Predictors of long length of hospital stay among elders admitted with seizures in a tertiary centre: a prospective study

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ABSTRACT
Population ageing is a global phenomenon, and life expectancy in Brazil is growing fast. Epilepsy is the third most important chronic neurological disorder, and its incidence is higher among elderly patients than in any other segment of the population. The prevalence of epilepsy is greater among inpatients than in the general population and it is related to long length of hospital stay (LOS), which is associated with hospital mortality and higher healthcare costs. Despite these facts, reports of elderly inpatients admitted with seizures and associated outcomes are scarce. Objective: To identify predictors of long LOS among elderly inpatients admitted with seizures. Methods: We prospectively enrolled elders admitted with epileptic seizures or who experienced seizures throughout hospitalization between November 2015 and August 2018. We analysed demographic data, neurological disorders, clinical comorbidities, and seizure features to identify risk factors. Results: The median LOS was 11 days, with an interquartile range (IQR) of 5–21 days. The frequency of long LOS (defined as a period of hospitalization ≥12 days) was 47%. Multivariate analysis showed there was an exponential increase in long LOS if a patient showed any of the following conditions: intensive care unit (ICU) admission (OR=4.562), urinary tract infection (OR=3.402), movement disorder (OR=5.656), early seizure recurrence (OR=2.090), and sepsis (OR=4.014). Conclusion: Long LOS was common among elderly patients admitted with seizures, and most predictors of long LOS found in this cohort might be avoidable; these findings should be confirmed with further research.

Keywords: Epilepsy; Seizure; Aged; Length of Stay; Risk Factors.

RESUMO
O envelhecimento populacional é um fenômeno global e o crescimento da expectativa de vida no Brasil tem sido rápido. A epilepsia é a terceira doença neurológica crônica mais importante e sua incidência em idosos é maior do que em qualquer outro segmento populacional. A prevalência de epilepsia é maior entre pacientes internados e está relacionada a longo tempo de internação (TDI), o qual está associado a custos elevados e mortalidade hospitalar. Apesar disso, são escassos os relatos de desfechos de pacientes idosos internados com crises epilépticas e resultados associados. Objetivo: Identificar fatores de risco de longo TDI em idosos admitidos com crises epilépticas. Métodos: Recrutamos prospectivamente pacientes idosos admitidos com crises epilépticas ou crise epiléptica para identificar fatores de risco. Resultados: A mediana do TDI foi 11 dias, com intervalo interquartil (IIQ) de 5–21 dias. A frequência de longo TDI (definido como TDI>12 dias) foi 47%. A análise multivariada mostrou que houve um aumento exponencial do TDI quando o paciente apresentou algumas dessas condições: admissão em unidade de terapia intensiva (UTI) (OR=4.562), infecção urinária (OR=3.402), recorrência precoce de crise epiléptica (OR=2.090) e sepse (OR=4.014). Conclusão: Longo TDI é um desfecho desfavorável importante e foi comum entre idosos admitidos com crises epilépticas. Muitos dos previsores de longo TDI encontrados na coorte podem ser evitados, o que deve ser confirmado com pesquisas futuras.

Palavras-chave: Epilepsia; Convulsões; Idoso; Tempo de Internação; Fatores de Risco.

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Population ageing is a worldwide phenomenon and it will become the most significant social transformation of the twenty-first century\(^1\). In Brazil, the population of individuals aged 260 years surpassed 30 million in 2017, and life expectancy in this country is growing faster than in developed nations\(^2\). Epilepsy is a common chronic neurological disorder, second only to cerebrovascular disease and dementia, and its incidence is higher in the elderly than in any other age group\(^3\). Long LOS is common among patients with epilepsy, particularly in the elderly who experience early seizure recurrence and who suffer from status epilepticus (SE), and it is associated with hospital mortality and excessive healthcare spending\(^4,5,6,7\). Although especially common in the elderly, long LOS can be prevented\(^8\). Studies of neurological disorders among elders admitted to a tertiary centre in Salvador found epilepsy in 16% of elderly inpatients, and the majority of them had a long LOS\(^9,10\). Notwithstanding these facts, reports of elderly inpatients admitted with epileptic seizures in Brazil are scarce\(^7,11,12,13,14,15,16\). The aim of the present study was to identify independent predictors of long LOS in a cohort of elderly inpatients who were admitted with epileptic seizures or experienced seizures during hospitalization.

**METHODS**

**Participants**

This prospective, observational, single-centre study included patients aged ≥ 60 years who were consecutively admitted to Hospital São Rafael, a general tertiary teaching hospital with 356 beds in Salvador, Brazil, between 1 November 2015 and 31 August 2019.

**Inclusion criteria**

We enrolled elderly inpatients with seizures that either led to their hospital admission or occurred in a period of care in the emergency department, or throughout hospitalization. Overall, patients were under the care of a neurology team.

**Exclusion criteria**

Elderly inpatients excluded from the study were: (1) those who had been admitted with a diagnosis of seizure that was not confirmed or who were later diagnosed with other paroxysmal neurological disorders such as syncope, delirium, or transient ischaemic attack; and (2) those who had seizures in the setting of acute traumatic brain injury (TBI) and were followed up by the neurosurgery team.

**Demographics**

We studied patient age and sex, age at the first seizure, marital status, admission to the intensive care unit, and discharge conditions, and their relationship with long LOS.

**Neurological disorders and clinical comorbidities**

We investigated the most common neurological disorders and comorbidities that are related to epileptic seizures among elderly inpatients. These disorders were classified according to the Tenth Revision of the International Statistical Classification of Diseases\(^17\). Dementia, delirium, and psychiatric disorders were diagnosed according to the DSM-5\(^18,19\).

**Neurological disorders**

We analysed the frequency of long LOS among neurological disorders which have been associated with epileptic seizures and might prolong hospitalization: epilepsy, cerebrovascular disease, ischaemic stroke, sequelae of stroke, brain haemorrhage, movement disorder, Parkinson’s disease, dementia, Alzheimer’s disease, vascular dementia, delirium, neurotoxic and metabolic encephalopathy, brain tumours, central nervous system (CNS) infection, brain injury, headache, CNS autoimmune disorders, and neuromuscular disorders.

**Clinical comorbidities**

Hypertension, diabetes mellitus, dyslipidaemia, cardiac arrhythmia, atrial fibrillation, myocardial infarction, congestive heart failure, kidney disease, gastrointestinal disorders, liver disease, endocrine and metabolic disorders, hypothyroidism, blood and haematopoietic disorders, acute respiratory disorder, chronic respiratory disorder, non-brain tumours, psychiatric disorder, lung infection, and urinary tract infection, as well as sepsis were investigated as predictors of long LOS in the study population.

**Epilepsy and seizure disorders**

We adopted the International League Against Epilepsy (ILAE) classification of epilepsy\(^20\). It presents three levels, starting with seizure type, assuming that the patient is having an epileptic seizure as defined by the ‘2017 ILAE Operational Classification of Seizure Types’\(^21\).

**Seizure characteristics and diagnosis**

The clinical characteristics of seizures were described according to the latest recommendations, based on the Operational Classification of Seizure Types by the ILAE\(^21\). An acute symptomatic seizure or provoked seizure was diagnosed as ‘a clinical seizure occurring at the time of a systemic insult or in close temporal association with a documented brain insult’\(^22\). 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 CNS infection, or during an active phase of multiple sclerosis or other autoimmune diseases’. Seizures occurring within 24 hours of severe metabolic derangements, drug or alcohol intoxication and...
withdrawal, or exposure to proconvulsant drugs were also considered acute symptomatic seizures\textsuperscript{22}.

To define an acute symptomatic (provoked) seizure resulting from metabolic imbalance, we used the following cut-off values, which are most likely to be associated with seizures: sodium: $<115 \text{ mg/dL}$ (or $>145 \text{ mmol/L}$), calcium: $<5.0 \text{ mg/dL}$, magnesium: $<0.8 \text{ mg/dL}$, serum glucose: $<36 \text{ mg/dL}$ (or $>450 \text{ mg/dL}$ when associated with ketoacidosis), blood urea: $>214 \text{ mg/dL}$, and creatinine: $>10 \text{ mg/dL}$\textsuperscript{22}.

Seizure aetiology was categorized as (1) symptomatic (known cause), including a) acute seizures (e.g. stroke, CNS infection, metabolic disorder, and autoimmune disease), b) remote seizures (e.g. post stroke, posttraumatic, and post-encephalitic), and c) progressive symptomatic (brain tumour and dementia); and as (2) unknown cause\textsuperscript{22,24}. An unprovoked seizure was defined as a seizure occurring in the absence of a temporary or reversible provocative factor\textsuperscript{25}. First unprovoked seizure might be considered epilepsy in special situations or in cases of relapse, according to the ILAE\textsuperscript{25}. Early recurrent seizure was defined as a second seizure event, unprovoked and separated from the first seizure by more than 24 hours up to the 30th day after the index seizure.

**Epilepsy**

After diagnosing the seizure type, the next step was the diagnosis of the type of epilepsy according to the recommendations of the ILAE Official Report\textsuperscript{25}. The diagnosis of SE included the revised concepts, definition, and classification from the report of the ILAE Task Force on Classification of Status Epilepticus\textsuperscript{24}.

Patient multimorbidity was defined as the coexistence of two or more chronic conditions\textsuperscript{26}. Investigation of seizure aetiology included laboratory tests (glucose, urea, magnesium, sodium, calcium, and creatinine), routine electroencephalogram (EEG), 24-hour video-EEG, and brain imaging data (computed tomography, magnetic resonance imaging [MRI], MRI angiography, and positron emission tomography). Some patients also underwent cerebrospinal fluid analysis. The following EEG results were considered abnormal: diffuse or focal slowing abnormalities and interictal or ictal paroxysms. This definition excluded records with nonspecific abnormalities.

Epilepsy, SE (convulsive and non-convulsive SE), acute symptomatic seizure (provoked), seizure types (focal onset, generalized onset, unknown onset), and epilepsy aetiology (structural, metabolic, immune, infectious, genetic, and unknown) were studied as independent predictors of long LOS.

**Long length of stay**

Long LOS was defined as a patient stay of 12 days or longer, since the median LOS in this population was 11 days.

**Statistics**

Quantitative variables with normal distribution were reported as means and standard deviations, whereas variables with non-normal distribution were expressed as medians and interquartile intervals. Normal variables were identified by graphic analysis and the Shapiro-Wilk test. Categorical variables were reported as frequencies and percentages. Student's t-test was used to perform bivariate comparisons between groups for numerical variables with normal distribution. Categorical variables were compared by Pearson's chi-square or Fisher's exact test when necessary. We performed a step-wise hierarchical logistic regression for multivariate analysis to increase the predictive power of the model. Independent variables were considered for multivariate analysis if recognized as having biological plausibility regarding the main study hypotheses and when bivariate tests showed a $p<0.25$, in accordance with the algorithm proposed by Hosmer and Lemeshow. Nagelkerke $R^2$, the Hosmer-Lemeshow test, Cox and Snell $R^2$ (ML), and the likelihood-ratio test were employed to measure the dimension of the model. A receiver operating characteristic (ROC) curve was obtained to assess the discriminant capacity of the model.

**Ethics**

This study was approved by the Research Ethics Committee of Hospital São Rafael on 24 November 2014 under the protocol number 904.379, version 5 (CAAE: 37689414.6.0000.0048).

**RESULTS**

**Demographics and neurological disorders**

This study enrolled 159 inpatients aged $\geq 60$ years who met our eligibility criteria; however, one patient was excluded from the analysis of long LOS as he was still in the hospital at the end of enrolment. The mean age of patients was 76.67±9.98 and the median was 77 years (IQR: 68–85 years). Mean age at first seizure was 75.4±11.6, with a median of 76 years (IQR: 67–85 years). Males were 51.6% of the study population, and 61% of patients were married. The median length of stay was 11 days, with an IQR of 5–21 days and a mean of 17.7±15.1 days. Long LOS occurred in 74 (47%) patients and hospital mortality in 14 (9%).

As expected, epilepsy was the most common neurological disorder among this elderly population who were admitted with epileptic seizures or who experienced seizures during hospitalization (127 [80%] patients). Epilepsy was followed in frequency by cerebrovascular disease and dementia. Table 1 shows associations of demographic data and neurological disorders with LOS.

**Clinical comorbidities**

Hypertension was the most frequent clinical comorbidity, followed by diabetes mellitus. Table 2 shows associations between clinical comorbidities and long LOS.
Seizure characteristics and epilepsy

Focal onset seizures were the most common clinical presentation in this study population, and we found a higher frequency of structural causes in patients diagnosed with epilepsy. Table 3 shows the univariate analysis of seizure disorders and epilepsy in relation to the occurrence of long LOS.

Univariate analysis

Female sex, age, mean age at first seizure, discharge home, admission to the ICU, number of comorbidities (patient multimorbidity), ischaemic stroke, sequelae of previous stroke, delirium, neurotoxic and metabolic disorders, movement disorder, Parkinson’s disease, CNS infection, urinary tract infection, endocrine and metabolic disorders, cardiac arrhythmia, atrial fibrillation, kidney disease, sepsis, lung infection, congestive heart failure, acute respiratory disorder, early seizure recurrence, SE (convulsive and non-convulsive), acute symptomatic seizure, unknown aetiology of seizure, and unknown aetiology of epilepsy were associated with length of stay according to the inclusion criteria for multivariate analysis (Tables 1, 2, and 3).

Multivariate analysis

Table 4 shows the results of the logistic regression on the aggregate variables hypothesized as predictors of long LOS, some of which had a statistically significant effect on the logit probability of long LOS.

Statistics for the evaluation of the model dimension effect proved to be adequate in the final adjustment as follows: pseudo-R2, Cox and Snell R2 (R2 CS=0.333), Nagelkerke R2 (R2N=0.421), Hosmer-Lemeshow test ($\chi^2$ HL(8)=10.616; $p=0.224$), and likelihood-ratio test ($G^2(7)=153.67; p<0.001$). The model yielded a sensitivity of 74.3% and a specificity of 81.9%, resulting in an accuracy of 76.6%, as shown in the ROC curve (Figure 1).

We found an exponential increase in the occurrence of long LOS when the patient showed any of these conditions: ICU admission, discharge home, number of comorbidities, ischaemic stroke, sequelae of previous stroke, delirium, neurotoxic and metabolic disorders, movement disorder, Parkinson’s disease, CNS infection, urinary tract infection, endocrine and metabolic disorders, cardiac arrhythmia, atrial fibrillation, kidney disease, sepsis, lung infection, congestive heart failure, acute respiratory disorder, early seizure recurrence, SE (convulsive and non-convulsive), acute symptomatic seizure, unknown aetiology of seizure, and unknown aetiology of epilepsy were associated with length of stay according to the inclusion criteria for multivariate analysis (Tables 1, 2, and 3).
Table 3. Univariate analysis of seizure disorders in relation to long length of stay in 158 elderly patients admitted to a tertiary medical centre.

| Seizure disorders                  | Long LOS |     |     |     |
|-----------------------------------|----------|-----|-----|-----|
|                                   | No       | Yes |     |     |
|                                   | n (%)    | n (%)| p-value|     |
| Seizure type                      |          |     |     |     |
| Focal onset                       | 54 (64.3)| 46 (62.2)| 0.782|     |
| Generalized onset                 | 24 (28.6)| 26 (35.1)| 0.376|     |
| Unknown type                      | 7 (8.3)  | 3 (4.1) | 0.338|     |
| Seizure disorders                 |          |     |     |     |
| Seizure early recurrence          | 15 (18.1)| 29 (39.2)| 0.003|     |
| SE                                | 19 (22.6)| 30 (40.5)| 0.015|     |
| Convulsive SE                     | 16 (19)  | 21 (28.4)| 0.167|     |
| Non-convulsive SE                 | 6 (7.1)  | 10 (13.5)| 0.185|     |
| Seizure aetiology                 |          |     |     |     |
| Symptomatic remote                | 22 (26.2)| 14 (18.9)| 0.277|     |
| Symptomatic acute seizure         | 12 (14.3)| 17 (23) | 0.159|     |
| Symptomatic progressive           | 13 (15.5)| 16 (21.6)| 0.319|     |
| Unknown aetiology                 | 20 (23.8)| 4 (5.4)  | 0.001|     |
| Aetiology of epilepsy             |          |     |     |     |
| Structural                        | 52 (61.9)| 49 (66.2)| 0.475|     |
| Unknown                           | 12 (14.3)| 3 (4.1)  | 0.090|     |
| Infectious                        | 1 (1.2)  | 4 (5.4)  | 0.291|     |
| Immune                            | 1 (1.2)  | 1 (1.4)  | 0.958|     |
| Metabolic                         | 0 (0)    | 0 (0)    | 0.786|     |
| Genetic                           | 0 (0)    | 0 (0)    | 0.786|     |

Data are expressed as number of patients, with percentages (%) in brackets; LOS: length of stay; SE: status epilepticus.

admission (356.2%), urinary tract infection (240.2%), movement disorder (465.6%), early seizure recurrence (109.0%), and sepsis (301.4%). However, there was a low chance of long LOS for patients with unknown aetiology of seizure (74.8%), female sex (45.8%), and hypothyroidism (65.0%).

The residual analysis plot for detecting influential cases showed only 7 cases (4.4%) in the dataset were potential outliers, since they had high values of standard residuals and were therefore incorrectly classified by the logistic model (Figure 2). However, they were kept in the final model, as

Table 4. Aggregate variables with a statistically significant effect (p<0.25) on the logit probability of long length of stay among 158 elderly patients admitted with seizures or who experienced seizures throughout hospitalization in a tertiary medical centre.

| Variable                          | Estimated coefficients | Wald chi-square | p-value | OR   |
|-----------------------------------|------------------------|-----------------|---------|------|
| Female sex                        | -0.610                 | 2.211           | 0.137   | 0.543|
| ICU admission                     | 1.518                  | 11.777          | 0.001   | 4.562|
| Movement disorder                 | 1.733                  | 4.502           | 0.034   | 5.656|
| Urinary tract infection           | 1.224                  | 6.969           | 0.008   | 3.402|
| Hypothyroidism                    | 1.050                  | 3.462           | 0.063   | 0.350|
| Sepsis                            | 1.390                  | 3.813           | 0.051   | 4.014|
| Early seizure recurrence          | 0.737                  | 2.488           | 0.115   | 2.090|
| Seizure of unknown aetiology      | 1.380                  | 3.429           | 0.064   | 0.252|

ROC curve: receiver operating characteristic curve; AUC: area under the curve; Sens: sensitivity; Spec: specificity; PV+: positive predictive value; PV-: negative predictive value.

Figure 1. ROC curve from the multivariate model of predictors of long length of hospital stay among 158 elders admitted with seizures in a tertiary centre.
DISCUSSION

Long LOS is common among elderly inpatients and it is one of the most important undesirable outcomes in that it is associated with hospital mortality and higher healthcare costs. In this study, we employed a comprehensive method of patient enrolment as we selected not only patients who were admitted with seizures but also patients who experienced seizures during hospitalization; in addition, it was a prospective collection. We studied a population of 159 elderly inpatients with a high mean age (25% of patients were 85 years old or older). These patients had a median of five comorbidities, with a range of 4 to 7 chronic diseases; patient multimorbidity is indeed quite common among elderly inpatients. We found a great number of variables associated with long LOS, not only in demographic data but also among the most frequent neurological disorders, comorbidities, and seizure disorders (Tables 1, 2, and 3). However, in the final model, we identified only five important variables (ICU admission, movement disorder, urinary tract infection, sepsis, and early seizure recurrence) as strong independent risk factors for long LOS and three variables associated with a low chance of long LOS (female sex, hypothyroidism, and seizure of unknown aetiology). ICU admission was very common in our cohort, occurring in 97 (61%) patients. Seizures in ICU patients may result from neurological disorders, clinical disorders, side effects of medication, and drug abstinence; patients can present with several clinical features, such as subtle twitching, convulsive seizures, or, more frequently, convulsive SE or non-convulsive SE, which are associated with high mortality. Additionally, cases of stroke and seizures usually demand a longer LOS when compared to other ICU patients. The present study population included some cases of convulsive and non-convulsive SE, which is usually an underdiagnosed condition and it is associated with longer length of stay. In this study, both clinical types of SE were related to long LOS according to study criteria; however, after multivariate analysis, SE was not a statistically significant predictor of long LOS. Both urinary tract infection and sepsis were identified as strong predictors of long LOS and they were quite common complications among our study patients, with urinary tract infections occurring in 45 (28%) and sepsis in 26 (16%) patients. In a retrospective study of 366 ICU records, the authors found urinary tract infection was the second most common infection (with pneumonia being the most common) and patients with infections had a longer LOS (with a median of 16 days) than other patients. Sepsis is a severe complication of infection, especially in elderly inpatients, and it is usually associated with high mortality and long LOS. Both urinary tract infection and sepsis are complications that can be prevented, e.g. by avoiding inappropriate use of urinary catheters and improving protocols for early recognition and management of infection. Movement disorder was another variable identified in this study as a predictor of long LOS, even though we had only 14 (9%) patients with this condition. Parkinson's disease, chorea, progressive supranuclear palsy, Huntington's disease, corticobasal degeneration, and other movement disorders have been reported to be related to seizures; in addition, focal dyskinesia and other involuntary movements are frequently associated with seizures in case reports of anti-NMDA receptor encephalitis. Parkinson's disease is the most common movement disorder, a complex disorder with motor and non-motor symptoms, which also negatively affects LOS; to avoid long LOS, it should hence be managed by specialists. Early seizure recurrence was an important outcome found in 44 (28%) patients in our population. The present study showed early recurrence of seizure was a strong predictor of long LOS. This condition was the subject of a recent study investigating potential predictors, which identified psychiatric disorder, sepsis, and cardiac arrhythmia as predictors of early seizure recurrence and also found an association of early recurrence of seizure with long LOS. It might thus be reasonable to regard patients with any of these conditions as patients with epilepsy and to treat them just after the first seizure to avoid recurrence and possibly long LOS.

One of the limitations of this study was that we included a relatively small sample of a heterogeneous population of elderly patients from a single centre, narrowing its scope to a more exploratory approach. However, long LOS was a common occurrence among elderly patients who were admitted with seizures or who experienced seizures throughout hospitalization. The identification of predictors of long LOS among
inpatients with seizures is a matter of interest in that we can avoid its consequences, such as increased morbidity and mortality, and higher healthcare costs. Although hospital mortality was not a subject discussed in this study, it is worth mentioning that the case fatality rate in the study population was 9%, which was quite high.

In conclusion, long LOS is a major undesirable outcome and it was common among the elderly patients who were admitted with seizures or experienced seizures during hospitalization in our study. We found ICU admission, urinary tract infection, movement disorder, early seizure recurrence, and sepsis to be independent predictors of long LOS, some of which are potentially preventable risk factors; these findings should be confirmed with further studies.

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