Received: 5 December 2023 | Accepted: 11 February 2025

DOI: 10.1002/epi4.70013

Epilepsia Open® Open Access

ORIGINAL ARTICLE

Prevalence and factors associated with seizures among patients with dementia: A retrospective clinic-based study

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Abstract

Objective: Chronic diseases associated with aging, such as dementia and seizures, are expected to rise significantly in the Philippines' growing elderly population. This study aims to determine the frequency, demographic characteristics, and clinical profile of dementia patients who developed new-onset seizures in an outpatient setting.

Methods: This descriptive, retrospective, cumulative prevalence study included 245 patients diagnosed with dementia at a tertiary hospital in Manila from February 2010 to February 2020, according to DSM-5 criteria. Patients were stratified into those who developed seizures and those who did not. Data on demographics, type, dementia severity, comorbidities, and seizure characteristics were collected and analyzed using descriptive statistics, bivariate, and multivariate logistic regression analyses.

Results: The study included 245 dementia patients, of whom 10 (4.1%) developed seizures, with a higher likelihood observed in those with severe dementia. Most patients were diagnosed with Alzheimer's disease, and seizures were mostly seen in individuals between the ages of 65 and 79. The majority of the seizures were classified as generalized (50%). Compared to mild cases, patients with moderate dementia are about 1.5 times more likely to experience seizures, whereas patients with severe dementia are about 10 times more likely to experience seizures compared to patients with mild dementia. The association is statistically significant for severe cases of dementia.

Significance: This study revealed that 4.1% of Filipino patients diagnosed with dementia in an outpatient setting at a tertiary hospital developed new-onset seizures. Seizures were mostly reported in patients with severe Alzheimer's disease. Conventional understanding of seizures among patients with dementia is important to identify features and predictors to provide efficient management among these patients to possibly improve their quality of life.

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Plain Language Summary: With the aging Filipino population, there is an expected rise in chronic diseases such as dementia and seizures. This study looked at dementia patients in an outpatient setting over 10 years and found that 4.1% developed seizures. Most patients had Alzheimer's disease, and seizures were more common in severe dementia cases.

KEYWORDS
dementia, epilepsy, seizure

1 | INTRODUCTION

1.1 | Background

Chronic diseases associated with aging are expected to increase exponentially along with population growth, particularly in a young demographic like the Philippines. Of an estimated 110 million people, approximately 6% of the total population is aged 65 years and older.[1] An unprecedented rise in aging-associated conditions is projected to become a significant public health burden in the coming years, with cases forecasted to triple by 2050. Among these, dementia is expected to be the most prevalent aging-associated disease.[2,3]

It is also widely recognized that aside from dementia, seizures are among the most common neurological disorders in the elderly.[4] An inpatient study reported that 15% of elderly inpatients with new-onset epilepsy experienced increased morbidity and mortality.[5] The risk of epilepsy has also been found to be higher in individuals with Alzheimer's disease (AD) and is associated with a faster rate of cognitive decline.[6–8] The cumulative incidence of seizures varies across dementia types: up to 10 times higher in patients with AD and dementia with Lewy Bodies (DLB), and 6 times higher in patients with frontotemporal dementia (FTD) compared to age-matched controls.[9] Seizures in AD have been studied more extensively than in other types of dementia, for which data remain limited.

The presence of epileptiform activity on electroencephalography (EEG) has been shown to have a significant impact on the rate of cognitive decline *among* patients with AD.[10] This has been attributed to network hyperexcitability, which is thought to be induced by abnormal proteins found in neurodegenerative diseases such as AD, Parkinson's disease (PD), and FTD.[9,11–13] Protein aggregates can disrupt network function and may clinically manifest as seizures. Notably, the incidence of seizures is significantly higher in patients with dementia compared to age-matched controls.[9]

Treatment of seizures in older individuals may be different in terms of dosing and response to medications compared to younger individuals. Whether a first unprovoked seizure in an elderly individual warrants treatment with antiseizure medication is still uncertain; though it is deemed reasonable in some cases due to the propensity for recurrences.[4]

Key points

- Seizures occur in 4.1% of Filipino dementia patients, commonly with Alzheimer's.
- Seizure risk increases with dementia severity; severe cases are most affected.
- Seizures were more frequent in dementia patients aged 65-79, but age link was not statistically significant.

Although certain clinical characteristics, such as dementia type and age of onset, have been identified as predictors of seizures in patients with dementia, data on seizures within Asian populations remain limited.[9] In this study, we aimed to determine the prevalence, demographic characteristics, and clinical profile of dementia patients who developed new-onset seizures in an outpatient clinic.

2 | METHODOLOGY

2.1 | Study design and participants

This is a descriptive, retrospective, cumulative prevalence study of all patients clinically diagnosed with dementia in an outpatient setting by a dementia specialist at a tertiary hospital in Manila between February 2010 and February 2020, based on the DSM-5 criteria for Major Neurocognitive Disorder. Patients who did not meet the DSM-5 Criteria for Major Neurocognitive Disorder, including Mild Cognitive Impairment were excluded.[4] Patients with dementia caused by sequelae of traumatic brain

injury, tumor, hydrocephalus, or hypoxia/arrest were also excluded. Dementia patients were identified and stratified into mild, moderate, and severe dementia using the Montreal Cognitive Assessment (MoCA) test.[14] Depending on the patient's language preference, either the MoCA English or MoCA Filipino test was administered. AD severity was classified according to publicly available standard MoCA test score ranges: mild AD (21–24), moderate AD (11–17), and severe AD (10 or less).[14–16] Demographic and clinical profiles were recorded, and patients were stratified into those who developed seizures and those who did not. Patients with a history of seizures before the diagnosis of dementia were excluded. Age, sex, type of dementia, age of onset of cognitive decline, age of onset of seizures, severity of dementia, medications, antiseizure medications, type of seizure, seizure manifestations, and comorbidities were included in the demographics and clinical profiles of patients. Epilepsy diagnoses were made by an adult neurologist. The seizure type was classified using the ILAE 2017 operational classification, and the diagnosis was made on clinical grounds and/or EEG findings if available.[17]

2.2 | Statistical analysis

Descriptive analysis of the demographic and clinical characteristics was done using frequencies and percentages for the categorical variables. Mean and IQR were calculated for continuous variables. Bivariate and multivariate logistic regression were used for comparison studies, and Odds ratio (OR) with a 95% confidence interval. All statistical analyses were performed using Stata (Version 14) with the level of significance set at <0.05.

3 | RESULTS

3.1 | Demographic and clinical profile of dementia patients

The study included 245 dementia patients, of whom 10 (4.1%) developed seizures (Table 1). Half of the patients were aged 65 to 79 years (50.6%), followed by those aged 80 years and older (37.1%). The majority of the outpatient dementia patients were female (65%). Common comorbidities were hypertension (53.1%) and cardiac disease (34.3%). AD was the most frequently diagnosed type of dementia (60.8%), followed by mixed-type dementia (MD) (22.9%) and vascular dementia (VD) (8.6%). Donepezil and Memantine were prescribed to 66.5% and 60.8% of patients, respectively. The majority had moderate dementia severity (54.7%), followed by mild (26.9%) and severe dementia (18.4%).

3.2 | Demographic and clinical profile of dementia patients who developed seizures

Among dementia patients who experienced seizures, the majority belonged to the 65 to 79-year-old age group (60%) (Table 1). Seizures were more frequent in female dementia patients than in male patients (80% vs. 20%). The primary comorbidities among patients who developed seizures were hypertension (50%) and cardiac disease (30%). Nearly half of the dementia patients who developed seizures had no comorbidities (40%). All patients in our cohort who developed seizures had AD, with the majority prescribed memantine (50%) and donepezil (40%).

As shown in Table 2, 10 patients out of 245 in the study sample developed seizures, with an average age of seizure onset at 76.3 ± 9.2 years. Among the patients with seizures, half had generalized onset (50%), followed closely by focal onset (40%), and 10% had unknown onset. Most seizures were characterized by motor manifestations (80%), while the rest exhibited nonmotor features (20%). A total of 30% of patients had provoked seizures, with 20% of seizures being metabolic in etiology, 10% resulting from hypoglycemia, and 10% from hyponatremia. The most common antiseizure medications prescribed were levetiracetam (50%) and valproic acid (40%). EEG findings revealed background activity slowing in two patients (20%), while one patient (10%) had unremarkable findings. Neuroimaging findings showed that half of the patients with seizures had cerebrocerebellar volume loss and chronic ischemic white matter changes.

3.3 | Association of demographic characteristics and seizure among dementia patients

As shown in Table 3, age and sex were not associated with the likelihood of seizures among dementia patients. No association was found between the age of cognitive decline onset and seizure likelihood. Similarly, no significant relationship was observed between comorbid conditions and seizure occurrence.

In the bivariate analysis (Table 3), seizure risk increased with dementia severity. Compared to patients with mild dementia, those with moderate dementia were approximately 1.5 times more likely to experience seizures, whereas patients with severe dementia were about 10 times more likely. This association was significant for severe dementia but not for moderate dementia.

The multivariate model (Table 3) showed a consistent trend, with the odds of seizures increasing proportionally with dementia severity, even after adjusting for age, sex, and comorbidities. Patients with moderate

TABLE 1 Demographic characteristics and clinical profiles of patients with dementia.

	With seizure ($n=10$) n (%)	Without seizure ($n=235$) n (%)	Total ($n=245$) n (%)	p-Value
Age				
<64	1 (3.3)	29 (96.7)	30 (12.2)	0.832
65–79	6 (4.8)	118 (95.2)	124 (50.6)	
80 and above	3 (3.3)	88 (96.7)	91 (37.1)	
Sex				
Female	8 (5)	151 (95)	159 (64.9)	0.307
Male	2 (2.3)	84 (97.7)	86 (35.1)	
Comorbidities				
Hypertension	5 (3.8)	125 (96.2)	130 (53.1)	0.930
Diabetes mellitus	1 (1.4)	69 (98.6)	70 (28.6)	
Cardiac disease	3 (3.6)	81 (96.4)	84 (34.3)	
Dyslipidemia	1 (2)	49 (98)	50 (20.4)	
Stroke	0 (0)	25 (100)	25 (10.2)	
Hypothyroidism	0 (0)	7 (100)	7 (2.9)	
Chronic kidney disease	0 (0)	2 (100)	2 (0.8)	
Parkinson's	0 (0)	2 (100)	2 (0.8)	
PTB	0 (0)	1 (100)	1 (0.4)	
Colon cancer	0 (0)	1 (100)	1 (0.4)	
Hyperthyroidism	0 (0)	1 (100)	1 (0.4)	
Prostate cancer	0 (0)	1 (100)	1 (0.4)	
None	4 (7.7)	48 (92.3)	52 (21.2)	
Number of comorbidities (mean ± SD)	1 ± 0.9	1.5 ± 1.1	1.5 ± 1.1	0.158
Type of dementia				
Alzheimer's disease	10 (6.7)	139 (93.3)	149 (60.8)	0.243
Mixed type dementia	0 (0)	56 (100)	56 (22.9)	
Vascular dementia	0 (0)	21 (100)	21 (8.6)	
Fronto-temporal	0 (0)	9 (100)	9 (3.7)	
Parkinson's	0 (0)	5 (100)	5 (2)	
Dementia of Lewy body	0 (0)	5 (100)	5 (2)	
Medications				
Donepezil	5 (3.1)	158 (96.9)	163 (66.5)	0.115
Memantine	6 (4)	143 (96)	149 (60.8)	
Citicoline	2 (20)	8 (80)	10 (4.1)	
Rivastigmine	0 (0)	17 (100)	17 (6.9)	
Gingko Biloba	0 (0)	11 (100)	11 (4.5)	
Levodopa-Carbidopa	0 (0)	2 (100)	2 (0.8)	
Age of onset of cognitive decline (mean ± SD)	72.5 ± 7.9	72.7 ± 9	72.7 ± 8.9	0.945
Severity of dementia				
Mild	1 (1.5)	65 (98.5)	66 (26.9)	0.0023*
Moderate	3 (2.2)	131 (97.8)	134 (54.7)	
Severe	6 (13.3)	39 (86.7)	45 (18.4)	

*p-Value < 0.05.

dementia were twice as likely to experience seizures compared to those with mild dementia, while patients with severe dementia were about 14 times more likely. A significant association was identified between severe dementia and an increased likelihood of seizures in the multivariate analysis.

TABLE 2 Clinical characteristics of dementia patients with seizures.

	n = 10 *n* (%)	*p*-Value
Age of onset of seizure (mean ± SD)	76.3 ± 9.2	0.001*
Type of seizure		
Focal onset	4 (40)	0.272
Generalized onset	5 (50)	
Unknown onset	1 (10)	
Seizure manifestations		
Motor	8 (80)	0.018*
Nonmotor	2 (20)	
Provoked seizures	3 (30)	0.057
Underlying cause of seizure		
Metabolic	2 (20)	0.50
Structural	2 (10)	
Infectious	1 (10)	
Unknown	5 (50)	
Antiseizure medications and dose		
Levetiracetam	5 (50)	0.097
Valproic acid	4 (40)	
Oxcarbazepine	1 (10)	
EEG		
Yes	3 (30)	0.205
No	7 (70)	
EEG findings		
Slowing	2 (20)	0.097
Normal	1 (10)	
Missing	7 (70)	
Neuroimaging findings		
Infarction/hemorrhage	1 (10)	0.040*
Chronic ischemic white matter changes	5 (50)	
Cerebrocerebellar volume loss	5 (50)	
Hippocampal atrophy	1 (10)	
None	2 (20)	

*p-Value < 0.05.

4 | DISCUSSION

This study revealed that 4.1% of Filipino patients diagnosed with dementia in an outpatient setting at a tertiary hospital developed new-onset seizures. Our data revealed an almost similar range to a study on the Taiwanese population by Cheng et al. Some reports showed higher incidence rates in other populations at 8.1%–11.5%,[6,9,18] while one study noted a lower seizure frequency of 1.5%.[19] These results, however, are not directly comparable due to differences in study population. A consistent finding across multiple studies is that seizures are quite uncommon in dementia.[6,7,9,18,19] Seizures were observed more in patients with AD than in those with other forms of dementia.[9] This is most likely because AD is the most common neurodegenerative disorder and dementia type.

Hypertension, the most prevalent noncommunicable disease in the Philippines, was the most common comorbidity observed in dementia patients with seizures.[20] Whereas Amatniek et al. (2006) suggested that treated hypertension may protect against the onset of seizures, other studies have shown that the presence of comorbidities, including hypertension, was not significantly associated with seizure occurrence.[5,6,18] The potential protective or negative effect of hypertension on seizures in Alzheimer's disease (AD) requires further investigation.[6]

The average age of onset of cognitive decline was also consistent with previous studies, which reported an earlier age of onset among dementia patients with seizures.[8,9,13,18,21] An accepted theory suggests that the accumulation of abnormal proteins influences neuronal excitability, thereby rendering them epileptogenic, which may also reflect our findings that seizure occurrence increased in direct proportion to the severity of dementia.[7,13,18] As worsening dementia symptoms entail greater accumulation of abnormal proteins, along with increased age and advancing neurodegenerative processes, the likelihood of seizures also increases.[22]

Seizures in patients with AD, DLB, and FTD lacked obvious distinguishing clinical features, suggesting that seizure semiology is not specific to the neurodegenerative syndrome.[9] Focal onset seizures have been reported as the most common type among dementia patients,[18,23–25] though others suggested that generalized onset seizures were more prevalent.[5,9,19] Nonmotor manifestations occurred more frequently than motor ones.[9] Given that the determination of the type of epilepsy was derived from reported seizure semiology, subtle focal onset or nonmotor seizure symptoms might have been inadequately characterized or less frequently reported by patients or caregivers.

Similar to other reports, the most commonly observed EEG abnormality was diffuse slowing.[18,19] In one study, epileptiform discharges on EEG have a low prevalence among patients with dementia, and their presence is not linked to lower MMSE scores, indicating minimal clinical significance in diagnosing epilepsy or dementia.[23] While the utility of EEG in the detection of epileptiform abnormalities is unclear, the presence of epileptiform discharges suggests a moderate risk of new-onset seizures in individuals with dementia.[23]

TABLE 3 Bivariate and multivariate logistic regression models on the association of demographic characteristics and seizure among dementia patients.

	Bivariate logistic regression		Multivariate logistic regression	
	Odds ratio (95% CI)	***p*-Value**	**Odds ratio (95% CI)**	***p*-Value**
Age				
<64	*Reference*		*Reference*	
65–79	1.47 (0.17–12.73)	0.724	0.81 (0.08–7.97)	0.854
80 and above	0.99 (0.1–9.88)	0.992	0.33 (0.03–4.34)	0.402
Sex				
Male	*Reference*		*Reference*	
Female	2.23 (0.46–10.72)	0.319	2.11 (0.4–11.09)	0.378
Comorbidity				
With	*Reference*		*Reference*	
Without	2.6 (0.7–9.57)	0.152	3.25 (0.78–13.61)	0.107
Number of comorbidities (mean ± SD)	0.6 (0.32–1.15)	0.122		
Age of onset of cognitive decline (mean ± SD)	1 (0.93–1.07)	0.932		
Severity of dementia				
Mild	*Reference*		*Reference*	
Moderate	1.49 (0.15–14.59)	0.733	2.17 (0.19–24.52)	0.532
Severe	10 (1.16–86.18)	0.036*	13.84 (1.32–144.78)	0.028*

*p-Value < 0.05.

Seizure recognition is often challenging and underreported, particularly among elderly patients with cognitive impairment. This issue presents similar challenges globally but is also shaped by local healthcare conditions.[26,27] Comprehensive history-taking aimed at identifying epileptic episodes could help uncover more cases and provide valuable data on clinical and therapeutic risk factors.[9] Seizures contribute to the worsening of behavioral and cognitive symptoms; therefore, recognizing and treating seizures is crucial for the effective management of dementia.[9]

5 | LIMITATIONS AND RECOMMENDATIONS

Limitations of a retrospective study include possible recall bias of the informants during clinical assessment. Some patients had no additional consultations or were lost to follow-up, which may fail to catch seizure occurrences through the years. Another limitation of this study is the small sample size, which may be attributed to logistical challenges that limit patient access to dementia specialists and memory centers, as well as the inaccessibility of certain diagnostic tests. We recommend conducting a more thorough, comprehensive multi-center study that includes additional tertiary and memory centers involved in dementia care. Additionally, we suggest incorporating EEG as a supplementary test for dementia cases with new-onset motor, behavioral, or cognitive deficits, as they may also present as non-motor seizures in the elderly.

AUTHOR CONTRIBUTIONS

All authors contributed to the conceptualization of the work, acquisition and analysis of data, drafting and revising, and approved the final version submitted.

FUNDING INFORMATION

There is no funding involved in the writing of this research.

CONFLICT OF INTEREST STATEMENT

All authors declared no conflicts of interest.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study has been reviewed and approved by the local ethics review board: The Medical City Institutional Review Board (TMC-IRB) on May 13, 2021, at the IRB office, Medical Library, Podium Building, The Medical City. The study has also been approved to no longer require the informed consent of the participants due to the retrospective nature of the study by TMC-IRB.

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How to cite this article: Quiles LE, Quintay PKP, Anlacan VM, Espiritu A, Mendoza V. Prevalence and factors associated with seizures among patients with dementia: A retrospective clinic-based study. Epilepsia Open. 2025;00:1–8. https://doi.org/10.1002/epi4.70013