizations, smaller tumor size, and good performance status prior to surgery. In terms of treatment modalities, patients with epilepsy < 1 year prior to glioma had a smaller proportion of

Table 1 Clinical and paraclinical characteristics by epilepsy status in 3,763 glioma patients

Characteristics	Epilepsy < 1 year prior to glioma No. (%)	Epilepsy 1–10 years prior to glioma No. (%)	No prior epilepsy No. (%)	Total No. (%)	*p* Value
	1160 (30.8)	196 (5.2)	2407 (64)	3763 (100)	
Age at diagnosis (years)					< 0.001
Mean (SD)	55.97 (15.7)	61.43 (14.2)	63.35 (12.9)	60.98 (14.3)	
Sex					0.003
Male	712 (61.4)	95 (48.5)	1421 (59.0)	2228 (59.2)	
Female	448 (38.6)	101 (51.5)	986 (41.0)	1535 (40.8)	
WHO-tumor grade					< 0.001
II	242 (20.9)	30 (15.3)	165 (6.9)	437 (11.6)	
III	251 (21.6)	30 (15.3)	293 (12.2)	574 (15.3)	
IV	667 (57.5)	136 (69.4)	1949 (80.9)	2752 (73.1)	
Charlson's comorbidity index					< 0.001
High	89 (7.7)	28 (14.3)	203 (8.4)	320 (8.5)	
Medium	165 (14.2)	47 (24.0)	354 (14.7)	566 (15.0)	
No comorbidity	906 (78.1)	121 (61.7)	1850 (76.9)	2877 (76.5)	
Focal symptoms[†]					< 0.001
Yes	460 (39.7)	110 (56.1)	1620 (67.1)	2185 (58.1)	
No	652 (56.2)	61 (31.1)	475 (19.7)	1188 (31.5)	
Missing	48 (4.1)	25 (12.8)	317 (13.2)	390 (10.4)	
Cognitive change					< 0.001
Yes	300 (25.9)	95 (48.5)	1135 (47.2)	1530 (40.7)	
No	808 (69.6)	73 (37.2)	934 (38.8)	1815 (48.2)	
Missing	52 (4.5)	28 (14.3)	338 (14.0)	418 (11.1)	
Headache					< 0.001
Yes	216 (18.6)	62 (31.6)	815 (33.9)	1093 (29.0)	
No	884 (76.2)	106 (54.1)	1230 (51.1)	2220 (59.0)	
Missing	60 (5.2)	28 (14.3)	362 (15.0)	450 (12.0)	
Contrast enhancement					< 0.001
Yes	820 (70.7)	144 (73.4)	1928 (80.1)	2892 (76.8)	
No	279 (24.0)	26 (13.3)	127 (5.3)	432 (11.5)	
Missing	61 (5.3)	26 (13.3)	352 (14.6)	439 (11.7)	
Unifocality					< 0.001
Yes	986 (85.0)	158 (80.6)	1748 (72.6)	2892 (76.9)	
No	135 (11.6)	17 (8.7)	342 (14.2)	494 (13.1)	
Missing	39 (3.4)	21 (10.7)	317 (13.2)	377 (10.0)	
Midline crossing					< 0.001
Yes	128 (11.0)	27 (13.8)	384 (16.0)	539 (14.3)	
No	945 (81.5)	140 (71.4)	1625 (67.5)	2710 (72.0)	
Missing	87 (7.5)	29 (14.8)	398 (16.5)	514 (13.7)	
Localization					< 0.001
Frontal	471 (40.6)	67 (34.2)	709 (29.5)	1247 (33.1)	
Temporal	346 (29.8)	45 (22.9)	606 (25.2)	997 (26.5)	
Parietal	186 (16.0)	25 (12.8)	337 (14.0)	548 (14.6)	
Occipital	63 (5.4)	17 (8.7)	203 (8.4)	283 (7.5)	
Other	54 (4.6)	21 (10.7)	239 (9.9)	314 (8.3)	
Missing	40 (3.4)	21 (10.7)	313 (13.0)	374 (10.0)	
Tumor size (mm)					< 0.01
< = 45 mm	683 (58.9)	91 (46.4)	1016 (42.2)	1790 (47.6)	
> 45 mm	431 (37.1)	82 (41.9)	1071 (44.5)	1584 (42.1)	

Table 1 (continued)

Characteristics	Epilepsy < 1 year prior to glioma No. (%)	Epilepsy 1–10 years prior to glioma No. (%)	No prior epilepsy No. (%)	Total No. (%)	*p* Value
Missing	46 (4.0)	23 (11.7)	320 (13.3)	389 (10.3)	
ECOG performance status prior to surgery					< 0.001
0–2	1059 (91.3)	150 (76.5)	1865 (77.5)	3074 (81.7)	
3–4	65 (5.6)	28 (14.3)	266 (11.0)	359 (9.5)	
Missing	36 (3.1)	18 (9.2)	276 (11.5)	330 (8.8)	
Type of surgery					< 0.001
Biopsy	319 (27.5)	68 (34.7)	782 (32.5)	1169 (31.0)	
Partial resection	456 (39.3)	53 (27.0)	743 (30.9)	1252 (33.3)	
Macrototal resection	385 (33.2)	75 (38.3)	882 (36.6)	1342 (35.7)	
Radiotherapy					0.15
Yes	809 (69.7)	125 (63.8)	1695 (70.4)	2629 (69.9)	
No	351 (30.3)	71 (36.2)	712 (29.6)	1134 (30.1)	
Chemotherapy					0.001
Yes	486 (41.9)	73 (37.2)	1181 (49.1)	1740 (46.2)	
No	674 (58.1)	123 (62.8)	1226 (50.9)	2023 (53.8)	

WHO World Health Organization, *ECOG* Eastern Cooperative Oncology Group

[†]Focal symptoms include motor and sensory symptoms in addition to visual and speech disturbances

biopsies and macrototal resections performed, whereas the proportion for partial resections was higher.

Meanwhile, in comparison to only patients with no prior epilepsy, similar distributions were seen regarding the administration of radiotherapy, whereas chemotherapy was administered less frequently among patients with epilepsy < 1 year prior to glioma diagnosis.

Association between prediagnosis epilepsy and glioma survival

The descriptive Kaplan–Meier plot showed the highest survival probability among patients in the epilepsy < 1 year group, whereas only minimal differences were seen between the 1–10 years and no prior epilepsy groups (Fig. 1). Similar patterns were seen in the Kaplan–Meier plot according to grade and epilepsy status (Fig. 1). In models adjusting for age and comorbidity, we found that patients with epilepsy < 1 year prior to glioma had a 32% statistically reduced risk of death (HR = 0.68; CI 0.63–0.75) compared to patients with no prior epilepsy; a survival benefit which was not seen among patients with epilepsy 1–10 years prior to glioma diagnosis (HR = 0.98; CI 0.83–1.16) (Table 2).

We found statistically significant differences in the association between epilepsy and risk of death according to tumor grade, type of surgery, radiotherapy, and chemotherapy, as illustrated in both Fig. 2 and in Table 3. Patients with epilepsy < 1 year prior to glioma had significant survival benefits compared to patients with no prior epilepsy within all tumor grades, namely WHO grade II (HR = 0.55; CI 0.39–0.77), III (HR = 0.59; CI 0.48–0.73), and IV (HR = 0.85; CI 0.77–0.94). A similar pattern was seen concerning all types of surgery and administration of radiotherapy, whereas concerning chemotherapy, a statistically significant survival benefit was seen only in patients not receiving chemotherapy (HR = 0.51; CI 0.45–0.57). No statistically significant difference in estimates was seen according to tumor size and ECOG performance status prior to surgery.

Results from analyses applying multiple imputations showed similar results as the complete case analysis (data not shown).

Discussion

We demonstrate for the first time in a nationwide population-based cohort study that patients with epilepsy < 1 year prior to glioma have a significant survival benefit compared to patients with no prior epilepsy, which was significant across all glioma grades II, III, and IV (Fig. 2, Table 3). Conversely, we were not able to see such survival benefit for patients with epilepsy 1–10 years prior to glioma diagnosis, irrespective of tumor grade.

A few studies have examined epilepsy according to tumor morphological characteristics [5, 37].

A previous retrospective study including 124 patients found that patients with LGGs presenting with seizures

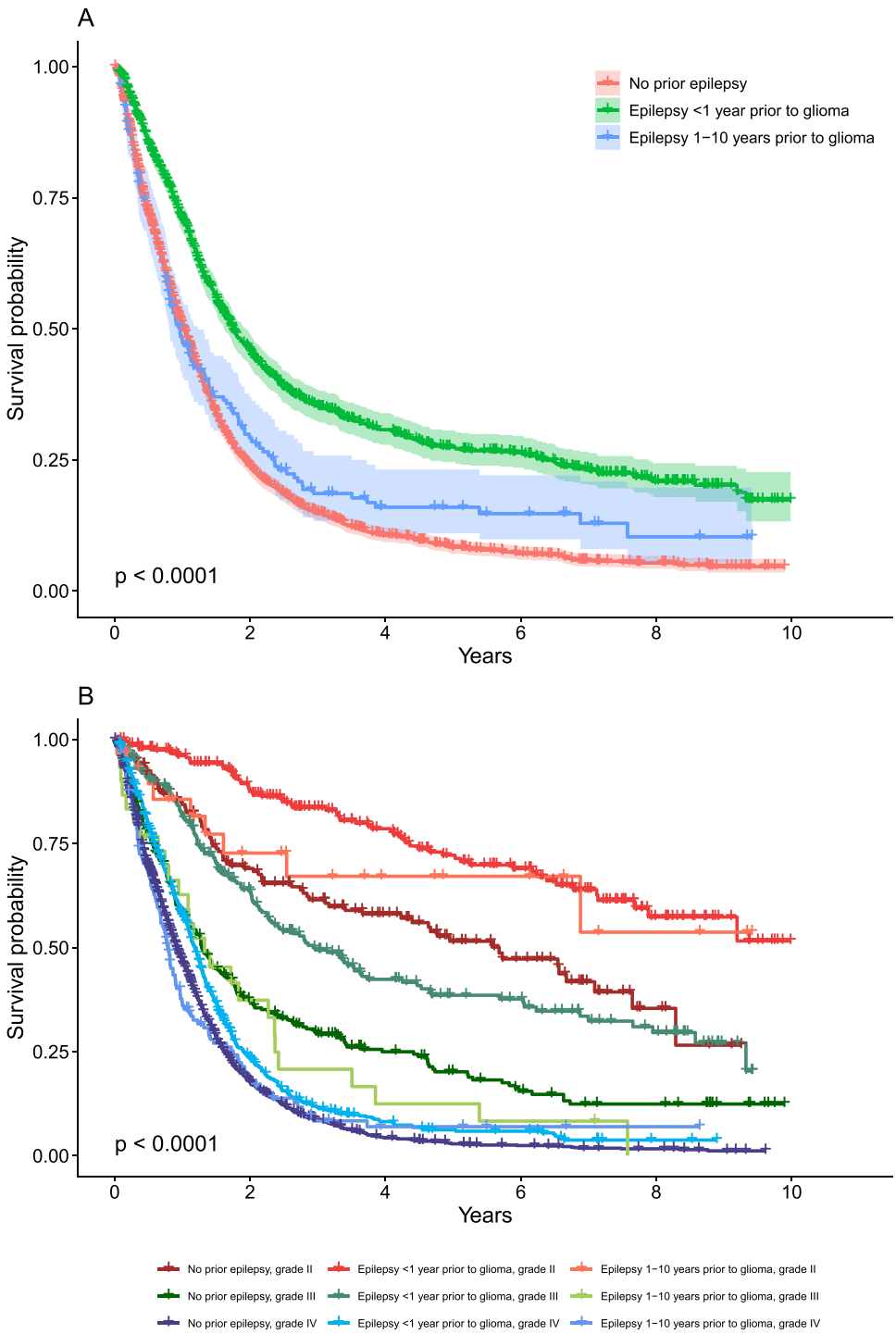

Fig. 1 Kaplan–Meier survival curves illustrating, respectively, survival probability according to epilepsy status (panel **A**) and according to epilepsy status and WHO grade (panel **B**) in 3763 glioma patients

tend to have larger tumors, while patients with HGGs tend to have smaller tumor sizes [5]. In addition, a more recent retrospective study on 160 glioblastoma patients also found that patients with preoperative seizures had lower tumor volume [37]. This is in line with our results, showing that patients with epilepsy < 1 year prior to glioma diagnosis have smaller tumor size (Table 1).

Association between prediagnosis epilepsy and glioma survival

To the best of our knowledge, no previous nationwide studies have examined the association between prior epilepsy and glioma survival according to various clinical and paraclinical characteristics and such a large scale of timing of

Table 2 Hazard ratios (HRs) and 95% confidence intervals (CIs) for association between epilepsy status and risk of death in 3763 glioma patients

	Hazard ratio (HR)	95% Confidence interval (CI)	*p*	Overall *p*
No prior epilepsy	1	(Reference)		< 0.001
Epilepsy < 1 year	0.68	(0.63–0.75)	< 0.001	
Epilepsy 1–10 years	0.98	(0.83–1.16)	0.81	

epilepsy. Patients with epilepsy < 1 year prior to glioma have a significantly lower risk of death compared to patients with no prior epilepsy, when considering age and comorbidity (Fig. 1, Table 2). We have hereby shown that glioma patients with epilepsy as an onset symptom do have survival benefits, and this pertains to both LGGs and HGGs. However, our analyses showed that the association varied according to tumor grade. A favorable prognosis was seen with all tumor grades II, III, and IV, yet the effect was higher for grades II and III and more modest for grade IV gliomas. This could be due to the biological nature of the tumors, as grade II and III gliomas are known to carry isocitrate dehydrogenase

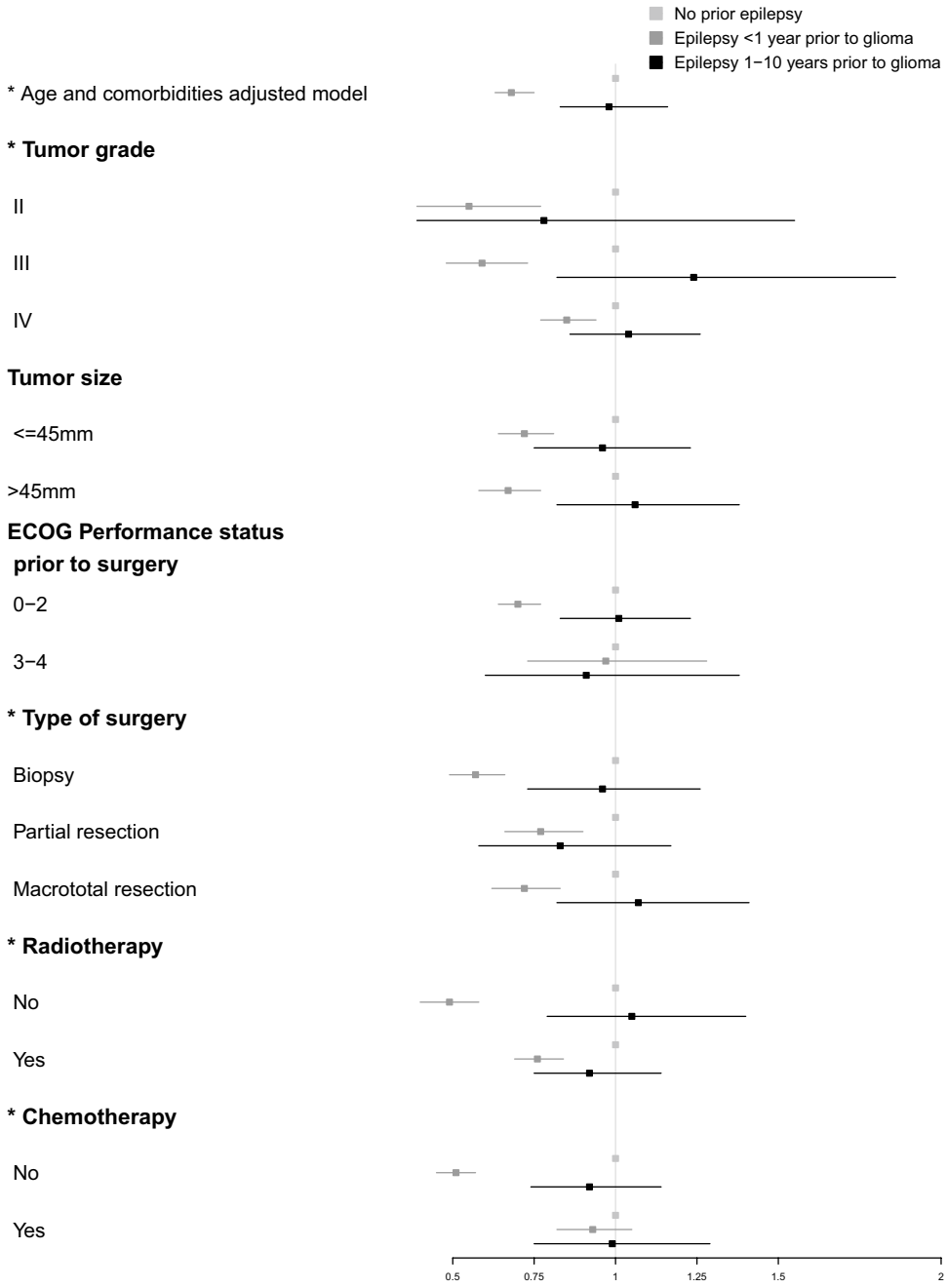

Fig. 2 Forest plot illustrating hazard ratios (HRs) and 95% confidence intervals (CIs) for association between epilepsy status and risk of death according to tumor grade, tumor size, Eastern Cooperative Oncology Group (ECOG) performance status prior to surgery, type of surgery, radiotherapy, and chemotherapy in 3763 glioma patients. *Factors with significant *p* values for interaction

Table 3 Hazard ratios (HRs) and 95% confidence intervals (CIs) for association between tumor grade, tumor size, ECOG performance status prior to surgery, type of surgery, radiotherapy, and chemotherapy and risk of death according to epilepsy status in 3763 glioma patients

		Hazard ratio (HR)	95% Confidence interval (CI)	*p* Value	*p* Value for interaction
Grade II	Epilepsy < 1 year	0.55	(0.39–0.77)	< 0.001	0.003
	Epilepsy 1–10 years	0.78	(0.39–1.55)	0.47	
Grade III	Epilepsy < 1 year	0.59	(0.48–0.73)	< 0.001	
	Epilepsy 1–10 years	1.24	(0.82–1.86)	0.30	
Grade IV	Epilepsy < 1 year	0.85	(0.77–0.94)	< 0.001	
	Epilepsy 1–10 years	1.04	(0.86–1.26)	0.69	
Tumor size < = 45 mm	Epilepsy < 1 year	0.72	(0.64–0.81)	< 0.001	0.56
	Epilepsy 1–10 years	0.96	(0.75–1.23)	0.77	
Tumor size > 45 mm	Epilepsy < 1 year	0.67	(0.58–0.77)	< 0.001	
	Epilepsy 1–10 years	1.06	(0.82–1.38)	0.66	
ECOG performance status prior to surgery 0–2	Epilepsy < 1 year	0.70	(0.64–0.77)	< 0.001	0.10
	Epilepsy 1–10 years	1.01	(0.83—1.23)	0.90	
ECOG performance status prior to surgery 3–4	Epilepsy < 1 year	0.97	(0.73–1.28)	0.81	
	Epilepsy 1–10 years	0.91	(0.60–1.38)	0.65	
Type of surgery: biopsy	Epilepsy < 1 year	0.57	(0.49–0.66)	< 0.001	0.03
	Epilepsy 1–10 years	0.96	(0.73–1.26)	0.75	
Type of surgery: partial resection	Epilepsy < 1 year	0.77	(0.66–0.90)	< 0.001	
	Epilepsy 1–10 years	0.83	(0.58–1.17)	0.29	
Type of surgery: macrototal resection	Epilepsy < 1 year	0.72	(0.62–0.83)	< 0.001	
	Epilepsy 1–10 years	1.07	(0.82–1.41)	0.60	
Radiotherapy	Epilepsy < 1 year	0.76	(0.69–0.84)	< 0.001	< 0.001
	Epilepsy 1–10 years	0.92	(0.75–1.14)	0.45	
No radiotherapy	Epilepsy < 1 year	0.49	(0.40–0.58)	< 0.001	
	Epilepsy 1–10 years	1.05	(0.79–1.40)	0.75	
Chemotherapy	Epilepsy < 1 year	0.93	(0.82–1.05)	0.24	< 0.001
	Epilepsy 1–10 years	0.99	(0.75–1.29)	0.91	
No chemotherapy	Epilepsy < 1 year	0.51	(0.45–0.57)	< 0.001	
	Epilepsy 1–10 years	0.92	(0.74–1.14)	0.43	

The reference level is 'No epilepsy prior to glioma' for each category of the corresponding variable

(*IDH*)-mutations in the majority of cases (> 60%), thus positively influencing the prognosis[6, 38]. The more modest survival benefit in patients with grade IV gliomas may be driven by the presence of a vast majority of *de novo* glioblastomas (i.e., *IDH*-wildtype glioblastoma) which account for 90% of all glioblastomas [39]. Secondary glioblastomas (i.e., *IDH*-mutant glioblastomas) account for the remaining 10% of glioblastomas [39], and patients typically present with seizures at glioma onset rather than focal neurological deficits [40]. Indeed, previous studies have been conducted on the potential association between *IDH*-mutations and presence of seizures in gliomas [22, 41, 42]; however, no consensus has been reached regarding all glioma grades and no large epidemiological studies have been conducted to corroborate these findings [22, 42].

Patients with epilepsy < 1 year prior to glioma diagnosis showed a survival benefit with all types of surgery, whereas regarding radio- and chemotherapy, the largest and most significant survival benefit was shown among patients who did not receive such treatment. One explanation for the latter result could be that prognosis may be worse for glioma patients qualifying for radio- and chemotherapy, as these treatment modalities generally imply that there is a tumor progression or malignant transformation after a primary surgical treatment [43].

Patients with epilepsy 1–10 years prior to glioma diagnosis constituted only 5% of the population under study, which in turn might be an indication that the majority of patients with glioma-related epilepsy are detected in a timely manner. An interpretation of the lack of survival benefit among these patients could be that this group includes patients with different types of epileptic seizures, i.e., not structural seizures related to a brain tumor, but idiopathic epilepsy or seizures caused by, e.g., cerebrovascular disorders, traumatic

brain injuries, nervous system infections, etcetera. On the other hand, some of the patients in this group with long-term epilepsy may potentially have an underlying tumor that goes undetected on initial brain imaging scans [44]. Physicians may also have opted for a 'watchful waiting' strategy, especially with regard to tumors resembling LGGs, situated in eloquent areas. A macrototal resection of tumors situated in these areas would imply severe functional decline in patients, and thus, pros and cons of a more radical surgery need to be carefully considered. However, it has been shown that even lesions considered to be stable, nevertheless grow in the course of 1 year with around 11% [45], which could explain the lack of survival benefits among glioma patients with epilepsy 1–10 years prior to glioma diagnosis.

Potential mechanisms

This study emphasizes that epilepsy constitutes an important prognostic factor in gliomas.

Patients across all glioma grades with epilepsy < 1 year prior to glioma diagnosis had significant survival benefits. This indicates a possible common pathway for epileptogenesis and oncogenesis, and calls for further improvements in molecular genetics studies, in addition to studies on whether epilepsy or specific antiepileptic drugs could be associated with the observed improved prognosis. Theories on potential mechanisms of epileptogenesis in gliomas have been proposed; however, they remain to be sufficiently verified. LGGs may be more epileptogenic due to their slow-growing nature [5] and the presence of mutations in the *IDH* enzyme causing production of 2-hydroxyglutarate [6] which activates N-methyl-D-aspartate (NMDA) receptors and grants epileptogenesis [7]. Thus, the presence of specific histopathology and/or molecular biomarkers, such as *IDH*-mutations, may potentially explain our results as well.

This study highlights that epilepsy represents a specific clinical predictor of outcome for glioma patients and emphasizes the importance of increased attention among clinicians treating patients with epilepsy, to improve early detection and the establishment of a specific diagnosis of the glioma.

Clinical implications

We cannot exclude that patients who experience epilepsy as an onset symptom of their glioma are more likely to get diagnosed early and having treatment initiated promptly. For the time being, the major 'weapon' in a neurologist's arsenal, concerning glioma patients with epilepsy at onset, is early diagnosis, which should be strived for through implementation of national clinical guidelines. Indeed, in some countries, patients presenting with new onset epileptic seizures are generally admitted to emergency departments to investigate the underlying cause [46]. When other causes (e.g., substance and alcohol abuse) are ruled out, further investigation continues by means of expeditious MRI scanning of the brain to identify a suspected primary brain lesion [46]. If no lesion is detected, then no further brain imaging is routinely performed unless the patient experiences recurrent seizures, changes in types of attack or frequency, or other alarm signs of a brain tumor (e.g., new onset of headache, cognitive change or focal neurologic deficits) suggesting possible lesions under development. Patients presenting with new onset epileptic seizures may get expedite diagnostics and rapid treatment. Whereas patients with other more unspecific presenting symptoms of glioma (e.g., headache, cognitive change, memory loss, and motor symptoms) may have longer diagnostic latency and consequently a higher risk for worse survival. The superiority in prognosis shown in patients with epilepsy as an onset symptom of glioma emphasizes the importance of implementing national standardized recommendations of expeditious cerebral MRI scanning to avoid that even a single glioma patient goes undiagnosed in a timely manner.

Strengths and limitations

To the best of our knowledge, this is the largest study to investigate the association between epilepsy prior to glioma diagnosis and survival. Registry data were collected prospectively, solely for administrative purposes, and independently of the hypothesis being tested in this study, and thus, systematic bias is expected to be almost absent.

The completeness of the DNOR has been previously established to be 92% in overall (ranging from 78 to 96%) [47], and this was determined as the proportion of glioma patients in the DNPR [48] and Danish National Pathology Registry (DNPaR) [49] who were registered in the DNOR [28]. Epilepsy diagnosis, which in the DNOR is reported from physician evaluations at glioma diagnosis [28], has been previously reported to have a validity of 90% [47]. In this case, validity was expressed as a percentage of agreement when comparing data on epilepsy in the DNOR to data on epilepsy from medical records, including 95% CIs [47]. We addressed this potential incompleteness by adding data from the DNPR regarding hospitalizations and outpatients visits with a diagnosis of epilepsy, which has a completeness of over 90% [33] and further by adding data on prescriptions of antiepileptic medications from the DNPrR [34]. No large studies have investigated the completeness for the DNPrR [34]. However, since pharmacies obtain public reimbursements for prescribed medications in the registry, this provides a potent incentive for recording all prescription medications dispensed [34]. In Denmark, glioma patients without seizures do not receive prophylactic antiepileptic medications as a routine, and thus, prescription of such medication is highly indicative

of an epilepsy diagnosis. However, some types of antiepileptic medications are administered in relation to other conditions (e.g., migraine and neuropathies), and thus, we cannot exclude a potential bias related to the misclassification of the exposure. As previously noted, the registries that we used cover different time periods (antiepileptic medication between 1999 and 2018 and epilepsy diagnosis at hospitalization between 2005 and 2017); however, as only few patients are hospitalized with epilepsy without being treated with antiepileptic medication, we do not expect this to have influenced our results.

Classifying time since epilepsy diagnosis into further categories could have provided information about specific important time points, yet, due to sample size, we were not able to do so. Hence, cut-off for time intervals should be validated in further studies.

The main limitation of our study was the lack of information on molecular biomarkers, which was integrated in the WHO-classification of brain tumors in 2016 [30]. Some of these biomarkers have a diagnostic and prognostic relevance [30] (e.g., presence of *IDH*-mutations and 1p/19q co-deletion, and O^6-methylguanine-DNA methyltransferase (MGMT) promotor methylation in relation to the chemotherapeutic agent temozolomide), and a lack of introduction of these biomarkers may represent a misclassification bias, as, e.g., LGG types could be interchanged when relying only on histological diagnosis [50].

Conclusions

We demonstrated that patients with epilepsy < 1 year prior to glioma diagnosis had significant survival benefits across all glioma grades compared to patients with no prior epilepsy. Our study indicates for the first time in a large population-based sample a possible common epileptogenic and oncogenic pathway which may be attributable to tumor-specific histopathology, molecular biomarkers, and early diagnosis in glioma patients with epilepsy at onset, resulting in a better prognosis. However, further studies on molecular diagnostics and epilepsy are needed.

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Availability of data and materials The data included in this study cannot be publicly accessed conforming to Danish legislature and the EU General Data Protection Regulation.

Code availability Analyses were performed using the statistical program R version 3.6.3.

Declarations

Conflicts of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval This study was approved by the Danish Cancer Society (No. 2018-DCRC-0054).

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