Association of Seizure Control with Mortality, Cognition, and Function in People With Dementia

Ifrah Zawar, MD, MS-CR [1], Mark Quigg, MD, MSc [1,2], Soutik Ghosal, PhD, [3] Vineet Punia, MD, MSc [4], Yamile Calle-Lopez, MD, [5] Carol Manning, PhD, [6] and Jaideep Kapur, MD, PhD [1]

Objectives: The effects of seizure control on outcomes in persons with dementia (PWD) remain unclear. Our study aimed to investigate the impact of seizure control on mortality, function, cognition, and mood among PWD.
Methods: This longitudinal, multicenter study is based on 39 Alzheimer's disease centers (ADCs) in the United States from September 2005 to December 2021. PWD were grouped by seizure status into recurrent (seizures in the past year), remote (prior seizures but none in the past year), and no seizures (controls). The primary outcome was all-cause mortality among seizure groups. We used Weibull survival analysis to assess the mortality risks by seizure status after adjusting for age, sex, education, race, ethnicity, hypertension, diabetes, hyperlipidemia, degree of cognitive impairment, dominant Alzheimer's disease (AD) mutation, brain trauma, stroke, Parkinson's disease, alcohol abuse, and depression. Cognition (Clinical Dementia Rating), function (physical dependence and nursing home residence), day-to-day activities (Functional Assessment Scores), and mood (Geriatric Depression Scale) were compared among seizure groups after adjusting for dementia duration and age.
Results: Among 26,501 participants, 374 (1.4%) had recurrent seizures and 510 (1.9%) had remote seizures. In multivariable survival analysis, recurrent seizures were associated with a higher mortality risk than remote and no seizures (adjusted hazard ratio [aHR], 95% confidence interval [95% CI]; recurrent aHR = 1.79, 95% CI = 1.51 to 2.12; remote aHR = 1.17, 95% CI = 0.98 to 1.38). Median time-to-death for recurrent, remote, and no seizures was 2.4, 4.0, and 4.7 years, respectively. People with recurrent seizures had worse cognition, day-to-day function, and physical dependence than those with remote seizures and controls.
Interpretation: PWD with poorly controlled recurrent seizures have worse mortality, functional, and cognitive outcomes than PWD with remote and no seizures. These findings underscore the need for timely identification and management of ongoing seizures in PWD.

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Seizures are a common comorbidity in people with dementia (PWD), affecting up to 64% of this population.[1–7] PWD have a 2 to 6-fold higher odds of developing epilepsy than age-matched controls.[1–5,8–10] Furthermore, PWD with co-morbid epilepsy tend to experience faster cognitive decline.[11–13]

Despite evidence that epilepsy adds to the clinical morbidity of PWD, the degree to which seizure control

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Address correspondence to Professor Ifrah Zawar, Department of Neurology, University of Virginia, School of Medicine, POB 800994, HSC, Charlottesville, VA 22908. E-mail: ifrah.zawar@gmail.com

From the [1]Comprehensive Epilepsy Program, Department of Neurology, University of Virginia, Charlottesville, VT; [2]Sleep Center, Department of Neurology, University of Virginia, Charlottesville, VT; [3]Division of Biostatistics, Department of Public Health Sciences, University of Virginia, Charlottesville, VT; [4]Epilepsy Division, Department of Neurology, Cleveland Clinic, Cleveland, OH; [5]Facultad de Medicina, Universidad de Antioquia UdeA, Hospital Universitario San Vicente Fundación, Medellín, Colombia; and [6]Memory Disorders Program, Department of Neurology, University of Virginia School of Medicine, Charlottesville, VA

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impacts the course of dementia remains unclear. Although dementia is an uncontroversial risk factor for premature mortality in people with epilepsy (PWE),[14] the impact of seizure control on mortality and other outcomes in PWD remains understudied.

We hypothesized that recurrent seizures, as opposed to remote seizures, adversely impact function, cognition, mood, and survival in PWD. Our primary objective was to investigate the impact of seizure control on mortality in PWD. We compared the risk of mortality in those with recurrent seizures in the preceding 12 months to remote seizures (history of seizures but none in the preceding 12 months) and no seizures. The secondary objective of our study was to compare cognition, mood, and function among the 3 groups. Management strategies to mitigate identified risks associated with recurrent seizures may improve outcomes in PWD.

Methods

Study Design

This study is based on longitudinal, multicenter data from 39 Alzheimer's Disease Centers (ADC) in the United States.[15–19] All ADCs maintain their separate Institutional Review Board (IRB) approval. Informed consent was obtained from participants at the respective ADCs. We followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[20]

Participants

Inclusion and Exclusion Criteria. We included participants with (1) cognitive impairment and (2) recurrent, remote, or no seizures at enrollment (Fig 1). Exclusion criteria were (1) unknown seizure status and (2) normal cognition.

Seizure Groups. We categorized participants into 3 groups by seizure status: recurrent, remote, or no seizures. Seizure status was determined clinically based on participant and co-participant reports, medical records, and observation. Participants in the recurrent seizure group were defined as those recurrent seizures in the preceding 12 months and/or requiring active treatment. Remote seizures were defined as those that occurred in the past but not in the preceding 12 months and required no active treatment. Therefore, active or recurrent seizures in the data are most consistent with poorly controlled active epilepsy,[21] and remote seizures are most consistent with resolved epilepsy. We designated participants with no history of seizures as the controls.

Primary Outcome. The primary outcome of this study was the association between seizure control (recurrent, remote, and no seizures) and all-cause mortality among PWD. The primary outcome was evaluated using time-to-event survival analysis. In the secondary analysis of mortality, we compared the proportion of deceased participants at the most recent follow-up, age at death, median time to death, and mortality rates among the 3 seizure groups.

Secondary Outcomes. In secondary outcomes, we compared cognition, function, and mood among the seizure groups. Cognitive status was categorized into cognitive impairment not meeting criteria for mild cognitive impairment (MCI), MCI, or dementia, as determined by expert clinicians and multidisciplinary committee consensus, evaluated at each visit, based on all available clinical, neuropsychological, neuro-imaging, and other data.[15–19] Cognitive impairment was quantified in severity using Clinical Dementia rating (CDR-global) and CDR-Sum-of-boxes (CDR-SOB).[22] CDR evaluates 6 cognitive domains: orientation, judgment, memory, problem-solving, community affairs, home function, hobbies, and personal care. CDR-SOB ranges from 0 to 18. Higher scores indicate worse cognition. CDR-Global score ranges from 0 to 3: normal cognition (0), MCI (0.5), and mild (1), moderate (2), and severe dementia (3).[22,23]

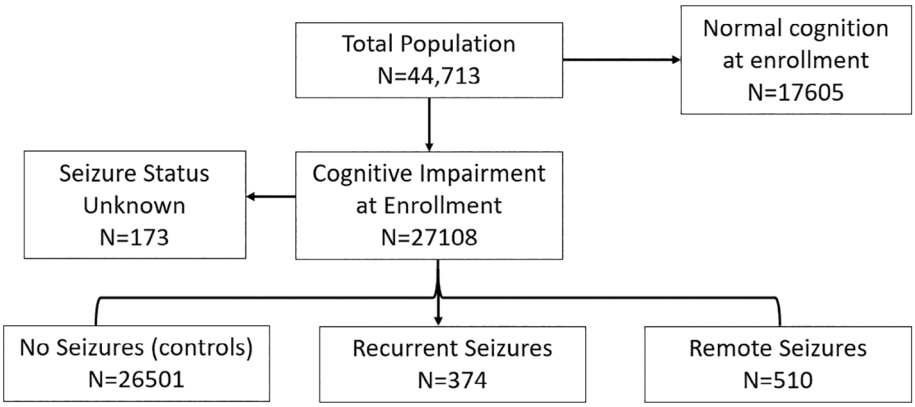

FIGURE 1: Study flow chart.

The activities of daily living were assessed using Functional Activities Scale (FAS) based on 10 domains of activities. Each functional domain was scored between 0 and 3, with 0 = normal, 1 = able to do with difficulty, 2 = requiring assistance, and 3 = dependent. The total FAS ranged from 0 (normal in all domains) to 30 (dependent in all domains). If individual domains were missing, the scores were prorated. A higher score meant a worse function.

Physical functional status was evaluated based on whether participants had some degree of dependence or were completely independent. Whether the participant resided in a nursing home was also investigated.

Mood was assessed using presence of active depression in the past 2 years, and the severity of depression was quantified using Geriatric Depression Scale (GDS; total range: 0–15).[24] The GDS is a well-validated screening tool to assess for depression in older adults.[24] A higher score meant worse depression.

Other Variables. Other variables included age at enrollment (total years), sex (female vs male patient), race (dichotomized to White vs non-White), ethnicity (Hispanic vs non-Hispanic), education (total years), cardiovascular risk factors including hypertension (actively present vs absent) and diabetes (actively present vs absent), hyperlipidemia (actively present vs absent), degree of cognitive impairment using final clinician determined diagnosis (cognitive decline but not MCI or dementia), history of clinically significant alcohol abuse over a 12-month period which manifested in 1 or more of the following areas: work, driving, legal or social (present or absent), Parkinson's disease (PD; present or absent), history of recent or remote stroke or transient ischemic attack (TIA; present or absent), traumatic brain injury (TBI; present or absent), dominant Alzheimer's disease (AD), mutation (present or absent), and Apolipoprotein ε4 (*APOE4*) allele (homozygous, heterozygous, or none).

Statistical Analysis

We used R software (version 4.2.0; R Foundation for Statistical Computing, Vienna, Austria) for statistical analyses.

Baseline Analysis. The relationship between seizure status and clinical characteristics of the participants were assessed using the 2-tailed Pearson χ^2 test or 2-tailed Fisher's exact probability for categorical variables as appropriate (details in Table 1 footnote). The Kruskal-Wallis Rank Sum test was used for continuous variables. Categorical variables are expressed as frequencies (N) and percentages (%), and continuous variables are expressed as median with interquartile range (IQR; Q1 and Q30).

Primary Outcome Analysis

Time-to-Event Survival Analysis. A multivariable survival analysis using Cox proportional hazard models was initially fitted but the global Cox assumptions were violated, suggesting that the mortality risk was not proportional during the length of follow-up. Therefore, we constructed a Weibull accelerated failure time (AFT) model[25] to study the effect of seizure status at enrollment with the reported date of death during the follow-up as the event time (Fig 2). AFT is one of the most robust statistical techniques for survival analysis in aging research.[25] Rightward censoring was utilized with the date of death or the last date of contact. We adjusted the model for age, sex, race, ethnicity, hypertension, diabetes, hyperlipidemia, degree of cognitive impairment, education, stroke or TIA, TBI, PD, alcohol abuse, depression, and dominant Alzheimer's disease (AD) mutation.

Secondary Analysis of Mortality. The unadjusted count and percentage of deceased among the 3 groups were calculated. The proportion of deceased participants was adjusted for seizure status and dementia duration at death using logistic regression. The marginal adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were calculated to compare recurrent and remote seizure groups and recurrent and control groups. Post hoc corrections for pairwise comparisons were made using the Tukey Method.

Mortality rates were calculated using the number of deaths in each seizure group divided by total person-time (the total amount of time each person was at risk of death during the study follow-up).

Cognition, Function, and Mood. Cognitive, function, and mood variables were adjusted for the duration of cognitive impairment and age.

The severity of cognitive impairment (CDR-global and CDR-SOB scores), depression (GDS score), and functional impairment (FAS scores) were analyzed as continuous variables. Unadjusted mean and standard deviation were calculated. Marginal means and standard errors were adjusted for seizure status, cognitive impairment duration, and age using linear regression. The estimated adjusted marginal mean differences and 95% CIs were calculated for pairwise comparisons between recurrent versus remote seizure groups and recurrent versus controls. Post hoc corrections for pairwise comparisons were made using the Tukey Method.

Unadjusted counts and percentages were calculated for categorical variables. For physical dependence and nursing home residence, analysis was adjusted for seizure status, duration of cognitive impairment, and age using logistic regression. The marginal aORs and 95% CIs were calculated for pairwise comparisons between recurrent and remote seizure groups and recurrent and no seizure groups.

TABLE 1. Baseline Characteristics of the Entire Cohort With Cognitive Impairment

Baseline characteristics of the entire cohort		Controls N = 26,501	Remote seizures (N = 510)	Recurrent seizures (N = 374)	Overall, N = 26,935	p[a]
Age at enrollment, yr, median (IQR)		74 (66, 80)	69 (62, 77)	70 (61, 78)	74 (66, 80)	***< 0.0001***
Age of cognitive decline, yr, median (IQR)		70 (62, 76)	64 (56, 72)	64 (55, 72)	69 (62, 76)	***< 0.0001***
Sex	0 = M, N (%)	12,505 (48%)	261 (51%)	194 (52%)	12,960 (48%)	0.1248
	1 = F, N (%)	13,546 (52%)	249 (49%)	180 (48%)	13,975 (52%)	
Education, yr, median (IQR)		16 (12, 18)	16 (12, 18)	14 (12, 16)	16 (12, 18)	0.0720
Race	Non-White, N (%)	4,824 (19%)	96 (19%)	67 (18%)	4,987 (19%)	0.9109
	White, N (%)	21,042 (81%)	405 (81%)	305 (82%)	21,752 (81%)	
Ethnicity Hispanic	No, N (%)	23,631 (91%)	451 (89%)	338 (91%)	24,420 (91%)	0.2381
	Yes, N (%)	2,311 (8.9%)	56 (11%)	35 (9.4%)	2,402 (9.0%)	
Hypertension	Absent, N (%)	13,270 (51%)	266 (52%)	198 (53%)	13,734 (51%)	0.6319
	Present, N (%)	12,691 (49%)	241 (48%)	175 (47%)	13,107 (49%)	
Diabetes mellitus	Absent, N (%)	22,472 (87%)	436 (86%)	320 (86%)	23,228 (87%)	0.9071
	Present, N (%)	3,500 (13%)	71 (14%)	52 (14%)	3,623 (13%)	
Hyperlipidemia	Absent, N (%)	13,204 (51%)	265 (53%)	206 (56%)	13,675 (51%)	0.1195
	Present, N (%)	12,561 (49%)	238 (47%)	159 (44%)	12,958 (49%)	
Recent or remote stroke or TIA	No, N (%)	23,259 (90%)	419 (84%)	287 (78%)	23,965 (90%)	***< 0.0001***
	Yes, N (%)	2,549 (9.9%)	82 (16%)	82 (22%)	2,713 (10%)	
PD	No, N (%)	25,253 (97%)	491 (96%)	355 (95%)	26,099 (97%)	***0.0491***
	Yes, N (%)	701 (2.7%)	18 (3.5%)	17 (4.6%)	736 (2.7%)	
History of TBI	No, N (%)	22,506 (87%)	361 (72%)	287 (79%)	23,154 (87%)	***< 0.0001***
	Yes, N (%)	3,217 (13%)	137 (28%)	77 (21%)	3,431 (13%)	
Alcohol abuse over a 1-yr period	No, N (%)	25,634 (99%)	501 (99%)	361 (97%)	26,496 (99%)	***0.0213***
	Yes, N (%)	303 (1.2%)	3 (0.6%)	10 (2.7%)	316 (1.2%)	
Active depression in the past 2 yr	No, N (%)	16,144 (63%)	268 (53%)	182 (49%)	16,594 (62%)	***< 0.0001***
	Yes, N (%)	9,623 (37%)	233 (47%)	188 (51%)	10,044 (38%)	
Dominantly inherited AD mutation	No, N (%)	25,964 (99.7%)	507 (99.4%)	368 (98.4%)	26,839 (99.6%)	***0.0021***
	Yes, N (%)	87 (0.3%)	3 (0.6%)	6 (1.6%)	96 (0.4%)	
APOE4 allele	None, N (%)	10,086 (52%)	204 (56%)	140 (55%)	10,430 (52%)	0.4307
	Heterozygous, N (%)	7,386 (38%)	126 (35%)	89 (35%)	7,601 (38%)	
	Homozygous, N (%)	1,786 (9.3%)	32 (8.8%)	27 (11%)	1,845 (9.3%)	

The *p* values in boldface italics represent statistical significance.

AD = Alzheimer's disease; ANOVA = analysis of variance; IQR = interquartile range; PD = Parkinson's disease; TBI = traumatic brain injury; TIA = transient ischemic attack.

[a]Kruskal-Wallis rank sum test was used for evaluating continuous variables because the comparison is between more than 2 groups and the assumptions of ANOVA were not met; Pearson's χ^2 test was used for comparing categorical variables when each cell in the contingency table had expected frequency of 5 or more; Fisher's exact test was used for comparing categorical variables when at least one cell in the contingency table had expected frequency of less than 5.

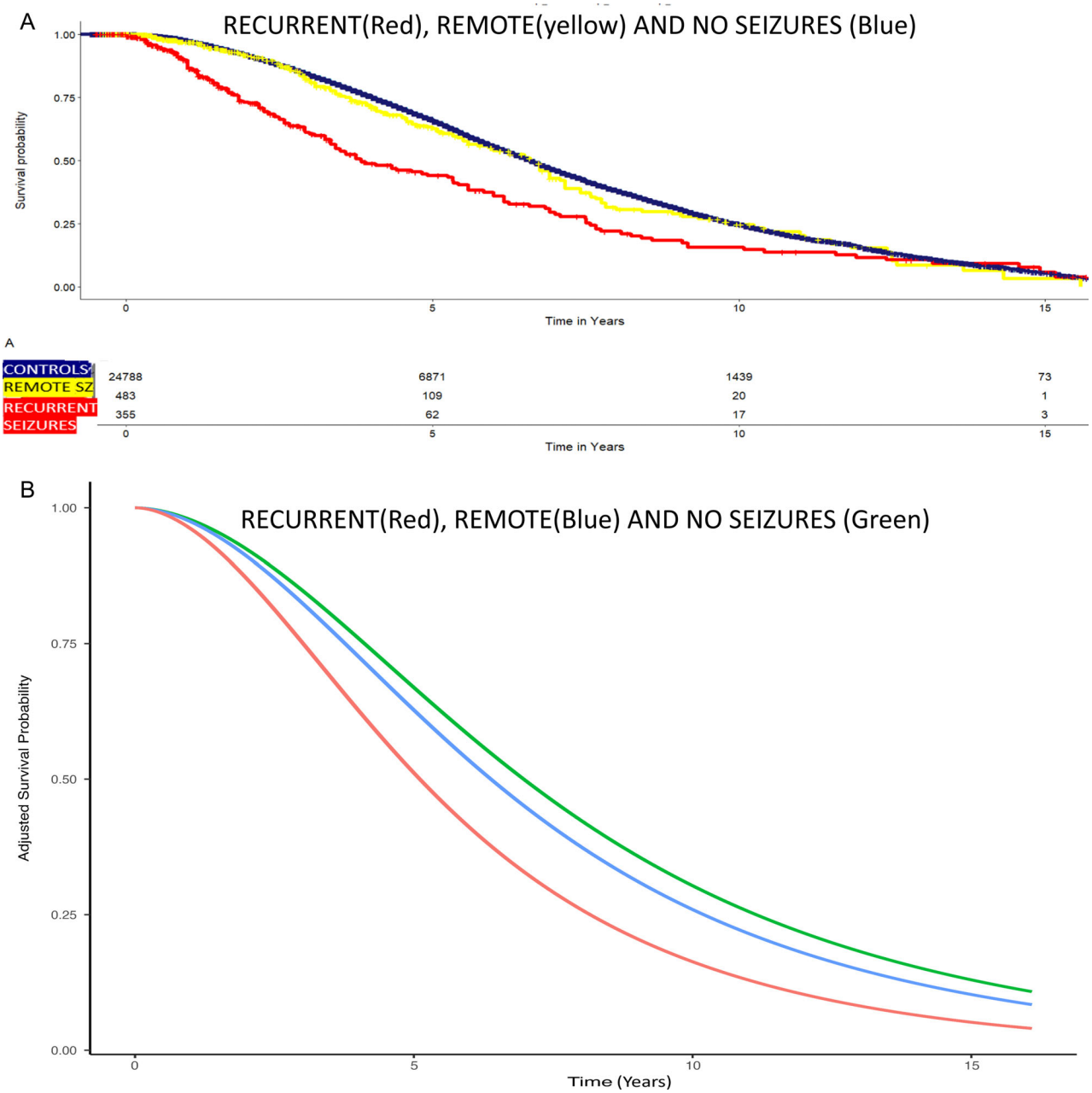

FIGURE 2: Survival curves for time to mortality by seizure status. (A) Survival (Kaplan Meier) curves for time to death with recurrent seizures, remote seizures and no seizures are shown with survival probabilities at each time point for each group. The total number at risk is given at the bottom for each group. (B) Survival curves for time to death by seizure status (recurrent, remote, and no seizures) show probabilities after adjusting for age, sex, education, race, ethnicity, hypertension, diabetes, hyperlipidemia, degree of cognitive impairment, dominant AD mutation, brain trauma (TBI), stroke, PD, alcohol abuse, and depression. AD = Alzheimer's disease; PD = Parkinson's disease; TBI = traumatic brain injury.

Post hoc corrections for pairwise comparisons were made using the Tukey Method.

The categories of cognitive impairment (cognitively impaired but not MCI, MCI, and dementia) were adjusted for seizure status, duration of cognitive impairment, and age using multinomial logistic regression.

Missing Data. For each variable, < 5% of data was missing except age at cognitive decline-onset and APOE4 status. Therefore, we excluded missing data from the analysis. We imputed age at the onset of cognitive decline because cognition, functional status, and mood were all adjusted for the duration of cognitive decline. APOE4 was not imputed because it was not statistically significant in the univariate analysis and was not utilized in further analyses.

The *P* values of all analyses were 2-sided with an alpha of 0.05 for all tests.

Results

Baseline Characteristics

Of the 26,935 participants with cognitive impairment (see Fig 1), 3.3% (N = 884) had a seizure history. Recurrent seizures were reported in 1.4% (N = 374), and remote seizures in 1.9% (N = 510).

Participants with recurrent or remote seizures were a median of 5 years younger than controls at the onset of cognitive decline (recurrent = 64, remote = 64, and controls = 69 years, $p < 0.0001$). Compared with controls, participants with recurrent or remote seizures had more neurologic comorbidities. Seizure groups had a higher proportion with stroke or TIA history (recurrent = 22%, remote = 16%, and controls = 9.9%, $p < 0.0001$), TBI (recurrent = 21%, remote = 28%, and controls = 13%, $p < 0.0001$), and PD (recurrent = 4.6%, remote = 3.5%, and controls = 2.7%, $p = 0.0491$) than controls. The groups also differed in terms of alcohol abuse (recurrent = 2.7%, remote = 0.6%, and controls = 1.2%, $p = 0.021$) and dominant AD mutation (recurrent = 1.6%, remote = 0.6%, and controls = 0.3%, $p = 0.0021$). The groups did not differ by sex, race, ethnicity, education, cardiovascular risk factors, and APOE4 status (see Table 1).

Mortality Outcomes

The mortality rate was 100.3 per 1,000 for the entire cohort. The mortality rate was 169.1 per 1,000 in those with recurrent seizures compared with 102.5 and 99.3 in those with remote and controls, respectively.

To examine mortality risks, we conducted a survival analysis using the Weibull AFT model (see Fig 2 and Table 2.). Figure 2A shows the number at risk for each seizure group. We adjusted the model for age, sex, race, ethnicity, education, hypertension, diabetes, hyperlipidemia, the severity of dementia, stroke or TIA, TBI, PD, alcohol abuse, depression, and dominant AD mutation (Supplementary Table S1 and Supplementary Fig 2B show the adjusted survival probabilities). We found that people with recurrent seizures were at a greater risk of death (see Table 2.) compared with those with remote and no seizures (recurrent: aHR = 1.79, 95% CI = 1.51 to 2.12, $p < 0.0001$, remote: aHR = 1.17, 95% CI = 0.98 to 1.38, $p = 0.0754$). The median time to death for those with recurrent, remote, and no seizures was 2.4, 4.0, and 4.7 years, respectively (Table 3.).

TABLE 3. Median Time to Death for Recurrent Seizures, Remote Seizures, and Control Groups

Seizure status	Median time to death, yr
Recurrent seizures	2.42
Remote seizures	4.00
Controls (no seizures)	4.66

At the most recent follow-up, 34.78% (N = 9,427) of the cohort was deceased. A significantly higher proportion of participants (Table 4.) with recurrent seizures had died compared with remote seizures (45.18% vs 31.57%, aOR = 1.99, 95% CI = 1.39 to 2.85, $p < 0.0001$) and controls (45.18% vs 34.65%, aOR = 1.49, 95% CI = 1.14 to 1.95, $p = 0.0014$). Age at death was 73.01, 76.26, and 79.72 years for those with recurrent, remote, and no seizures, respectively (Supplementary Table S2).

Cognition

Table 5. shows adjusted and unadjusted cognitive, functional, and mood statuses among the 3 seizure groups. There was a significantly higher proportion of people with recurrent seizures who had dementia compared with those with remote (aOR = 2.94, 95% CI = 2.69 to 5.10, $p = 0.0001$) and no seizures (aOR = 1.75, 95% CI = 1.09 to 2.80, $p = 0.0207$). Recurrent seizure participants performed significantly worse than remote (mean difference CDR-SOB = 2.88, 95% CI = 2.24 to 3.52, $p < 0.0001$), and no seizure groups (mean difference CDR-SOB = 3.10, 95% CI = 2.60 to 3.59, $p < 0.0001$).

Function

People with recurrent seizures were more likely to have physical dependence than those with remote (aOR = 2.26, 95% CI = 1.57 to 3.26, $p < 0.0001$) and

TABLE 2. The aHRs and 95% CIs for Mortality

Seizure status	Unadjusted HR (95% CI)	*p*	aHR (95% CI)	*p*
Remote seizures	1.03 (0.87 to 1.23)	0.6931	1.17 (0.98 to 1.38)	0.0754
Recurrent seizures	1.78 (1.50 to 2.10)	***< 0.0001***	1.79 (1.51 to 2.12)	***< 0.0001***

The *p* values in boldface italics represent statistical significance.
aHRs = adjusted hazard ratios; CIs = confidence intervals; HR = hazard ratio.

TABLE 4. Mortality Outcomes Among Various Seizure Groups

	Controls (N = 26,501)	Remote (N = 510)	Recurrent (N = 374)	Recurrent versus remote		Recurrent versus none	
				OR (95% CI)[a]	*p*[a]	OR (95% CI)[a]	*p*[a]
Deceased	9,027 (34.65)	161 (31.57)	169 (45.18)	1.99 (1.39, 2.85)	***< 0.0001***	1.49 (1.14, 1.95)	***0.0014***

The *p* values in boldface italics represent statistical significance.
CI = confidence interval; OR = odds ratio.
[a]Adjusted for disease duration at death in logistic regression model and pairwise comparisons corrected with the Tukey Method. The marginal adjusted odds ratios (aOR), 95% CI and *p* values were calculated for comparisons between recurrent and remote seizure groups, and recurrent and control groups.

no seizures (aOR = 2.26, 95% CI = 1.68 to 3.03, $p < 0.0001$). People with recurrent seizures had worse FAS scores than remote (adjusted-mean difference = 5.18, 95% CI = 3.66 to 6.70, $p < 0.0001$) and no seizure controls (adjusted-mean difference = 5.47, 95% CI = 4.30 to 6.63, $p < 0.0001$; see Table 5.).

Mood

The prevalence of active depression differed among the seizure groups (recurrent = 51%, remote = 47%, and controls = 37%, $p < 0.0001$). GDS score was comparable for those with recurrent and remote seizures but higher in those with recurrent seizures than controls (adjusted-mean difference = 0.59, 95% CI = 0.18 to 1.00, $p = 0.0021$).

Discussion

We found that PWD with recurrent seizures had a higher mortality risk compared with those with remote or no seizures. Specifically, recurrent seizures in PWD are associated with ~1.8 times higher risk of premature mortality. PWD have worse cognition and daily function and more physical dependence than those with remote seizures. Finally, PWD with recurrent seizures have worse mood compared with controls.

The present study is one of the largest longitudinal multicenter studies investigating mortality amongst PWD with recurrent seizures based on robust clinical evaluation. Our study is novel and significant because it examined the impact of seizure control on PWD. The effect of seizures on mortality among PWD has been studied in only a handful of studies. A small sampled study of Lewy Body dementia investigating mortality among PWE compared to no-epilepsy controls found no difference.[26] Late-onset myoclonic epilepsy in Down syndrome, which closely relates to symptomatic AD, has been identified as a risk factor for mortality in Down syndrome.[27] Our longitudinal, multicenter, observational study expands the existing literature by showing higher premature mortality associated with recurrent seizures, a phenomenon not observed in cases of remote seizures in PWD.

The "chicken-and-egg" question is another important consideration when assessing mortality in the context of dementia and co-morbid seizures because dementia can cause seizures, and seizures can worsen dementia. In addition, both can independently impact mortality. Therefore, we accounted for dementia severity as a covariate in our multivariable model. Even after accounting for dementia severity, we found recurrent seizures to be significantly associated with early mortality compared to other seizure groups.

The etiology of mortality in people with seizures is multifaceted.[28] Several mechanisms may account for the impact of recurrent seizures on mortality.[29] Some of these include sudden unexpected death in epilepsy (SUDEP), status epilepticus and epilepsy itself, seizure-related frailty, medication side effects, and seizure-related injury. Death in recurrent seizures or status epilepticus may be from a mix of respiratory difficulties, respiratory failure, central apnea, failure to arouse, arrhythmias, and heart dysfunction.[30] Repeated seizures and uncontrolled epilepsy can lead to ictal and postictal apnea, transiently reduced ventilation frequency, and other acute compromises of the respiratory control system and eventually centrally mediated severe alteration of cardiorespiratory dysfunction leading to death.[31] Other acute effects include ictal spread to the amygdala that may cause apnea and respiratory arrest.[32] People with uncontrolled seizures are more likely to suffer fatal injuries to the head, trunk, and limbs.[33] Systemic complications, such as those related to the kidneys and heart, may also contribute to mortality in ongoing recurrent seizures and status epilepticus.[34] Recurrent hippocampal seizures in rats may induce epileptiform activity in the brainstem, leading to death from dyspnea and respiratory arrest.[30] Serial seizures and status epilepticus can also cause death through hyperthermia, heart arrhythmias, and lactic acidosis.[35]

TABLE 5. Cognition, Mood, and Functional Status Among Various Seizure Groups

Cognition, mood, functional status		Controls N = 26,501	Remote seizures (N = 510)	Recurrent seizures (N = 374)	Recurrent versus remote		Recurrent versus none	
					Mean difference or *OR (95% CI)[a]	p[a]	Mean difference or OR (95% CI)	p[a]
Cognition								
Unadjusted CDR-SOB, mean + SD		4.28 ± 4.24	4.91 ± 5.08	7.95 ± 6.45	-	-	-	-
Adjusted CDR-SOB, mean + SE[a]		4.29 + 0.02	4.50 + 0.18	7.39 + 0.21	2.88 (2.24, 3.52)	< ***0.0001***	3.10 (2.60,3.59)	< ***0.0001***
Unadjusted global CDR, mean + SD		0.84 ± 0.67	0.94 ± 0.81	1.40 ± 1.03	-	-	-	-
Adjusted global CDR, mean + SE[a]		0.84 + 0.00	0.88 + 0.03	1.32 + 0.03	0.44 (0.34, 0.54)	< ***0.0001***	0.48 (0.40, 0.56)	< ***0.0001***
Cognitive categories^	Cognitive decline but not MCI	1904 (7.31%)	57 (11.18%)	19 (5.08%)	-	-	-	-
	MCI	9,450 (36.27%)	172 (33.73%)	85 (22.73%)	1.52 (0.85, 2.73)	0.1558	1.03 (0.62,1.70)	0.9049
	Dementia	14,697 (56.42%)	281 (55.1%)	270 (72.19%)	2.94 (1.69,5.10)	***0.0001***	1.75 (1.09,2.80)	***0.0207***
Mood								
Unadjusted total GDS score, mean ± SD		2.74 + 2.84	3.61 + 3.38	3.55 + 3.19	-	-	-	-
Adjusted GDS score, mean + SE[a]		2.75 + 0.02	3.44 + 0.14	3.34 + 0.17	−0.09 (−0.61, 0.42)	0.9036	0.59 (0.18,1.00)	***0.0021***
Functional status								
Some degree of dependence, N (%)		14,005 (54.27)	289 (57.00)	275 (74.93)	2.26 (1.57,3.26)	< ***0.0001***	2.26 (1.68,3.03)	< ***0.0001***
Permanently in a nursing home, N (%)		292 (1.12)	2 (0.39)	7 (1.87)	4.70 (0.71,31.02)	0.1331	1.60 (0.65, 3.98)	0.4451
Unadjusted FAS total, mean ± SD		10.97 + 9.89	12.11 + 10.46	17.65 + 11.14	-	-	-	-
Adjusted FAS total, mean + SE[a]		11.00 + 0.06	11.29 + 0.42	16.47 + 0.49	5.18 (3.66,6.70)	< ***0.0001***	5.47 (4.30,6.63)	< ***0.0001***

The p values in boldface italics represent statistical significance.

CDR-SOB = clinical dementia rating sum of boxes; CI = confidence interval; FAS = functional assessment scale scores; GDS = Geriatric Depression Scale; MCI = mild cognitive impairment; OR = odds ratio; SD = standard deviation; SE = standard error.

[a]Continuous variables: CDR-global, CDR-SOB scores, GDS score, and total FAS scores were analyzed as continuous variables. Unadjusted mean and standard deviation and adjusted mean and standard error are presented. Marginal means and standard errors were adjusted for seizure status, cognitive impairment duration and age using linear regression. The estimated adjusted marginal mean differences, 95% CI and p values were calculated for pairwise comparisons between recurrent and remote seizure groups, and recurrent and no seizure controls. For categorical variables, unadjusted counts and percentages were calculated. For physical dependence and nursing home residence, analysis was adjusted for seizure status, duration of cognitive impairment and age. The marginal adjusted OR, 95% CI, and p values were calculated for pairwise comparisons between recurrent and remote seizure groups, and recurrent and no seizure groups. Post hoc corrections for pairwise comparisons are make using Tukey Method.

Recurrent seizures are not only associated with higher mortality but also worse morbidity across various health dimensions. Similar to previous studies, our study found more severe cognitive impairment in people with recurrent seizures despite being younger. The association between seizures and cognitive decline is well-documented.[11,12,14,36–38] PWD with seizures have more neuronal loss and decline in language and cognition

compared to PWD without seizures.[12,36] People with poorly controlled seizures experience faster cognitive decline, and better seizure control is associated with a beneficial impact on cognition.[39] PWD with subclinical interictal epileptiform discharges (IEDs) on electroencephalogram (EEG) without overt clinical seizures also experience a faster decline in global cognition and executive function compared to PWD without subclinical IEDs.[11] In temporal lobe epilepsy, hippocampal IEDs interrupt short-term memory.[40,41] Long-term hippocampal network remodeling due to IEDs can also adversely affect cognition.[42]

Whereas dementia is one of the most significant risk factors for late-onset seizures (> 65 years of age),[43] the relative risk of seizure occurrence is highest among people with younger ages of onset of cognitive decline.[2,44] Consistent with existing literature, we found a younger age of cognitive decline in those with seizures compared with controls.

Poorly controlled seizures impact function in younger PWE.[45] Our study extends these findings to older PWD. Even after adjusting for age and dementia duration, PWD with recurrent seizures were more likely to be physically dependent and had limited ability to function in daily life. Thus, our findings demonstrate that poorly controlled seizures may exacerbate both cognitive and physical decline, thereby contributing to decline in functional status in older PWD.

Seizure control was not associated with more severe depression in our study. These findings are similar to a previous study of 143 PWE in whom depression was equally prevalent in those with well-controlled and poorly controlled epilepsy.[46]

Our study has several limitations. Some anti-seizure medications (ASMs) may slow cardiac conduction,[47] cause osteoporosis and subsequent fractures, and lead to higher lipid levels, increasing cardiovascular risks.[48] Older generation ASMs are also associated with increased mortality in PWD.[47] However, due to incomplete documentation, we could not assess the impact of ASMs on mortality. We did not have information on the ASM types, numbers, or compliance. The cause, type, frequency, or severity of seizures and EEG findings were not available. It is very likely that the semiology or the type of seizures may influence mortality. Investigating how generalized versus focal recurrent seizures may impact mortality in this patient population needs to be pursued in future studies. The duration of recurrent seizures beyond the preceding year was not known. The rates of recurrent seizures and remote seizures are lower in our study than those reported in literature in older adults, likely because seizures are subtle and often underestimated in the context of dementia.[49–51] Therefore, some participants with seizures may not have been recognized in our dementia cohort. The documentation of participants who had no seizures at enrollment but developed new-onset seizures is incomplete in the dataset. Therefore, we excluded this group from the current analysis. Variables differed in availability—via updates to versions—through the years. Our analysis focused on all-cause dementia; differentiating among dementia subtypes was not feasible due to the relatively small number of seizure participants. Due to the study's observational design, it is not possible to establish cause-and-effect relationships. Missing data may have impacted the results of the study, such as introducing systematic biases. Last, the data are neither population-based nor nationally representative, which may affect the generalizability of our results. Therefore, prospective randomized controlled trials are needed to confirm these findings.

In summary, recurrent seizures in PWD are associated with earlier mortality, worse cognition, worse daily and physical function, and worse mood compared to PWD who have either remote or no seizures. The implication of our findings is that the identification and treatment of seizures in at-risk populations may improve mortality and other outcomes. However, seizures are often subtle and under-recognized in PWD.[49–51] Advances in cognitive health care are required to develop protocols that can efficiently and effectively screen appropriately selected high-risk PWD for epilepsy, such as those with earlier age of dementia onset, male sex, severe dementia, dominant AD mutation, stroke/TIA, TBI, PD, brain tumors, and alcohol abuse.

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Author Contributions

I.Z. and J.K. contributed to the conceptualization and design of the study. I.Z. and S.G. contributed to the acquisition and analysis of data. I.Z., S.G., M.Q., C.M., V.P., Y.C.L., S.A.M., and J.K. contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

Nothing to report.

Data availability

De-identified data for this article is available via the National Alzheimer's Coordinating Center (NACC data query request process | National Alzheimer's Coordinating Center).

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