Article

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Robust and Specific Association Between Seizure at Presentation and Improved Survival in Patients With Primary Brain Tumors

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Background: Whether seizure presentation in patients afflicted with primary brain tumors (PBT) is associated with clinical prognosis remains an open question. We explore this association using the Nationwide Readmission Database (NRD).

Methods: A systematic literature review was conducted to summarize prior studies focusing on the association between the presence of seizure and outcomes of PBT/brain metastases (BM). The statistical power of the study was defined as a function of the effect size. We identified 50,380 and 32,789 PBT and BM patients in the NRD (2010–2018), respectively. Multivariable logistic regression models were utilized to assess the risk of mortality and the related factors.

Results: In a multivariable model accounting for known survival pertinent variables (age, gender, insurance status, income, hospital length of stay, discharge disposition, hospital features), the adjusted odds ratio (aOR) of death for PBT patients who presented with seizures and underwent craniotomy was 0.67 [95% Confidence Interval (CI): 0.52–0.86, p = 0.002] relative to those presented without seizures. The aOR of death for PBT patients who presented with seizures and underwent biopsy was 0.55 (95% CI: 0.30–1.00, p = 0.048) relative to those without seizures. This association was not observed for BM patients; the aOR of death for BMs who presented with seizures was 0.91 (p = 0.483) and 0.32 (p = 0.090) relative to those presented without seizures for craniotomy and biopsy patients, respectively. A comprehensive review of the literature showed that the predominance of the available studies supported the reported association.

Conclusions: We report an association between seizure at presentation and decreased mortality risk for PBT patients. The association was robust in both patients who underwent craniotomy as well as stereotactic needle biopsy but was not observed in BM patients.

Keywords: seizure; brain tumor; brain metastases; mortality; National Readmission Database; survey-based

Introduction

Seizure is a common comorbidity in patients afflicted with primary brain cancers, affecting 40–60% of patients with glioblastoma [1] and 60–88% of low-grade gliomas (LGG) [2]. Historically, the pathogenesis of tumor-associated seizure was thought to relate to mass effect or peri-tumoral edema secondary to the tumor [3]. However, recent studies revealing dynamic, bi-directional cross-talks between oncogenesis and epileptogenesis suggest complexities beyond these previous conceptual frameworks. For instance, optogenetic stimulation of neuronal firing enhanced glioblastoma growth in pre-clinical models [4,5], and tumors with select oncogenic mutations harbor a capacity for synapse formation [6,7]. Such intricate interactions have yet to be reported for brain metastases (BM) and may bear pertinence to clinical prognosis or response to therapy.

The literature investigating tumor-associated seizure and clinical outcomes for primary brain tumor (PBT) patients is rift with inconsistencies, with studies reporting improved [8–21], compromised [22–24], or no significant survival association [25–37]. Of note, this literature is largely restricted to retrospective studies of a limited number of patients treated at selected centers. Moreover, many of these studies lack statistical rigor, including pre-specified study design and statistical power determination. A meta-analysis of the literature did suggest an association between seizure presentation and improved survival for adult diffuse glioma [38]. However, the interpretation of this study is limited by the intrinsic heterogeneity of the various datasets analyzed.

In this context, we adopted a population-based approach, using the National Readmission Database (NRD), to assess whether tumor-associated seizure is associated with survival outcome. We posited that if the association is specific to crosstalk between PBTs and neurons, such association should not be seen in patients afflicted with BM.

Materials and Methods

Datasets and Populations

This is a retrospective cohort study of primary and secondary brain tumor patients derived from the de-identified NRD (2010–2018). The NRD is developed for the Healthcare Cost and Utilization Project (HCUP) by the Agency for Healthcare Research and Quality (AHRQ) to support a variety of analyses of national readmissions for all patients (https://hcup-us.ahrq.gov/nrdoverview.jsp). The total unweighted 2020 NRD contains data from approximately 17 million discharges and the estimated total weighted discharges are roughly 32 million, which addresses a large gap of lacking nationally representative information on hospital readmissions in healthcare data [39]. All data provided by HCUP is de-identified, this study was exempt from informed consent and the Institutional Review Board at the University of Minnesota and consent to publish was granted through HCUP. All methods were performed in accordance with the Declaration of Helsinki.

Study Subjects and Study Periods

We included de-identified patients from the NRD with (1) primary or secondary malignant neoplasm in brain (PBT and BM) between 2010 and 2018 using the International Classification of Diseases (ICD) 9th and 10th edition diagnostic and procedural codes (ICD-9-CM and ICD-10-CM/PCS); (2) the index admission was defined as the earliest observation/record for a patient underwent either biopsy or craniotomy [40]; (3) the presence status of seizure at index admission could be identified (Yes vs. No). Exclusion criteria were applied as follows: (1) patients younger than 18 years old at index admission; (2) concomitant diagnostic codes for PBT and BM; (3) concurrent procedural codes for biopsy and craniotomy; (4) missing values in covariates (routine discharge disposition, income, and facility features). Please see the ICD-9-CM and ICD-10-CM/PCS codes that we used to identify seizure, PBT, BM, biopsy, and craniotomy in **Supplementary Material 1**.

Predictors, Covariates, and Outcomes

Based on definitions established by previous database studies [41], seizure at the index admission was identified using ICD-9-CM (345* –epilepsy and recurrent seizures: 345.0, 345.1, 345.3, 345.4, 345.8, 345.9) and ICD-10-CM/PCS codes (G40* – epilepsy and recurrent seizures: G40.0, G40.1, G40.2, G40.3, G40.4, G40.5, G40.8, G40.9) and further classified into two categories: Yes vs. No. Covariates include socio-demographics (age, sex, insurance, income quartile of ZIP code of residence as supplied by Claritas to HCUP), facility features (hospital bed size, hospital location, teaching status, and hospital ownership), and clinical characteristics [PBT vs. BM, length of hospital stay (LOS), routine discharge disposition, extent of resection (craniotomy vs. biopsy)]. Mortality was defined as any all-cause death occurring during hospitalization, which was coded from the discharge disposition of patients. Please see the details in the **Supplementary Material 1**.

Systematic Literature Review Methods

The systematic literature review was conducted following the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines (PRISMA) [42]. We searched related literatures on the PubMed, Medline, Web of Science, and the Cochrane databases. The search keywords strategy was a combination of the following: "seizure" or "epilepsy"; "brain tumors" or "glioblastoma" or "glioma" or "astrocytoma" or "oligodendroglioma" or "oligoastrocytoma" or "brain metastasis" or "brain metastases"; "survival" or "mortality" or "prognosis". The search results were imported into Zotero 6.0.30 (George Mason University, Fairfax, VA, USA) for further management and screening. The retrieved studies would be excluded based on the following criteria: (1) publication types: book chapters, conference abstracts, review articles, guidelines, case reports, or case series; (2) publication year: prior to 2000; (3) language: not English; (4) *In vitro* or animal experiment studies. The eligibility of studies was further assessed based on the abstract and/or full text: (1) seizure/epilepsy was not the exposure/predictor of interest; (2) impact of seizure on survival outcomes was not investigated; (3) only seizure patients were included, and no comparison could be conducted between patients with seizure vs. those without seizure; (4) seizure was defined as status epilepsy; (5) no full text was found; (6) other irrelevant articles. The flow diagram of eligible studies based on the PRISMA was presented in Fig. 1 and the **Supplementary Material 2**. A summary of literature reviews including seizure definition, study design, sample size, data source, main findings, etc. was presented in **Supplementary Fig. 1**.

Statistical Analysis

A pre-study power calculation was performed and showed that the sample size (N = 305) allows the detection of an effect size of 20%, with an $\alpha = 0.05$ and $\beta = 0.20$. Descriptive statistics were presented to depict the cohort characteristics by extent of resection and seizure status for categorical [frequency (%)] and continuous variables [median (interquartile range)], respectively.

The multivariable binary logistic regression models using survey framework were performed to assess the association between seizure status and mortality for patients with brain tumors (total cohort) after adjusting all the covariates including age, sex, insurance, income, tumor sequence, length of stay, routine discharge, hospital bed-size, hospital location, teaching status, and hospital ownership. Stratification analysis by tumor sequence (PBT or BM) and surgical procedure (biopsy or craniotomy) were also examined to reason that an intrinsic association between PBT and survival should remain robust irrespective of the proce-

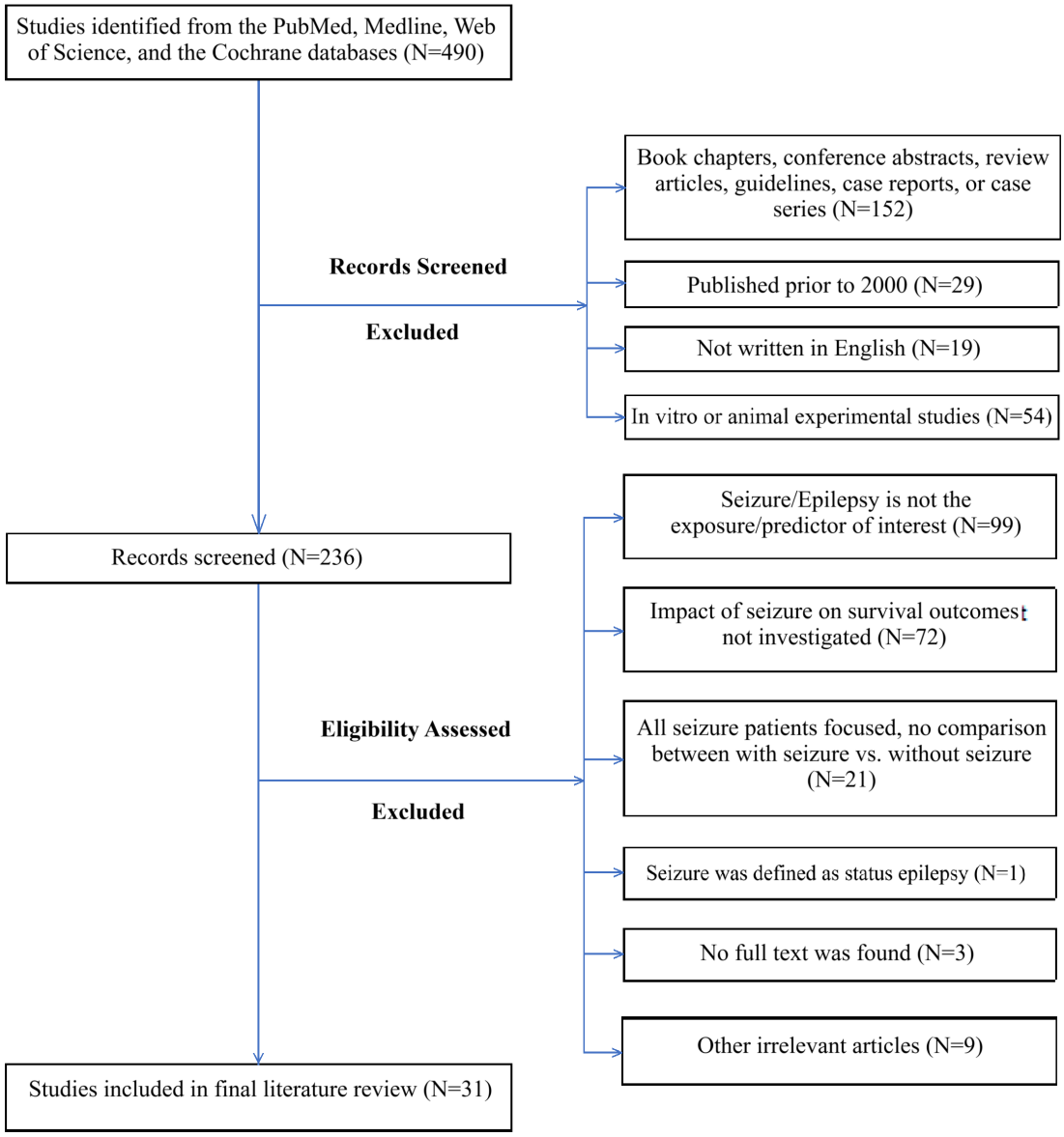

Fig. 1. Flow diagram of eligible studies derived from the systematic literature review [PRISMA flowchart, flow diagram was created using Microsoft PowerPoint for Mac, Version 16.77 (Microsoft, Seattle, WA, USA)].

dure performed (i.e., craniotomy or biopsy). The regression models rendered adjusted odds ratio (aOR) estimates and 95% confidence interval (CI). Strata, survey weight, and clusters were accounted to produce national estimates [39]. Statistical analyses were performed with SAS (version 9.4; SAS Institute, Cary, NC, USA) and R (version 4.1.2; R Core Team 2021, Vienna, Austria) using the "survey" package. p values were two-sided and considered statistically significant at $p < 0.05$. Data for which there are less than 11 observations are suppressed per the HCUP guidelines.

Results

Demographics and Clinical Characteristics of Brain Tumor Patients

In total 83,169 brain tumor patients were identified, including 50,380 PBT patients and 32,789 BM patients. The majority of patients underwent craniotomy (85.4%, 71,050/83,169) and only 14.6% of patients underwent biopsy. The proportion of patients who presented with a seizure at the time of initial diagnoses was approximately 13% for both patients who underwent craniotomy (13.7%) or stereotactic needle biopsy (13.1%). In the craniotomy sub-cohort, the majority of patients are male (52.6%), have public insurance (55.4%), have a primary tumor (55.9%), are routine discharge to home (61.9%), getting treatments

Table 1. Patients, clinical, and hospital characteristics by seizure and extent of resection in the total cohort.

	Craniotomy		Biopsy	
Variables	Seizure	Non-seizure	Seizure	Non-seizure
Total	9720	61,330	1591	10,528
Socio-demographics				
Age, median [IQR]	60 [50, 69]	59 [50, 68]	65 [54, 74]	64 [53, 73]
Female vs. male, N (%)	4762 (49.0)	28,923 (47.2)	577 (36.3)	4683 (44.5)
Private vs. public insurance, N (%)	4334 (44.6)	27,345 (44.6)	580 (36.5)	3811 (36.2)
Income, quartiles, N (%)				
Q1	2173 (22.4)	13,322 (21.7)	394 (24.8)	2463 (23.4)
Q2	2510 (25.8)	15,687 (25.6)	399 (25.1)	2721 (25.8)
Q3	2420 (24.9)	15,963 (26)	421 (26.4)	2629 (25)
Q4	2617 (26.9)	16,358 (26.7)	378 (23.7)	2714 (25.8)
Clinical characteristics				
Primary tumor vs. brain metastases, N (%)	5302 (54.5)	34,392 (56.1)	1362 (85.6)	9324 (88.6)
Length of stay, median [IQR]	6 [3, 10]	6 [3, 10]	4 [2, 8]	4 [1, 9]
Routine discharge, N (%)	5859 (60.3)	38,092 (62.1)	1024 (64.4)	6652 (63.2)
Facility features				
Hospital bed-size, N (%)				
Small	575 (5.9)	3538 (5.8)	54 (3.4)	518 (4.9)
Medium	1502 (15.5)	10,357 (16.9)	327 (20.5)	2023 (19.2)
Large	7643 (78.6)	47,435 (77.3)	1211 (76.1)	7987 (75.9)
Hospital location, N (%)				
Large metropolitan area	6055 (62.3)	38,415 (62.6)	883 (55.5)	6008 (57.1)
Small metropolitan area	3537 (36.4)	22,128 (36.1)	681 (42.8)	4368 (41.5)
Micropolitan area	127 (1.3)	787 (1.3)	27 (1.7)	152 (1.4)
Hospital teaching status, N (%)				
Metropolitan non-teaching	1318 (13.6)	8099 (13.2)	336 (21.1)	1888 (17.9)
Metropolitan teaching	8274 (85.1)	52,444 (85.5)	1228 (77.2)	8488 (80.6)
Non-metropolitan hospital	127 (1.3)	787 (1.3)	27 (1.7)	152 (1.4)
Government vs. private ownership, N (%)	8129 (83.6)	52,273 (85.2)	1373 (86.3)	9067 (86.1)

Abbreviations: IQR, interquartile range; Q1–Q4, Quartile 1–Quartile 4.

from the hospital with large bed-size (77.5%), located in the large metropolitan area (62.6%), and owned by the government (85.0%). A similar distribution of features was observed in the biopsy sub-cohort as well (Table 1).

Clinical Variables Associated With Seizure at Presentation

We first identified clinical variables associated with seizure at presentation for the patients who underwent craniotomy and biopsy, separately. As shown in Table 2, a multivariable analysis of the craniotomy patients showed the following variables to be associated with seizure at initial presentation: older age (aOR: 0.98, $p < 0.001$), female (aOR: 0.89, $p = 0.002$), PBT (aOR: 2.23, $p < 0.001$), private insurance (aOR: 0.85, $p < 0.001$), prolonged length of stay (LOS, aOR: 1.02, $p < 0.001$), discharge to home/others (aOR: 0.83, $p < 0.001$), hospital located in small metropolitan area (aOR: 0.76, $p < 0.001$), and hospital owned by government (aOR: 1.20, $p = 0.011$). For patients who underwent biopsy, variables to be associated with seizure at initial presentation included: older age (aOR: 0.98, $p < 0.001$), PBT (aOR: 1.34, $p = 0.028$), and prolonged LOS (aOR: 1.01, $p < 0.001$). The only variables consistently associated with seizure at presentation for both cohorts were: older age, diagnosis of PBT (relative to BM), and prolonged length of stay after the procedure.

Association Between Seizure at Presentation and Mortality

We next performed a series of multivariable analyses to explore whether seizure at the initial presentation was associated with the risk of death for the total cohort (Table 3) and stratification by tumor sequence [PBT (Table 4) and BM (Table 5)]. As shown in Table 4, for PBT patients who underwent craniotomy, seizure at the time of presentation was associated with a 33% reduction in the odds of mortality (aOR: 0.67, 95% CI: 0.52–0.86, $p = 0.002$). Similarly, such association was observed in patients who underwent biopsy and had seizures as well (aOR: 0.55, 95% CI: 0.30–1.00, $p = 0.048$). Other predictors for mortality include age (aOR: 1.02, $p < 0.001$), prolonged LOS (aOR: 1.01, $p = 0.005$), discharge to home or other (aOR: 0.73, $p = 0.005$) (craniotomy group) and age (aOR: 1.02, $p = 0.007$) (biopsy group).

These associations were not observed in patients who presented with metastatic brain tumors, irrespective of the

Table 2. Multivariable survey-based logistical regression of factors associated with seizure in total cohort*.

	Craniotomy			Biopsy		
	aOR	95% CI	*p*	aOR	95% CI	*p*
Socio-demographics						
Age, years	0.98	0.97–0.98	<0.001	0.98	0.98–0.99	<0.001
Female vs. male	0.89	0.83–0.96	0.002	0.93	0.77–1.13	0.466
Primary tumor vs. brain metastases	2.23	2.06–2.41	<0.001	1.34	1.03–1.73	0.028
Private vs. public insurance	0.85	0.78–0.93	<0.001	0.99	0.81–1.22	0.959
Income quartiles (Q2 vs. Q1)	0.95	0.84–1.06	0.354	0.98	0.75–1.27	0.878
Income quartiles (Q3 vs. Q1)	0.97	0.87–1.09	0.650	1.10	0.83–1.46	0.507
Income quartiles (Q4 vs. Q1)	1.06	0.94–1.20	0.368	0.96	0.73–1.25	0.742
Clinical characteristics						
Length of stay, days	1.02	1.01–1.02	<0.001	1.01	1.01–1.02	<0.001
Discharge to home or other	0.83	0.77–0.90	<0.001	1.13	0.89–1.43	0.305
Facility features						
Hospital bed size (medium vs. small)	0.90	0.71–1.15	0.400	1.18	0.80–1.75	0.397
Hospital bed size (large vs. small)	0.91	0.81–1.03	0.126	0.92	0.71–1.21	0.560
Hospital location (small metropolitan area vs. large metropolitan area)	0.76	0.68–0.84	<0.001	0.85	0.69–1.04	0.119
Hospital location (micropolitan vs. large metropolitan area)	0.81	0.54–1.21	0.302	1.45	0.71–2.94	0.305
Hospital teaching (metropolitan teaching hospital vs. metropolitan non-teaching hospital)	1.07	0.96–1.20	0.234	1.05	0.84–1.32	0.648
Government vs. private ownership	1.20	1.04–1.38	0.011	1.10	0.85–1.43	0.458

*: Multivariable logistic regression incorporating survey design after adjusting age, sex, insurance, income, tumor sequence, length of stay, routine discharge, hospital bed size, hospital location, teaching status, and hospital ownership.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; Q1–Q4, Quartile 1–Quartile 4.

surgical procedure (craniotomy or biopsy). In patients with BM who underwent craniotomy, the aOR of mortality was 0.91 ($p = 0.483$) for patients who presented with a seizure at the time of initial diagnosis relative to those who did not. Similarly, for BM patients who underwent a biopsy, the aOR of mortality was 0.32 ($p = 0.090$) for patients who presented with seizure at the time of initial diagnosis relative to those who did not (Table 5).

Comprehensive Literature Review

To characterize the state of the current literature on the association between seizure and survival outcomes, we performed a comprehensive search of the literature. The specific search algorithm was described in the methods and materials. The publications identified in this search are shown in **Supplementary Fig. 1** and reviewed below.

After inclusion/exclusion criteria and eligibility screening (Fig. 1), a total of 31 studies (published between 2001 and 2022) were identified. Despite significant heterogeneity in the definition of seizure and study design, the reported results are remarkably consistent. There were twelve studies that reported no significant association between seizure presentation and overall survival in patients afflicted with PBTs (**Supplementary Fig. 1**). Notably, all twelve studies involved cohorts of <300 patients. Based on our power calculation, a sample size of 305 would detect an effect size of 20% with α and β of 0.05 and 0.20, respectively. In contrast, all except three of the fourteen studies demonstrated an association between seizure presentation and improved survival involving a study cohort of >300 patients. Finally, the three studies that showed an association between seizure presentation and poor survival specifically studied peri-operative or post-operative seizure.

Discussions

While previous studies have attempted to address the clinical implications of seizure presentation in PBT patients, these studies were limited by sample size and the absence of a pre-specified statistical design. Moreover, the previous studies have not accounted for the influence of surgical resection versus biopsy on overall survival. Finally, none of the available literature directly compared the seizure-associated survival patterns between BM and PBT patients. Here, we present the first large-scale examination of the association between seizure at presentation and mortality of PBT patients using the NRD. Given the fundamen-

Table 3. Multivariable survey-based logistical regression of mortality in total cohort stratifying by extent of resection*.

	Total cohort					
	Craniotomy			Biopsy		
Variables	aOR	95% CI	*p*	aOR	95% CI	*p*
Seizures vs. no seizures	0.78	0.65–0.94	0.008	0.52	0.30–0.90	0.021
Socio-demographics						
Age, years	1.01	1.01–1.02	<0.001	1.02	1.00–1.03	0.009
Female vs. male	0.91	0.81–1.02	0.106	0.84	0.64–1.09	0.189
Private vs. public insurance	0.84	0.74–0.96	0.010	0.87	0.63–1.21	0.409
Income quartiles (Q2 vs. Q1)	0.89	0.76–1.04	0.153	0.85	0.60–1.21	0.375
Income quartiles (Q3 vs. Q1)	1.01	0.86–1.19	0.930	0.75	0.52–1.08	0.124
Income quartiles (Q4 vs. Q1)	1.05	0.89–1.25	0.550	0.88	0.60–1.28	0.497
Clinical characteristics						
Primary tumor vs. brain metastases	0.55	0.49–0.63	<0.001	0.79	0.57–1.09	0.150
Length of stay, days	1.01	1.01–1.02	<0.001	1.01	1.00–1.02	0.185
Discharge to home or other	0.73	0.64–0.83	<0.001	0.68	0.52–0.89	0.006
Facility features						
Hospital bed size (small vs. large)	1.13	0.91–1.40	0.281	0.54	0.29–1.02	0.057
Hospital bed size (medium vs. large)	1.00	0.86–1.17	0.985	0.99	0.72–1.38	0.967
Hospital location (small metropolitan area vs. large metropolitan area)	1.19	1.05–1.36	0.006	1.20	0.91–1.59	0.203
Hospital location (micropolitan vs. large metropolitan area)	1.02	0.61–1.70	0.951	0.99	0.30–3.21	0.983
Hospital teaching (metropolitan teaching hospital vs. metropolitan non-teaching hospital)	0.77	0.67–0.90	<0.001	0.87	0.64–1.18	0.364
Government vs. private ownership	0.98	0.84–1.14	0.787	0.84	0.56–1.26	0.395

*: Multivariable logistic regression incorporating survey design after adjusting seizure, age, sex, insurance, income, tumor sequence, length of stay, routine discharge, hospital bed-size, hospital location, teaching status, and hospital ownership.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; Q1–Q4, Quartile 1–Quartile 4.

tal differences in biology between BM and PBT, we pre-specified our analysis to compare these two tumor types. We further pre-specified association-associated NRD variables [43] and incorporated these variables in our multivariable analysis. Finally, we performed power calculations to demonstrate that the NRD database affords reasonable detection of association with an effect size of 20% (N = 305) at an α and β of 0.05 and 0.20, respectively. Our analysis indicates that seizure at presentation is associated with reduced mortality risk for patients afflicted with PBT. The association was robust in that it was observed in PBT patients who underwent craniotomy or biopsy. And, the survival association was cancer type specific, given its absence in BM patients. A comprehensive search of the available literature revealed fourteen studies that support the findings of our study.

Based on our systematic literature review of 31 related studies (published 2001–2022), those studies explored the association between seizure and survival outcomes for different brain tumors, including LGG, isocitrate dehydrogenase (*IDH*)-wild type GBM, BM, etc., by using retrospective cohort study design. Seventy-four percent of these studies used single institution dataset (N = 23, Sample sizes: N = 49–867), six studies were based on multicenter data (Sample sizes: N = 99–1792), and only two studies utilized a population-based Denmark database (N = 3763).

Eleven studies demonstrated the significantly beneficial impact of seizure (25% to 61% reduced risk of death) on glioma overall survival (OS). Berendsen *et al.* [12] and Lapointe *et al.* [10] also considered the potential confounder of antiepileptic drug (AED). They concluded that seizure presence was an independent prognostic factor and AED usage or AED prophylaxis had no significant impact on OS. In addition, Ge *et al.* [19] and Marku *et al.* [20] identified the differential survival influence of seizure by glioma grade [Ge *et al.* [19]: significant only for grade IV gliomas, adjusted hazard ratio (aHR) = 0.46, $p < 0.001$; Marku *et al.* [20]: significant for all glioma grades: grade II-aHR = 0.55, grade III-aHR = 0.59, grade IV-aHR = 0.85, all $p < 0.001$]. On the other hand, four papers observed the unfavorable effect of seizure (24% to 403%, varied by tumor type-PBT or BM, tumor grade, and seizure type-status epilepsy or not, *de novo* epilepsy or not) on glioma/BM prognosis. Moreover, another thirteen studies reported a non-significant association between seizure and brain tumor survival. Henker *et al.* [33] utilized two institutional data to explore the impact

Table 4. Multivariable survey-based logistical regression of mortality in primary brain tumor cohort stratifying by extent of resection*.

	Primary tumors					
	Craniotomy			Biopsy		
Variables	aOR	95% CI	*p*	aOR	95% CI	*p*
Seizures vs. no seizures	0.67	0.52–0.86	0.002	0.55	0.30–1.00	0.048
Socio-demographics						
Age, years	1.02	1.01–1.03	<0.001	1.02	1.00–1.03	0.007
Female vs. male	0.88	0.71–1.09	0.242	0.84	0.63–1.14	0.265
Private vs. public insurance	0.82	0.66–1.04	0.097	0.86	0.60–1.24	0.424
Income quartiles (Q2 vs. Q1)	0.88	0.66–1.17	0.390	0.90	0.61–1.32	0.594
Income quartiles (Q3 vs. Q1)	1.05	0.79–1.40	0.748	0.74	0.49–1.12	0.153
Income quartiles (Q4 vs. Q1)	0.96	0.71–1.30	0.793	0.93	0.61–1.42	0.740
Clinical characteristics						
Length of stay, days	1.01	1.00–1.02	0.005	1.01	1.00–1.02	0.263
Discharge to home or other	0.73	0.58–0.91	0.005	0.74	0.55–1.01	0.055
Facility features						
Hospital bed size (small vs. large)	0.86	0.58–1.28	0.466	0.56	0.29–1.09	0.086
Hospital bed size (medium vs. large)	1.17	0.90–1.51	0.245	1.05	0.74–1.51	0.774
Hospital location (small metropolitan area vs. large metropolitan area)	1.08	0.87–1.35	0.462	1.18	0.87–1.61	0.291
Hospital location (micropolitan vs. large metropolitan area)	1.35	0.63–2.88	0.439	1.12	0.24–5.22	0.883
Hospital teaching (metropolitan teaching hospital vs. metropolitan non-teaching hospital)	0.88	0.68–1.13	0.307	0.86	0.61–1.22	0.407
Government vs. private ownership	1.07	0.81–1.40	0.643	0.79	0.51–1.23	0.296

*: Multivariable logistic regression incorporating survey design after adjusting seizure, age, sex, insurance, income, length of stay, routine discharge, hospital bed size, hospital location, teaching status, and hospital ownership.
Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; Q1–Q4, Quartile 1–Quartile 4.

of pretreatment seizure on OS for patients with *IDH*-wild type GBM, but led to non-significant results (seizure no vs. yes: HR = 1.22, $p = 0.357$). Kumar *et al.* [37] reported preoperative seizure and Levetiracetam (LEV) as significant prognostic survival factors in univariable analysis for glioma patients, whereas only LEV was kept as a significant factor after adjusting covariates. Interestingly, one study detected the significant controversial survival effect for *de novo* GBMs by seizure types [seizure at onset (SAO): aHR = 0.82, $p = 0.030$, early postoperative seizure (EPS): aHR = 1.41, $p = 0.009$] [44].

Several potential explanations may account for the observed association between seizure at presentation and survival prognostication in PBT patients. A seemingly less impactful explanation involves lead time bias, wherein seizure presentation might enable earlier detection of a brain tumor, potentially creating a deceptive perception of extended survival. However, existing literature suggests that such lead time bias is unlikely to explain the magnitude of the observed association in our study [45]. Another consideration revolves around the potential anti-neoplastic effects of anti-seizure medications, which could conceivably impede tumor growth and improve survival. Kerkhof *et al.* [1] demonstrated that GBM patients using Valproic acid (VPA) in combination with temozolomide showed an improved median OS of 69 weeks over 61 weeks in the group without VPA (aHR = 0.63, 95% CI: 0.43–0.92, $p = 0.016$), after adjusting age, extent of resection, and O^6-methylguanine-DNA methyltransferase (*MGMT*) promoter methylation status (N = 291), which might be related to inhibition of histone deacetylase and synergistic anti-glioma activity with radiation therapy.

An equally intriguing hypothesis posits that tumor-associated epilepsy may be linked to cancer states generally associated with a more favorable prognosis, such as the presence of *IDH* mutation [46], high levels of *MGMT* and epidermal growth factor receptor (*EGFR*) expression [47]. Alternatively, tumors capable of eliciting epileptogenic activity, such as those affecting the Phosphoinositide 3-kinase signaling cascade [7] might exist in a more differentiated cell state, exhibiting neuron-like behavior and tending to manifest less aggressive behavior compared to tumors in a more stem-cell-like state [48,49]. These explanations are not necessarily mutually exclusive, and the NRD lacks the granularity required to discern the relative contributions of these possibilities. As such the above proposed hypotheses remain speculative and await investigation by future studies.

Table 5. Multivariable survey-based logistical regression of mortality in brain metastases cohort stratifying by extent of resection*.

	Brain Metastases					
	Craniotomy			Biopsy		
Variables	aOR	95% CI	*p*	aOR	95% CI	*p*
Seizures vs. no seizures	0.91	0.71–1.17	0.483	0.32	0.08–1.20	0.090
Socio-demographics						
Age, years	1.00	1.00–1.01	0.363	1.00	0.97–1.03	0.869
Female vs. male	0.91	0.78–1.05	0.187	0.78	0.43–1.41	0.415
Private vs. public insurance	0.84	0.72–0.99	0.036	0.94	0.40–2.22	0.886
Income quartiles (Q2 vs. Q1)	0.89	0.73–1.09	0.258	0.60	0.25–1.42	0.244
Income quartiles (Q3 vs. Q1)	0.99	0.82–1.20	0.930	0.78	0.35–1.75	0.548
Income quartiles (Q4 vs. Q1)	1.22	0.93–1.35	0.248	0.60	0.25–1.44	0.252
Clinical characteristics						
Length of stay, days	1.01	1.01–1.02	<0.001	1.01	0.99–1.03	0.517
Discharge to home or other	0.72	0.62–0.85	<0.001	0.42	0.22–0.80	0.008
Facility features						
Hospital bed size (small vs. large)	1.24	0.97–1.60	0.088	0.39	0.05–3.11	0.374
Hospital bed size (medium vs. large)	0.91	0.74–1.12	0.375	0.67	0.31–1.49	0.329
Hospital location (small metropolitan area vs. large metropolitan area)	1.25	1.07–1.47	0.006	1.31	0.68–2.52	0.419
Hospital location (micropolitan vs. large metropolitan area)	0.86	0.44–1.68	0.660	0.74	0.08–6.84	0.793
Hospital teaching (metropolitan teaching hospital vs. metropolitan non-teaching hospital)	0.73	0.61–0.87	<0.001	0.90	0.44–1.82	0.770
Government vs. private ownership	0.94	0.76–1.15	0.529	1.25	0.49–3.17	0.638

*: Multivariable logistic regression incorporating survey design after adjusting seizure, age, sex, insurance, income, length of stay, routine discharge, hospital bed size, hospital location, teaching status, and hospital ownership.
Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; Q1–Q4, Quartile 1–Quartile 4.

As with any population-database study, there are several inherent limitations in the present study. First, it is difficult to control for selection bias, recall bias or confounders, as the database was not designed specifically to test the association between seizure at presentation and overall survival. Critical variables that could impact our conclusions, such as the molecular and histopathological tumor profiles (e.g., *IDH* mutation, *MGMT*-promoter methylation status), patient's utilization of anti-seizure medication, clinical condition, and procedural outcomes/complications, remain unavailable in the database [43]. Additionally, the NRD is an administrative database that collects electronic health record data from approximately 50% of all hospitals and only covers around 22 states in the USA, which may limit the generalizability of our conclusions. Classification of seizure status based on ICD codes may introduce misclassification bias. Moreover, brain tumor patients who suffered minor head injuries or other conditions that may influence seizure risk not captured by the ICD code may also affect our study results. Finally, the accuracy of data collected in the NRD also warrants scrutiny due to the potential for coding errors, coding inconsistencies, and the presence of missing values. In this study, we used both ICD-9-CM and ICD-10-CM/PCS to identify seizure, PBT, BM, biopsy, and craniotomy to prevent potential miscoding and coding inconsistencies. Furthermore, deaths occurring outside the hospital before readmission are not captured in the NRD, posing another limitation [50]. Despite these limitations, the NRD has served as a useful platform for hypothesis generation and testing in clinical investigations. We present our results in this context. The conclusions of this study are particularly intriguing in light of the evolving understanding of the tumor environment in terms of epileptogenesis [48], laying a foundation for future investigations into this domain.

Conclusions

Our results demonstrate an association between seizure at presentation and decreased mortality risk for patients afflicted with PBTs, irrespective of the surgical procedure that the patients underwent. This association is specific to PBTs and was not observed in patients afflicted with BM.

Availability of Data and Materials

The data that support the findings of this study are available from the HCUP, but restrictions apply to the availability of these data, which were used under the HCUP data protection policy, and so are not publicly available.

Author Contributions

PZ and AC contributed to the study conception and design. Data acquisition, preparation, and statistical analysis were performed by PZ, AC, TD, and KC. The first draft of the manuscript was written by PZ and AC. And all authors commented on previous versions of the manuscript. All authors read, critically revised, and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All data provided by HCUP is de-identified, this study was exempt from informed consent and the Institutional Review Board at the University of Minnesota and consent to publish was granted through HCUP. All methods were performed in accordance with the Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202537197.88.

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