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Predictors of early seizure recurrence among elderly inpatients admitted to a tertiary center: A prospective cohort study

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ABSTRACT

Purpose: Early seizure recurrence is common among elderly inpatients and is related to increased morbidity and a longer length of hospital stay. There are few studies on the short-term outcomes of seizures in the elderly population. We aimed to identify the predictors of early seizure recurrence among elderly inpatients.
Methods: We prospectively enrolled patients aged 60 years and older from a tertiary center who had seizures that either led to their hospital admission or occurred during hospitalization. We analyzed the demographic and hospitalization data, characteristics and etiology of seizures, and neurological and clinical comorbidities. Kaplan–Meier analysis was performed to determine the 30-day cumulative recurrence rates. The logrank test was used to analyze the risk of seizure recurrence within 30 days after the index seizure. Multivariable logistic regression analysis was used to identify risk factors for the recurrence of seizures within 30 days.
Results: Overall, 109 patients (mean age: 75.9 ± 9.6 years) were enrolled. The mean age at the first-ever seizure was 74 ± 11.7 years. Unprovoked seizures occurred in 59.6% of the patients. Cerebrovascular disorders were the most prevalent etiology (52.3%). Early seizure recurrence, defined as within 30 days, occurred in 27.5% of patients. Multimorbidity was found in 95.4% of our inpatients (6.3 ± 2.3 [95% confidence interval, 5.4–7.2]), and the number of comorbidities was higher among those who had seizure recurrence than that among those who did not have seizure recurrence ($p = 0.02$). The probability of seizure recurrence was similar among the subgroups of patients who experienced acute seizures versus unprovoked seizures (both $p = 0.03$), and seizure recurrence was associated with a longer length of hospital stay ($p = 0.005$) compared to that of patients who did not experience seizure recurrence. After multivariate analysis, sepsis ($p = 0.011$), psychiatric disorders ($p = 0.032$), and cardiac arrhythmias ($p = 0.037$) were identified as risk factors for early seizure recurrence.
Conclusions: Higher multimorbidity and a longer length of stay were associated with early seizure recurrence; and sepsis, psychiatric disorders, and cardiac arrhythmias were independent risk factors for early seizure recurrence among elderly inpatients.

1. Introduction

The incidence of epilepsy increases with age, and in the elderly population, it ranges from 82.8 to 135.4 per 100.000 people [1]. The prevalence of active epilepsy among elderly individuals is up to 1.5%, which is almost three times higher than that in younger individuals, and may surpass 5% among nursing home residents [2]. Moreover, approximately 25% of new-onset epilepsy occurs in the elderly population [3]. A population-based study of acute symptomatic and first unprovoked seizures showed that the risk of a subsequent unprovoked seizure was 37.4% over a 10-year period in a subset of individuals aged ≥65 years [4]. After a stroke, elderly inpatients are at a higher risk of seizure recurrence than that of their younger counterparts, particularly among those individuals who present a persistent structural brain lesion [5].

Additionally, recurrent seizures are common long-term complications of a brain injury in elderly inpatients [6,7]. Retrospective studies have showed that treatment is frequently delayed in older patients with new-onset epilepsy; the authors hypothesized that a delay in treatment may have been the reason for seizure recurrence in some of the patients in their cohort [8,9]. Elderly people who present with seizures are more likely to have recurrence than younger individuals [10]. However, data on the risk factors for recurrent seizures in the elderly population are inconclusive or are not known for the majority of patients.

A study from the Veterans Health Administration showed that the hospitalization rate is higher in people aged 60 years and older with new-onset epilepsy in comparison with that of elderly people without

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epilepsy (52% vs 15%) [11]. Moreover, another population-based study, including all ages, reported excess mortality and hospitalization risks among those with new-onset epilepsy [12]. New-onset seizures are common among hospitalized patients, and are also typically recurrent; furthermore, the risk of recurrence is higher in patients with new-onset seizures than that in patients with a history of previous seizures [13]. Hence, the first seizure in an elderly individual should be carefully evaluated to identify the clinical circumstances associated with a likelihood of a lowered seizure threshold, i.e., subsequent epileptic seizures. It is important to note that if a person with a single seizure has associated clinical risk factors for seizure recurrence, the recurrence risk is approximately 60% [14,15]. The burden of seizure outcomes in this population (i.e., older people) has been underestimated; thus, the inclusion of elderly people in research should be performed to eliminate these gaps in knowledge [16]. Most studies on short-term outcomes of seizures among elderly inpatients are retrospective and include patients of all age groups [4]. Moreover, we did not find studies on the risk factors for early seizure recurrence in elderly inpatients from developing countries.

This study aimed to analyze demographic factors, etiologies of seizures, and comorbidities to identify independent predictors of early seizure recurrence among elderly inpatients.

2. Methods

2.1. Participants

This prospective, observational, single-center study was conducted with patients aged ≥60 years who were consecutively admitted to Hospital São Rafael, a general tertiary teaching hospital with 356 beds in Salvador, Brazil, between November 2015 and April 2018.

2.1.1. Inclusion criteria

We enrolled elderly inpatients with seizures that either led to their hospital admission or occurred during a period of care in the emergency room or during hospitalization. All patients were under the care of a neurological team.

2.1.2. Exclusion criteria

The exclusion criteria consisted of (1) elderly inpatients who had been admitted with a diagnosis of seizure that had not been confirmed or who were later diagnosed with other paroxysmal neurological disorders such as syncope, delirium, or transient ischemic attack; (2) patients who had seizures in the setting of an acute traumatic brain injury (TBI) and were followed up by the neurosurgery service; and (3) patients who were lost to follow-up.

2.1.3. Diagnostic criteria

The diagnosis of epilepsy followed the recommendations of the International League Against Epilepsy (ILAE) Official Report [14]. The status epilepticus (SE) diagnosis included the revised concepts, definition, and classification from the Commission on Classification and Terminology and the Commission on Epidemiology of the ILAE [17].

The characteristics of the seizures were described, following the more recent recommendations, based on the Operational Classification of Seizures Types by the ILAE [18].

Acute symptomatic seizure was diagnosed according to the ILAE recommendation that defined the condition as "a clinical seizure occurring at the time of a systemic insult or in close temporal association with a documented brain insult" [19]. Brain insult, according to the Commission, was specified as "events occurring within one week of stroke, TBI, anoxic encephalopathy, or intracranial surgery; at first identification of subdural hematoma; at the presence of an active phase of multiple sclerosis or other autoimmune diseases." Seizures occurring within 24 h of severe metabolic derangements, drug or alcohol intoxication and withdrawal, or exposure to proconvulsant drugs were also considered acute symptomatic seizures [19].

To assign an acute symptomatic seizure to electrolyte imbalance, we used the following cutoff point values, which are most likely to be associated with seizures: sodium: <115 mg/dL (or >145 mmol/L), calcium: <5.0 mg/dL, magnesium: <0.8 mg/dL, glucose fasting: <36 mg/dL (nonfasting associated with ketoacidosis: >~450 mg/dL), urea: >100 mg/dL, and creatinine: >10 mg/dL [19].

The etiology of seizures was categorized as (1) symptomatic (known cause), including a) acute seizures (e.g., stroke, central nervous system [CNS] infection, metabolic disorder, and autoimmune), b) remote seizures (e.g., poststroke, posttraumatic, and postencephalitic), and c) progressive symptomatic (brain tumor and dementia); and as (2) unknown cause [5,17].

In addition, for the meaningful analysis of outcomes, we grouped the seizures into two following groups, according to the etiology:

(1) acute symptomatic seizures, including patients with a) acute seizures (known cause); and b) patients with remote and/or progressive seizures (epilepsy) who had, by the time of the study, a seizure because of an acute cause; and
(2) unprovoked seizures (epilepsy), including patients with a) remote seizures, b) progressive seizures, or c) both types of etiologies (remote and progressive), and patients who had, by the time of the study, a seizure of unknown cause.

Late-onset seizures/epilepsy were conventionally defined as seizures first occurring in subjects older than 60 years [20,21].

New-onset seizures were defined as a first-ever seizure, including acute symptomatic seizures or unprovoked seizures, occurring at the time of the study.

Unprovoked seizure was defined as a seizure occurring in the absence of precipitating factors and that may have been caused by a static or progressive injury [22]. First unprovoked seizure might be considered epilepsy in special situations or in cases of relapse, according to the ILAE [14].

The index seizure was the seizure that led the patient to be included in the study.

Early recurrent seizure was defined as a second seizure event, unprovoked, and separated from the first seizure by more than 24 h up to the 30th day after the index seizure.

Patient multimorbidity was defined as the coexistence of two or more chronic conditions [23].

Investigation of seizure etiology included laboratory exams (glucose, urea, magnesium, sodium, calcium, and creatinine). Routine electroencephalogram (EEG), 24-h video-EEG, and brain imaging data (computed tomography, magnetic resonance image (MRI), MRI angiography, and positron emission tomography) were also collected as needed. Some patients underwent cerebrospinal fluid analysis.

The following results of EEG were considered abnormal: diffuse or focal slow abnormalities and interictal or ictal paroxysms. This definition has excluded records with nonspecific abnormalities.

2.2. Main outcome: early recurrent seizure

Early recurrent seizure assessment (up to 30 days) was prospectively performed through close scrutiny of the inpatient medical records or via telephone interview for patients who had been discharged from the hospital. The seizure should have been clearly recognized by a witness during hospitalization or at home for the patients who had already been discharged. The caregiver/relative/patient had received detailed information concerning the seizure's characteristics, and regarding the aim of the study when filling out the informed consent form. The authors obtained a detailed description of the seizures to exclude other conditions, and the principal investigator examined most patients in

the outpatient department, or made a telephone call to the remaining patients after 30 days of the index seizure.

2.3. Analysis methods

2.3.1. Predictors of early recurrent seizure

The following data were analyzed: (1) demographic data, including age, gender, and socioeconomic level (healthcare users/public health users); (2) clinical disorders, such as comorbidities of epilepsy, or the etiology of an acute symptomatic seizure; (3) hospitalization data, including intensive care unit (ICU) admission and the length of hospital stay (LOS); (4) characteristics of the seizure disorders during the index seizure, such as SE, acute symptomatic seizures, single unprovoked seizure, epilepsy, seizure type, age at onset of the first seizure; (5) prescription of antiepileptic drugs (AEDs) at the time of index seizure and/or at time of discharge (yes/no); (6) etiology of the seizure (underlying type of cause); and (7) presence or absence of other nervous system diseases, including cerebrovascular disorders (ischemic and hemorrhagic stroke), dementias, movement disorders, encephalopathies, brain tumors, CNS infections, delirium, and miscellaneous (motor neuron disease, polyneuropathy, demyelinating disease).

2.3.2. Statistics

The sample was dichotomized between patients who had an early recurrence of seizure and patients who had no recurrence of seizure.

Quantitative variables with a normal distribution are expressed as their mean and standard deviation. Variables with a nonnormal distribution are expressed as their median and interquartile interval. Normal variables were identified by the graphical analysis of histograms and box plots and by the Kolmogorov–Smirnov test. Categorical variables are reported as frequencies and percentages.

Bivariate comparisons between groups were performed using a Student's *t*-test for numerical variables with a normal distribution and the Mann–Whitney test for those with a nonnormal distribution. Categorical variables were compared by a Pearson chi-square or Fisher's test when necessary. Independent variables were considered for multivariate analysis if the variable was recognized as being plausible according to the main study hypotheses and when the bivariate tests showed a p value ≤0.25 according to the algorithm proposed by Hosmer and Lemeshow [24].

A stepwise forward hierarchical logistic regression was performed for the multivariate analysis; such analyses were sequentially performed in three blocks, to increase the power of the model, with demographic variables followed by seizure etiologies and comorbidities.

This study considered a p value of ≤0.05 as statistically significant for univariate and multivariate analyses. Kaplan–Meier survival analysis was performed to determine the 30-day cumulative recurrence rates, comparing inpatients by age and seizure etiology, including acute seizure and unprovoked seizure. Data were censored at the time of a recurrent seizure or death. The logrank test was used to examine the risk of death or of subsequent unprovoked seizures and to compare the distribution of survivors between the subgroups of acute symptomatic and unprovoked seizures.

A receiver-operating characteristic (ROC) curve was generated to define the accuracy of the predictors of recurrence of seizures.

Cox proportional-hazards regression was performed to examine the effect of acute seizure, compared with unprovoked seizure and comorbidities, on the risk of early seizure recurrence.

The statistical analyses were performed with the International Business Machines Corporation (IBM) Statistical Package for the Social Sciences software (SPSS®, Chicago, IL, USA) version 25.0 and R (R Programming Language and Microsoft Excel ® 2016).

2.3.3. Ethics

The Ethical Committee for Research of the Hospital São Rafael approved this study (no. 904.379) on November 24, 2014. A written informed consent was obtained from all participants.

3. Results

3.1. Demographic data and clinical characteristics

One hundred twelve inpatients aged ≥60 years who met our eligibility criteria were enrolled in the study. Of those patients, three patients were excluded: one was inappropriately included in the study but was later recognized to be younger than 60 years, one was later found to have syncope, and one patient was unavailable for follow-up. Overall, 109 patients (97.3%; mean age: 75.9 ± 9.6 years) were followed up. The median age was 76 years (interquartile range [IQR], 67–85 years). Men comprised 56% of this population. Most patients were admitted to the neurological ICU (62 patients; 56.9%). The median LOS was 11 days (IQR, 5–23; mean, 16 days). The demographic and hospitalization data are summarized in Table 1.

All enrolled elderly inpatients were ≥60 years, and the mean age at the first-ever seizure was of 74 ± 11.7 years.

One hundred and three patients in our cohort (94.5%) had their first seizure at the age of 60 years or later (i.e., late-onset seizure/epilepsy); 22 out of the 103 patients over the age of 60 had a previous diagnosis of epilepsy at the time of hospital admission; and 81/109 (74.3%) patients presented with new-onset seizures. Among the group of patients with new-onset seizures, 55/81 (68%) had unprovoked seizures, and 26/81 (32%) presented with acute symptomatic seizures. We should emphasize that only six elderly inpatients (5.5%) had their first seizure before 60 years (young-adult onset epilepsy), and they were enrolled in this study because they had a new seizure during the hospital admission at which point they were already over the age of 60. Furthermore, the diagnosis of epilepsy was well established, according to the ILAE criteria, in 83/109 (76.1%) patients among the whole cohort; this subgroup of 83 patients with diagnosis of epilepsy was comprised of 55 patients with new-onset unprovoked seizures (ILAE criteria) plus 6 patients with a history of epilepsy with onset before 60 years, plus 22 patients with late-onset epilepsy. Of the 30/109 (27.5%) patients who presented SE, 18/30 (60%) had SE at the manifestation of their first seizure. Focal

Table 1
Univariate analysis of the demographic data and characteristics of the seizures among 109 elderly inpatients.

All patients	Recurrence		
	Yes	No	
N = 109	30	79	p-Value
Demographic data			
Age, y	77 ± 10	76 ± 10	0.45
Age at onset, y	78 (67–86)	75 (64–82)	0.23
Female	13 (44.8)	35 (43.8)	0.93
SUS[a]	1 (3.3%)	11 (13.9%)	0.12
LOS[b]	18 (9–30)	8 (4–16)	0.005
ICU[c]	21 (70%)	41 (51.9%)	0.090
Seizure disorders			
Status epilepticus	10 (33.3%)	20 (25.3%)	0.40
Epilepsy	22 (73.3%)	61 (77.2%)	0.67
Acute symptomatic	9 (30%)	17 (21.5%)	0.35
Single unprovoked	0 (0%)	4 (5.1%)	0.21
Seizure type			
Focal	20 (66.7%)	43 (54.4%)	0.25
Generalized	9 (30%)	29 (36.7%)	0.51
Unknown onset	0 (0%)	8 (10.1%)	0.07
Seizure etiology			
A + R/A + P/A[d]	17 (56.7%)	27 (34.2%)	0.03
Unprv (R + P + RP + unknown)[e]	13 (43.3%)	52 (65.8%)	0.03

Data are presented as the total patient numbers, and percentages are shown inside the parentheses (%).

[a] SUS = Sistema Único de Saúde (Unified Brazilian Health Public System).

[b] LOS = length of stay.

[c] ICU = intensive care unit.

[d] A + R/A + P/A = acute seizures + remote/acute + progressive/acute.

[e] Unprv (R + P + RP + unknown) = unprovoked seizures (remote + progressive + remote/progressive + unknown).

seizures were recognized as the most frequent seizure type in 63/109 (57.8%) patients (Table 1).

Overall, 28/109 (25.7%) patients with previously diagnosed epilepsy were taking AEDs at admission; however, at discharge, 95/109 (87%) patients had a prescription for at least one AED, of which 20/26 (77%) were patients with initial diagnosis of acute symptomatic seizures. None of the patients were under AED use for any other conditions apart from epilepsy.

Ninety-seven (89%) patients underwent EEG; 96 patients had a routine EEG and only one had a prolonged video-EEG. Of them, 55 (56.7%) fulfilled the predefined criteria for having abnormal records. Of these, 49/55 (89%) presented generalized slowing patterns; 2/55 (3.6%) showed focal slowing patterns; and 4/55 (7.3%) had epileptiform discharges in their EEG. Sixty-nine patients (63.3%) underwent MRI, and the most common brain imaging abnormalities found were gliosis alone in 21/69 (30.4%), gliosis in combination with leukoaraiosis or acute ischemic lesions in 25/69 (36.2%), leukoaraiosis alone in 14/69 (20.3%), and acute ischemic lesions alone in 14/69 (20.3%). Computed tomography was performed during hospitalization in 91 patients (83.5%), and was normal in 25.3% of patients, whereas the most common alterations were leukoaraiosis (24.2%), gliosis (19.8%), and acute ischemic lesions (14.3%).

3.2. Underlying type of seizure, by category

Acute symptomatic seizures alone and in combination with other etiologies (remote or progressive causes) were present in 44 (40.4%) patients. Sixty-five (59.6%) patients in this cohort had unprovoked seizures, characterized by remote and/or progressive symptomatic and unknown causes (Table 1).

3.3. Etiology

In the group of patients with acute symptomatic seizures, ischemic stroke was the most common etiology in 11/26 patients (42.3%), followed by seizures because of the use of proconvulsant drugs in 8/26 patients (30.8%), i.e., carbapenem, quinolone, and olanzapine; the remaining patients had water-electrolyte imbalances (hypomagnesemia, hyponatremia, hyperglycemia, and also dehydration) that caused their seizures. Other etiologies of seizures in this group included hemorrhagic stroke, infection (sepsis and urinary infection), postanoxic and toxic metabolic encephalopathy, meningoencephalitis, alcohol, and benzodiazepine withdrawal.

Twenty-four patients (22%) with remote etiologies of their seizures had poststroke seizures; neurocryptococcosis and encephalitis complications, cerebral cavernous malformation, brain injury complications, and mesial temporal sclerosis occurred in 1 (0.9%) patient each. Progressive symptomatic etiologies were associated with neurodegenerative disorders (dementias and movement disorders), metastatic neoplasms of the brain (breast, pulmonary and parotid cancer, and melanoma), primary brain tumor (meningioma and oligodendroglioma), and multiple sclerosis.

Twenty-one (19.3%) patients presented more than one underlying condition associated with the seizure etiology. We found 11 patients with poststroke epilepsy who also presented acute symptomatic seizures that were associated with stroke recurrence, AED withdrawal, CNS infection (meningoencephalitis), other infections, hyponatremia, and the use of proconvulsant drugs (ertapenem and quinolone). One patient with epilepsy from a post-TBI presented acute symptomatic seizures secondary to dehydration and pulmonary infection. Three patients had a combination of poststroke epilepsy with dementia. Moreover, 6 (5.5%) patients who presented with progressive brain injury (brain neoplasia and dementia) also had acute symptomatic seizures associated with proconvulsant drug use (olanzapine and ertapenem), hyponatremia, hypomagnesemia, infections, and benzodiazepine withdrawal. Among the 30 (27.5%) patients who had SE, 10 (33.3%) cases were associated with acute stroke; in the remaining patients, SE occurred in the setting of dementia, sepsis, metabolic disorder, CNS infection, neoplasm, cerebral cavernous malformation, autoimmune encephalitis, and drug withdrawal. In 9 (8.3%) patients, nonconvulsive SE was identified. The etiology of SE was not elucidated in 4 (13.3%) patients. Overall, cerebrovascular disorders (represented by ischemic stroke and intracerebral hemorrhage) were the most frequent etiology in 57 (52.3%) patients in both unprovoked and acute seizures, and the underlying cause of seizures was unclear (unknown etiology) in 17 (15.6%) patients.

3.4. Comorbidities

We found a high frequency of patient multimorbidity (95.4%) among our population. Overall, the mean number of comorbidities was 6.3 ± 2.3 (95% confidence interval, 5.4–7.2).

Cerebrovascular disorder was the most frequent etiology, as well as the most common neurological disorder, followed by dementia. The other neurological disorders are displayed in Table 2.

Arterial hypertension and dyslipidemia were the most common clinical comorbidities followed by diabetes mellitus. Electrolyte imbalance was common since we found that 26 (23.9%) patients had severe hypomagnesemia and 9 (8.2%) patients had severe hyponatremia at their hospital admission. Other clinical disorders and their distributions are shown in Table 2.

Table 2
Univariate analysis of the neurological and clinical comorbidities among 109 elderly inpatients.

All patients	Recurrence		
	Yes	No	
N = 109	30	79	*p* value
Comorbidities			
Number of comorbidities	7 (5–7)	5 (4–7)	0.02
Neurological disorders			
Cerebrovascular disorders	17 (56.7%)	40 (50.6%)	0.57
Ischemic stroke	*15 (50%)*	*38 (48.1%)*	*0.86*
Hemorrhagic stroke	*3 (10%)*	*2 (2.5%)*	*0.10*
Dementias	7 (23.3%)	22 (27.8%)	0.63
Movement disorders	2 (6.7%)	6 (7.6%)	0.87
Encephalopathies	3 (10%)	9 (11.4%)	0.84
Brain tumors	2 (6.7%)	3 (3.8%)	0.52
CNS[a] infections	1 (3.3%)	2 (2.5%)	0.82
Delirium	2 (6.7%)	8 (10.1%)	0.58
Miscellaneous	6 (20%)	8 (10.1%)	0.17
Clinical disorders			
Systemic arterial hypertension	27 (90%)	63 (79.7%)	0.20
Diabetes mellitus	14 (46.7%)	24 (30.4%)	0.11
Dyslipidemia	15 (50%)	39 (49.4%)	0.95
Cardiovascular diseases			
Cardiac arrhythmias	*11 (36.7%)*	*15 (19%)*	0.053
Congestive heart failure	*4 (13.3%)*	*8 (10.1%)*	0.73
Myocardial infarction	*3 (10%)*	*8 (10.1%)*	0.63
Systemic infections	17 (56.7%)	29 (36.7%)	0.06
Pulmonary	*5 (16.7%)*	*12 (15.2%)*	0.85
Urinary	*11 (36.7%)*	*14 (17.7%)*	0.036
Sepsis	*9 (30%)*	*7 (8.9%)*	0.005
Neoplasms except brain tumors	5 (16.7%)	18 (22.8%)	0.49
Metabolic disorders	8 (26.7%)	18 (22.8%)	0.30
Liver disease	3 (10%)	6 (7.6%)	0.67
Renal disease	9 (30%)	15 (19%)	0.68
Acute pulmonary disease	2 (6.7%)	2 (2.5%)	0.22
Chronic pulmonary disease	2 (6.7%)	6 (7.6%)	0.87
Psychiatric disorders	13 (43.3%)	20 (25.3%)	0.07
Miscellaneous	11 (37%)	18 (23%)	0.14

Data are presented as total patient numbers and inside parenthesis percentages within title headings numbers (%).

[a] CNS = central nervous system.

3.5. Main outcome: early seizure recurrence

Within the 30 days of follow-up, subsequent unprovoked seizures occurred in 30 (27.5%) patients, of whom 12 (40%) suffered from more than one seizure recurrence. Patients with recurrent seizures had a higher number of comorbidities than that of patients who had no seizure recurrence (median: 6.5 comorbidities [IQR, 5–7] versus median: 5 comorbidities [IQR, 4–7]; $p = 0.02$). The distribution of the rates of recurrent seizures versus nonrecurrent seizures in the subgroups of acute and unprovoked seizures was as follows: 17/30 (56.7%), $p = 0.03$ and 13/30 (43.3%), $p = 0.03$, respectively. Overall, seizure recurrence was associated with several patient characteristics, including patients who had longer LOS ($p = 0.005$; Fig. 1). In addition, a high proportion of patients who had relapses (70%) were admitted to the neurological ICU, but this finding was not statistically significant (Table 1). Although patients with acute symptomatic and unprovoked seizures had a different median LOS (15 [IQR, 8.5–30] and 7 [IQR, 4–16], respectively; $p = 0.008$), the difference in recurrence at 30 days was not statistically significant between the groups (Fig. 2).

In this cohort, SE occurred in 33% of patients who had recurrent seizures, but statistical significance for the association with the risk of recurrence could not be reached.

None of the patients who had seizure recurrence died during the follow-up period.

Multivariate analysis, in which logistic regression was performed, identified that sepsis ($p = 0.011$), psychiatric disorders ($p = 0.032$), and cardiac arrhythmias ($p = 0.037$) were risk factors for early seizure recurrence (Table 3). The standard ROC and analysis of the area under the curve quantified the power of prediction for this model and demonstrated the accuracy of the model for the predictors of the early recurrence of seizures (area under the curve = 0.7; Fig. 3).

3.6. Mortality

Among this population, the mortality rate at the 30-day follow-up was 5.5% (6/109 patients). The mortality rate among patients with SE was 13.3% (4/30 patients).

4. Discussion

We assessed the etiology and potential risk factors for early seizure recurrence among elderly inpatients with seizures/epilepsy. The rate of seizure recurrence observed in this cohort during the 30-day follow-up was comparable to that in other prospective studies, which showed lower rates of seizure recurrence compared with those found in retrospective studies (23% to 71%, respectively, at 2 years) [25]. The different methodologies that were used in the prospective and retrospective studies may explain this reported variation [25]. In addition, although patients with acute seizures had a higher risk of recurrence than that in those with unprovoked seizures, this study was unable to find a statistically significant difference between the two groups. One large population-based study (Rochester Epidemiology Project, Minnesota) reported a lower risk for seizure recurrence for those with a first acute symptomatic seizure than for those with a first unprovoked seizure; however, the authors studied a population of outpatients of all age groups and examined the long-term risks of seizures instead of the short-term risks. Moreover, the studies' etiologies were limited to stroke, TBI, and CNS infections [4]. We found that patients who had sepsis, cardiac arrhythmias, and psychiatric disorders were at a higher risk of developing early seizure recurrence than that of patients without these conditions.

In this inpatient population, sepsis occurred in 14.7% of the patients who had SE, and we have identified sepsis as a risk factor for the recurrence of seizures in the short-term (up to 30 days). We believe that this result may be extrapolated to the long-term risk, corroborating the findings of a retrospective population-based cohort study that identified an association between sepsis and the long-term risk of seizures. In that study, the authors also confirmed the findings in elderly patients [26].

We observed a higher rate of comorbidities in this study than that in a similar population of older inpatients [27]. Our findings support the association of a higher number of comorbidities with early seizure recurrence; thus, we hypothesize that patient multimorbidity is a risk factor for early seizure recurrence. This observation is relevant since patient multimorbidity is frequent among elderly neurological inpatients. The association of particular patient multimorbidity patterns

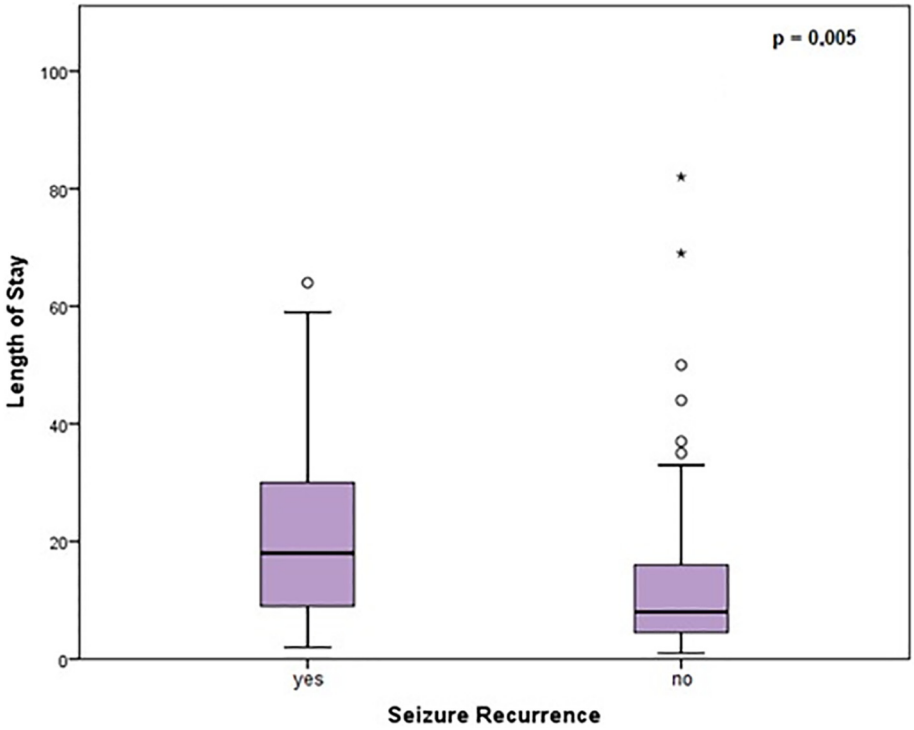

Fig. 1. Length of hospital stay (LOS) among the patients with and without seizure recurrence.

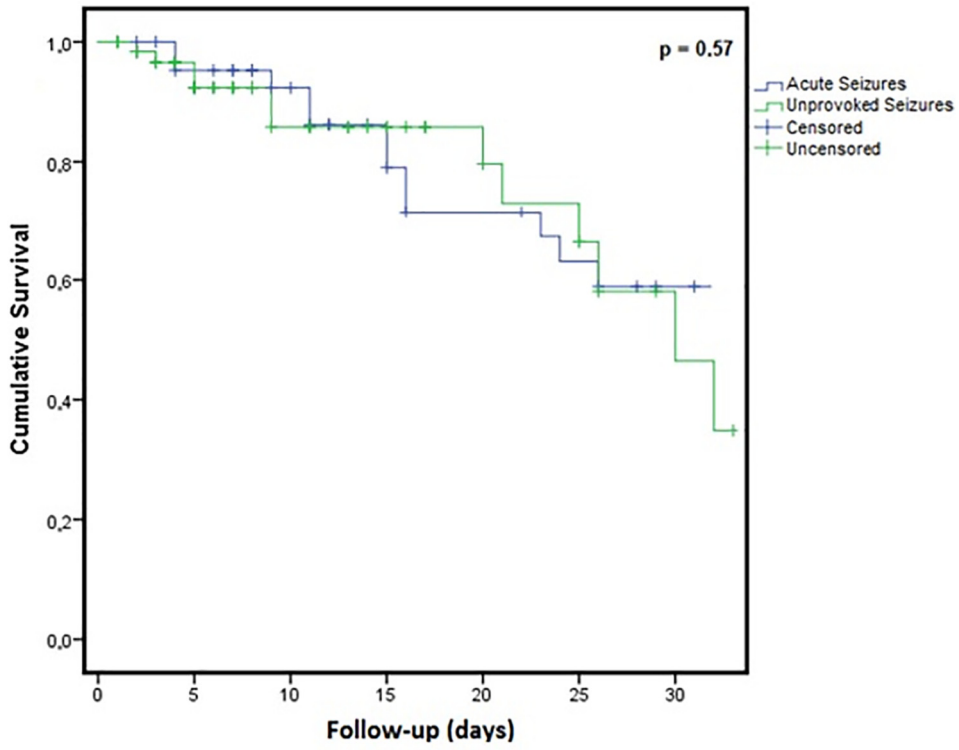

Fig. 2. Kaplan–Meier plot for the 30-day seizure recurrence among patients with acute and unprovoked seizures.

with early seizure recurrence should be studied in future research. Depression, anxiety, and mood disorders, grouped as "psychiatric disorders", occurred with high prevalence in our studied population and were reported as common comorbidities in the elderly population [5,28]. A large retrospective study of elderly patients found that new-onset epilepsy in the elderly population was associated with an increased risk of recurrent seizures, psychiatric disorders, and hospitalization [11]; these results are in agreement with the present study.

Metabolic disturbances and water-electrolyte imbalances cooccurred in 23.9% of patients, and three patients presented seizures because of severe hypomagnesemia. We hypothesized that the role of these metabolic derangements might occur through lowering the seizure threshold, as these disorders may trigger seizures in patients with enduring brain injury [29]. Metabolic disorders are common causes of acute symptomatic seizures in elderly inpatients and in elderly outpatients, and the more rapidly the disorder develops, the more likely it is to induce seizures [6,19]. We also found that patients who had early recurrent seizures had a longer LOS than that of patients who did not relapse, which might be explained by the severity of their illness, given that most of the patients were admitted to the neurological ICU.

Since we considered all neurological disorders and comorbidities that affected each elderly inpatient, we found that several of these disorders were associated with the etiology of acute symptomatic and unprovoked seizures. Actually, cerebrovascular disorders (ischemic stroke and intracerebral hemorrhage) were the most frequent neurological disorders, affecting half of the patients with both acute and unprovoked seizures. This finding is also consistent with the results of our previous retrospective study of elderly inpatients [7]. The etiology of the seizures was not recognized in 15.6% of the patients. Our data are in agreement with previous studies of elderly inpatients showing rates of 12.5% to 22.3% of seizures of unknown causes [7,30]. Reports from population-based cohort studies have suggested that unexplained late-onset seizures can be considered a biomarker of an underlying cerebrovascular disease [31,32]. We found a greater number of normal EEG records (42/43.3%) than was previously reported in a retrospective hospital-based study of older patients [5]. However, as we did not perform EEG on all patients of our cohort, and the majority of EEG performed was routine EEG, no conclusion concerning these results could be reached. The results of neuroimaging exams showed that leukoaraiosis, gliosis, and acute ischemic lesions were the most prevalent abnormalities. In a recent systematic review with meta-analysis, the authors concluded that the role of white matter changes in poststroke epilepsy remains to be elucidated [33].

It is noteworthy that some of the patients who relapsed were not using AEDs at the time of recurrence; these were patients who had suffered acute symptomatic seizures and that started AEDs only in the follow-up period. As a part of the follow-up, we obtained information on the prescription of AEDs for these inpatients; nevertheless, we decided not to evaluate the adequacy of treatment since it was not within the scope of this study. However, we hypothesized that the attending physician assumed a low risk of recurrence for those patients and decided to not prescribe an AED at the time of the index seizure. Longer-term treatment with AEDs (>1 week) might be considered for those patients at a higher risk of subsequent unprovoked seizures [34].

Unlike in younger patients, the effects of seizures in the elderly population have been poorly investigated. In addition, divergence between the various studies regarding the long-term management of seizures in the elderly population makes it even more challenging to make decisions regarding these patients [34,35]. Not only should the decision of whether to treat the first seizure in elderly people be a matter of

Table 3
Multivariate analysis of the risk factors for early seizure recurrence among 109 elderly inpatients (adjusted odds ratio and final *p* values according to the Wald statistic).

	Odd ratio (95% CI)	*p* value
Cardiac arrhythmias	2.96 (1.07–8.20)	0.037
Sepsis	4.52 (1.42–14.36)	0.011
Psychiatric disorders	2.88 (1.09–7.60)	0.032

CI = confidence interval.

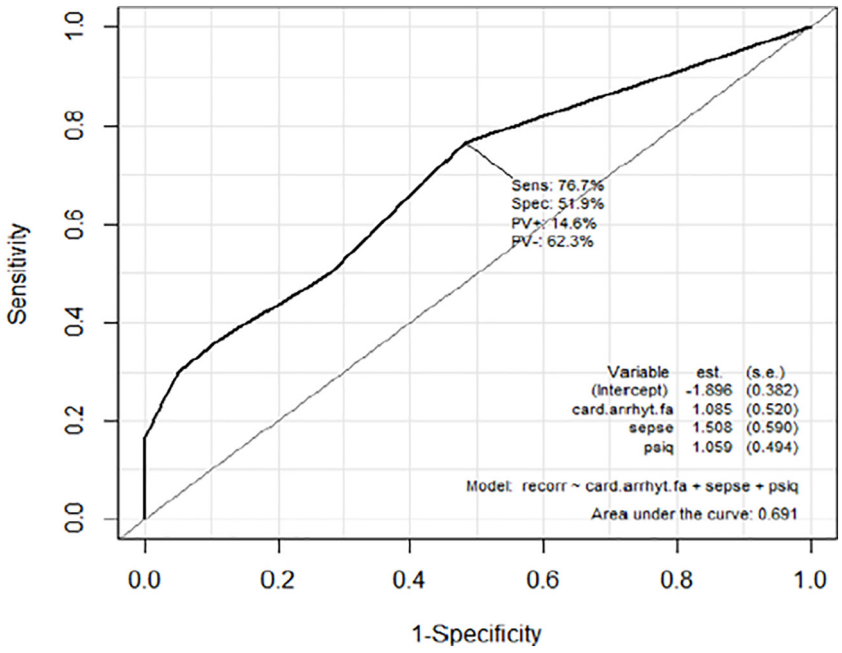

Fig. 3. Receiver-operating characteristic (ROC) curve from the multivariate model of seizure recurrence prediction in 109 patients.

concern but how long the patients should use AEDs should also be considered. The revised definition of epilepsy, which is an operational definition designed to be applied to particular circumstances, might support neurologists in evaluating each specific situation and choosing the best approach for each of situation [14].

Finally, elderly inpatients with epilepsy are at increased risk for early seizure recurrence and for patient multimorbidity, which can hamper seizure management, increase healthcare costs, and shorten the life span [5,36]. Identifying patients who are at the highest risk for early recurrence might help to avoid longer LOS and its consequences.

The general mortality rate in this cohort, including the mortality rate in the subgroup of patients who presented with SE, was similar to that in previous reports and was even lower than that in some others reports [37–39]. Because of the small sample size and small number of events (death), we did not study the risk factors that were associated with death.

The limitations of this study included a relatively small sample size of an elderly heterogenous population from a single center, which narrowed this study to a more exploratory approach. Our decision to study seizure recurrence up to 30 days could also be considered a limitation, since many seizures recur after this period [40]. However, the seizure recurrence is frequent during hospital stay and is associated with risk of death [13]; thus, the identification of risk factors for recurrence in this population of patients may advocate earlier treatment with appropriate AED. A further limitation was that not all the patients in our cohort underwent neuroimaging and EEG during hospitalization, and some patients were required to undergo these exams during outpatient follow-up in order to have a shorter LOS. The exclusion of outpatients and institutionalized elderly patients also limits the generalizability of these results to other populations of elderly patients.

The main strength of this study was its prospective design, which allowed us to truly identify acute seizures as well as epileptic and nonepileptic events and to classify the seizure type and etiology according to the ILAE recommendations. Moreover, our method of comprehensively scrutinizing the inpatient records permitted us to avoid inconsistencies from the International Classification of Diseases that were described in their charts.

Overall, our study suggests that the identified risk factors in this population, such as sepsis, cardiac arrhythmias, and psychiatric disorders, should be taken in consideration when deciding whether to perform early treatment of these patients with a proper AED to avoid seizure recurrence.

Finally, we observed that the role of underlying diseases in early seizure recurrence was not established, but we highlighted the significance of some comorbidities on this outcome. These findings need to be confirmed in further studies.

5. Conclusions

The rate of early recurrent seizures was high, and early seizure recurrence was associated with patient multimorbidity as well as with longer LOS. Moreover, sepsis, psychiatric disorders, and cardiac arrhythmias were identified as independent risk factors for early seizure recurrence.

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Availability of data and material

All data are available without restriction from the corresponding author upon reasonable request.

Authors' contributions

TA designed the study, collected the data, and drafted the manuscript; AB collected data and drafted the manuscript; GC and EP collected the data; and OJN critically reviewed the article for the intellectual content and drafted the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

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