Received: 31 October 2023 | Revised: 19 December 2023 | Accepted: 3 January 2024

DOI: 10.1002/epi4.12900

SHORT RESEARCH ARTICLE

Causes and prognosis of adults experiencing a first seizure in adulthood: A pilot cohort study conducted in five countries in Latin America

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Funding information
University of Cuenca, Ecuador, Grant/Award Number: 028-2021

Abstract

There are limited data on first seizure (FS) among adults in low and middle-income countries. We describe findings from a prospective cohort study involving 180 adults presenting with seizures in emergency departments in five Latin American countries. Overall, 102 participants (56.7%) had acute symptomatic seizures (ASyS) while 78 (43.3%) had unprovoked seizures (UPS). Among patients with ASyS, 55 (53.9%) had structural causes, with stroke ($n = 24$, 23.5%), tumor ($n = 10$, 9.8%), and trauma ($n = 3$, 3%) being the most frequent. Nineteen patients (18.6%) had infectious causes, including four (4%) with meningoencephalitis, three (3%) neurocysticercosis, and two (2%) bacterial meningoencephalitis. Twenty patients (19.6%) had metabolic/toxic evidence, including four (4%) with uremic encephalopathy, two (2%) hyponatremia, and three (3%) acute alcohol intoxication. Immune dysfunction was present in seven (7%) patients and neurodegenerative in two (2%). Among participants with UPS, 45 (57.7%) had unknown etiology, 24 (30.7%) had evidence of structural disorders (remote symptomatic), four (5%) were related to infectious etiology (>7 days before the seizure), and five (6.4%) had genetic causes. During the 3- and 6-month follow-up, 29.8% and 14% of patients with UPS, respectively, experienced seizure recurrence, while 23.9% and 24.5% of patients with ASyS had seizure recurrence. Longer follow-up is necessary to assess seizure recurrence for patients with ASyS after the acute cause is resolved and to determine the 10-year risk of recurrence, which is part of the definition of epilepsy.

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Plain Language Summary: We monitored 180 adults who presented with their first seizure in emergency departments across five Latin American countries. Among these patients, 57% had acute symptomatic seizures, with structural causes such as stroke (23%), infection (17%), or tumor (10%) being more prevalent. Among the 43% with unprovoked seizures, 58% showed no identifiable acute cause, while 6.4% were due to genetics. Within 3 months after their initial seizure, 26.6% of individuals experienced a second seizure, with 11.9% continuing to have seizures in Months 3–6. Between Months 3 and 6, an additional 20% of patients encountered a second seizure. Research is needed to better understand the cause and prognosis of these patients to improve outcomes.

KEYWORDS

acute symptomatic seizures, epilepsy, etiology, first seizure, neurocysticercosis

1 | INTRODUCTION

Seizures affect 8%–10% of the world population.[1] Epileptic seizures (ES) are transient occurrences of signs and/or symptoms due to abnormal brain activity,[2] categorized as acute symptomatic (ASyS) or unprovoked (UPS) seizures. ASyS occur due to an identifiable cause and cease once the underlying issue is resolved. UPS occurs without any apparent acute cause and may be genetic.[3,4] Non-epileptic seizures mimic seizures but lack abnormal brain electrical activity[4,5] and include syncope (blood pressure related) and functional seizures (psychological distress).[5] Differentiating these from ES often requires electroencephalogram (EEG) and neuroimaging, although clinical history can reliably aid in diagnosis.[6]

Around 3% of emergency department (ED) visits are due to seizures.[7] Investigating the cause and recurrence risk is crucial when adults experience a first seizure (FS).[6] Immediate management is needed for ASyS due to life-threatening underlying conditions and distinguishing ASyS from UPS influences decisions regarding antiseizure medication.[8,9] The risk of recurrence for UPS is highest in the first 3–6 months.[10] In untreated individuals, 40%–50% with UPS experience recurrence within 2 years, but treatment can halve this risk.[9] Data on ASyS recurrence are lacking,[11] complicating prognosis and treatment.

Epilepsy is defined as (a) having two UPS more than 24 h apart or (b) one UPS with at least a 60% risk of further seizures over 10 years.[2] Not all seizure patients develop epilepsy, but recurrence can have serious psychological and social implications.[12] ASyS may lead to UPS and epilepsy, while some with an initial UPS may not experience recurrence. Syncope and functional seizures are not considered epilepsy. Understanding seizure types, causes, and epilepsy development is challenging, especially in low- and middle-income countries (LMICs) due to different risk factors.[13] Causes of seizures and epilepsy likely differ between high-income versus LMICs due to varying prevalence of risk factors,[13] making it challenging to estimate the 10-year risk of seizure recurrence, which is part of the definition of epilepsy.[14]

Key points

- Stroke, CNS tumors, infections, and metabolic disorders, are the common causes in adult patients with a first acute symptomatic seizures.
- The risk of recurrence for unprovoked seizures is highest in the first 3-6 months pf follow-up
- Neurocysticercosis, often considered a significant cause of epilepsy globally, was found in only 2.9% of the cohort in this study.
- Immediate management is crucial for acute symptomatic seizures due to potentially life-threatening underlying conditions.

To address these gaps, a prospective cohort study involving 180 adults with FS in LMICs is underway in Argentina, Brazil, Chile, Ecuador, and Mexico. The study aims to describe seizures distribution, causes and recurrence among these populations. Six-month follow-up data are available, providing insights into participants, their seizures baseline, and their 3- and 6-month follow-up.

2 | METHODS

2.1 | Recruitment and enrollment

Between April 1, 2022, and January 31, 2023, we recruited adults from nine participating EDs who experienced their

first seizures (See algorithm—Annex S1). Eligible patients were ≥16 years old and presented at a participating ED within 48 h of their first epileptic seizure, as confirmed by a neurologist.

2.2 | Data collection

Following informed consent, a baseline questionnaire was adminestered to collect demographic and clinical data. Follow-up assessments occurred every 3 months, including information on seizure recurrence, results from laboratory tests, electrocardiogram, electroencephalogram (EEG), and computed tomography (CT) scans (with contrast media). EEG recordings were classified as normal or abnormal, which were subcategorized as epileptiform (focal or generalized) or non-epileptiform (such as focal or generalized slowing). Similarly, the findings of CT scans were defined as normal and abnormal (such as subarachnoid hemorrhage, intraparenchymal hemorrhage, cerebral infarction, encephalomalacia, space-occupying lesion, hydrocephalus, venous sinus thrombosis, and "other", e.g., small white matter hyperintensities, lacunes, unspecific hypo intensities, diffuse edema, and cortical atrophy not related to age). The study received approval from the research ethics boards of participating hospitals, and the results adhere to the Standards of Reporting of Neurological Disorders (STROND) checklist.[15]

2.3 | Measures

Demographic data included age, gender, occupation, and urban/rural residence, and comorbid conditions.[16] Depression and anxiety were diagnosed by the participant neurologist, according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.[17] Country income status was determined based on World Bank GDP classifications.[18]

Epileptic seizures[2] were classified as (a) ASyS, defined as clinical seizures occurring during or in close temporal relationship with, a documented central nervous system (CNS) or systemic insult,[4] or (b) UPS, defined as clinical seizure occurring in the absence of a CNS or systematic insult or infection, or beyond the estimated time for the occurrence to be attributed to a previous insult.[3] Seizure types were classified according to the International League Against Epilepsy (ILAE) definitions.[2] EEG and CT scan findings were reclassified, and seizure etiology was assessed according to ILAE classification.[19] An additional category, neurodegenerative, was included based on the ILAE curriculum.[13] We report recurrence of seizures at three and 6-month follow-ups.

2.4 | Statistical analysis

Participant characteristics, seizure features, etiology, and recurrence, were described and stratified by seizure type (ASyS vs. UPS). We also described the causes of the seizure for ASyS and UPS when an identifiable cause (i.e., genetic) or a previous CNS insult was described outside of the period defining the seizure as ASyS. Statistical significance of associations for categorical variables were assessed using Fisher's exact test and for numeric variables with the Wilcoxon rank sum test. R (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria) was used, and significance was set at $\alpha = 0.05$.

3 | RESULTS

3.1 | Description of the sample

Out of 203 patients with seizure-like symptoms, 23 were excluded due to non-epileptic seizures (12 syncope, 4 functional, 2 migraine, and 5 transient ischemic attack). Among the 180 patients with epileptic seizures, 47.8% were female, most of whom were engaged in domestic labor (26.7%), or were students (23.9%); 88.9% resided in urban areas with 47.2% residing in low-middle-income countries (<$10 000 GDP per capita).

ASyS was present in 56.7% of participants, while 43.3% had UPS. Patients with ASyS were older (mean age of 49.5 years vs. 32.8 years, $p < 0.001$) and more likely to work in domestic labor (34.3% compared with 16.7%, $p = 0.016$). Comorbidities were more common in ASyS patients (46.1% $p < 0.015$), including alcoholism and cardiovascular disease (both 17% vs. 4.5%, $p < 0.045$) (Table 1).

3.2 | Description of the seizures

Most seizures had a generalized onset/unknown onset (53.9%) or were focal to bilateral tonic–clonic (28.3%), with fewer being focal with impaired awareness and focal aware (13.3%, 5.0% respectively), with a similar distribution in ASyS and UPS. EEG abnormalities were observed in 61.6% of patients, with epileptiform activity in 59.7%. CT scans showed abnormalities in 46.7% of participants, with higher rate in ASyS vs. UPS (58.6% vs. 30.8%; $p < 0.001$). Abnormalities included space-occupying

TABLE 1 Clinical and demographic characteristics of 180 patients with first epileptic seizure.

Characteristics	Total	ASyS[a]	UPS[b]	*p*-Value[c]
Total, *n* (%)	180	102 (56.7)	78 (43.3)	0.086
Age—Median (IQR)	40 (38.5)	49.5 (37.8)	31.5 (32.8)	**<.001**
Sex, *n* (%)				
Male	94 (52.2)	52 (51.0)	42 (53.8)	0.764
Female	86 (47.8)	50 (49.0)	36 (46.2)	
Occupation, *n* (%)				
Domestic labor	48 (26.7)	35 (34.3)	13 (16.7)	**0.016**
Agriculture worker	6 (3.3)	2 (2.0)	4 (5.1)	
Student	43 (23.9)	17 (16.7)	26 (9.4)	
Construction	50 (27.8)	25 (24.5)	25 (33.3)	
Professional	15 (8.3)	10 (9.8)	5 (32.1)	
Commercial activities	2 (1.1)	2 (2.0)	0 (6.4)	
Other[d]	16 (8.9)	11 (10.8)	5 (0.0)	
Residence, *n* (%)				
Rural	20 (11.1)	13 (12.7)	7 (9.0)	0.481
Urban	160 (88.9)	89 (87.3)	71 (91.0)	
Country GDP[d] per capita				
(<$10,000)	85 (47.2)	41 (40.2)	44 (56.4)	**0.036**
(≥$10,000)	95 (52.8)	61 (59.8)	34 (43.6)	
Comorbidity, *n* (%)	69 (38.3)	47 (46.1)	22 (28.2)	**0.015**
Comorbidity type, *n* (%)				
Depression	6 (8.7)	4 (8.5)	2 (9.1)	0.615
Anxiety	4 (5.8)	2 (4.3)	2 (9.1)	0.786
Migraine	4 (5.8)	1 (2.1)	3 (13.6)	0.196
Alcoholism	9 (13.0)	8 (17.0)	1 (4.5)	**0.045**
Stroke	6 (8.7)	2 (4.3)	4 (18.2)	0.241
Cardiovascular diseases	9 (13.0)	8 (17.0)	1 (4.5)	**0.045**
Diabetes	13 (18.8)	10 (21.3)	3 (13.6)	0.126
Other[d]	32 (17.7)	20 (19.6)	12 (15.4)	0.463
Type of seizure, *n* (%)				
Focal aware	9 (5.0)	6 (5.9)	3 (3.8)	0.734
Focal impaired awareness	24 (13.3)	14 (13.7)	10 (12.8)	1
Focal to bilateral tonic-clonic	50 (28.3)	26 (26.5)	24 (30.8)	0.526
Generalized onset	81 (45.0)	46 (45.1)	35 (44.9)	1
Unknown onset	16 (8.9)	10 (10.8)	6 (6.4)	0.429
E.E.G. *n* (%)[e]	125 (69.4)	64 (62.7)	61 (78.2)	
Abnormal[f]	77 (61.6)	42 (65.6)	35 (57.4)	0.343
Epileptiform[f]	46 (59.7)	19 (45.2)	27 (77.1)	**0.005**
Non-epileptiform[f]	31 (40.3)	23 (54.8)	8 (22.9)	
Abnormal CT scans, *n* (%)	84 (46.7)	60 (58.8)	24 (30.7)	**<.001**
Type of abnormality *n* (%)				
Subarachnoid hemorrhage[g]	5 (6.0)	5 (8.3)	0 (0.0)	
Intraparenchymal hemorrhage[g]	9 (10.7)	7 (11.7)	2 (8.3)	
Cerebral infarction[g]	15 (17.9)	9 (15.0)	6 (25.0)	

TABLE 1 (Continued)

Characteristics	Total	ASyS[a]	UPS[b]	*p*-Value[c]
Encephalomalacia	14 (16.7)	4 (6.7)	10 (41.7)	
Space occupying lesion[g]	20 (23.8)	18 (30.0)	2 (8.3)	
Venous sinus thrombosis[g]	3 (3.6)	3 (5.0)	0 (0.0)	
Other[d,g]	18 (21.4)	14 (23.3)	4 (16.7)	

Note: Bold values indicate significant difference at $p < 0.05$.

[a]Acute symptomatic seizure.

[b]Unprovoked seizure Gross Domestic Product.

[c]*p* value for Fisher's exact test.

[d]"Other" are detailed in the text.

[e]Electroencephalogram in 125 patients.

[f]Percentages are based on abnormal EEGs.

[g]Percentages are based on abnormal CT scans.

lesions, intraparenchymal hemorrhage, and cerebral infarction. (Table 1).

3.3 | Etiology and recurrence of first epileptic seizure

The most frequent potential etiologic causes of seizures for all patients were as follows: structural (43.9%), infectious (12.8%), metabolic/toxic (11.1%), immune (3.3%), genetic (2.7%), and neurodegenerative (1.1). Among participants with UPS, 57.7% had unknown etiology, 30.7% showed evidence of structural disorders, of which 17.9% were due to stroke that had occurred >7 days before the seizure, 6.4% tumor, 2.5% trauma, and 1.2% were associated with hippocampal sclerosis (Table 2). Two patients (2.5%) with UPS had evidence of a potential previous infectious cause, specifically calcified neurocysticercosis, and 6.4% had genetic causes. In patients with ASyS, 53.9% had structural causes, with stroke (23.5%), malformations 17.6%. tumor (9.8%), and trauma (2.9%) being the most frequent. Overall, 18.6% had evidence of infectious causes, including viral meningoencephalitis (3.9%), neurocysticercosis (2.9%), bacterial meningoencephalitis (1.9%), and one patient (1%) had tuberculous meningitis. Nineteen percent had metabolic/toxic evidence, including uremic encephalopathy (3.9%), hyponatremia (1.9%), and acute alcohol intoxication (2.9%). Immune dysfunction was present in 5.9% and neurodegenerative causes were found in 1.9% of participants with ASyS. (Table 2 and Figure 1).

Among ASyS patients, those with neurodegenerative, metabolic, and structural causes were older (median age 74.5, 56.6, and 52.5 years, respectively) compared to those with infections and immune causes (39.3 and 32.4 years, respectively, $p = 0.002$). Those with immune disorders were more likely to reside in rural areas (66.7%) compared to those with metabolic disorders (15.0%), structural disorders (7.2%), infections (10.5%), and neurodegenerative disorders (0.0%, $p = 0.008$) (Data not shown).

Seizure recurrence was similar between ASyS and UPS patients of both three and 6-month follow-ups. One hundred twenty-four (69%) patients completed the 3-month follow-up assessment, and among them, 33 patients (26%) had experienced seizure recurrence by follow-up with no difference between those with ASyS and UPS ($p = 0.542$). Eighty-two patients (45.5%) completed 6-months follow-up. Among these, 59 (88.1) had not experienced any more seizures since baseline. Of the 23 (11.9%) who did experience seizure recurrence at any point over the 6-month period, eight (11.9%) only experienced seizures in the first 3 months of follow-up, three (20%) experienced recurrent seizures only between 3- and 6-month follow-up, and 12 (80%) experiences multiple seizures both at 1–3 month and at 3–6 month follow-up. However, again there was no significant difference between those experiencing ASyS and UPS ($p = 1.0$) (Table 2).

4 | DISCUSSION

In this cohort of adults presenting at emergency departments with a first seizure in Latin America, a slight majority presented with ASyS (56.7%), among whom stroke (23.5%), CNS tumors (9.8%), infections (18.6%), and metabolic disorders (17.1%) were the most common causes. This is in line with two studies in India,[20,21] where stroke (23% and 32.6%), CNS infection (21% and 26.8%), and metabolic disorders (12% and 13.0%) were the most common causes of adult-onset seizures. A study conducted in Nigeria[22] found that the most common ASyS causes were infections (36.2%), stroke (29.8%), and metabolic alterations (12.8%). This differs from high-income countries where traumatic brain injury (16%), stroke (16%), alcohol withdrawal (14%), brain tumors (8%), and metabolic

TABLE 2 Etiology and seizure recurrence in 180 patients with first epileptic seizure.

Etiology	Total	ASyS[a]	UPS[b]	*p*-Value[c]
Total, *n* (%)	180	102 (56.7)	78 (43.3)	
Structural	**79 (43.9)**	55 (53.9)	24 (30.7)[d]	**<0.001**
Stroke	38 (21.1)	24 (23.5)	14 (17.9)	
Tumor	15 (8.3)	10 (9.8)	5 (6.4)	
Trauma	5 (2.7)	3 (2.9)	2 (2.5)	
Malformation	20 (11.1)	18 (17.6)	2 (2.5)	
Hippocampal sclerosis	1 (0.5)	0 (0.0)	1 (1.2)	
Infectious	23 (12.8)	19 (18.6)	4 (5.1)	**0.007**
Viral meningoencephalitis	6 (3.3)	4 (3.9)	2 (2.5)	
Bacterial meningoencephalitis	2 (1.1)	2 (1.9)	0 (0.0)	
Tuberculous meningitis	1 (0.5)	1 (0.9)	0 (0.0)	
Neurocysticercosis	5 (2.7)	3 (2.9)	2 (2.5)[e]	
Other[f]	9 (5.0)	9 (8.8)	0 (0.0)	
Genetic	5 (2.7)	0 (0.0)	5 (6.4)	**0.014**
Metabolic/toxic	20 (11.1)	20 (19.6)	0 (0.0)	**<0.001**
Hyperglycemia	2 (1.1)	3 (2.9)	–	
Hyponatremia	2 (1.1)	2 (1.9)	–	
Acute alcohol intoxication	3 (1.6)	3 (2.9)	–	
Uremic Encephalopathy	4 (2.2)	4 (3.9)	–	
Other[f]	8 (4.4)	8 (7.3)	–	
Immune	6 (3.3)	6 (5.9)	0 (0.0)	**0.037**
Neurodegenerative	2 (1.1)	2 (1.9)	0 (0.0)	0.599
Unknown	45 (25.0)	0 (0.0)	45 (57.7)	**<0.001**
Seizure recurrence at follow-up				
Three-month follow-up completed, *n* (%)	124 (68.9)	67 (65.7)	57 (73.1)	
No recurrence, *n* (%)	91 (73.4)	51 (76.1)	40 (70.2)	0.542
Seizure recurrence, *n* (%)	33 (26.6)	16 (23.9)	17 (29.8)	
Six-month follow-up completed	82 (45.5)	46 (45.1)	36 (46.2)	
Never had seizures (baseline to 6 months)	59 (88.1)	31 (88.6)	28 (87.5)	1.000
No longer recurrence (only 1–3 months)	8 (11.9)	4 (11.4)	4 (12.5)	
Only recurrence on 3–6 months	3 (20.0)	2 (18.2)	1 (25.0)	1.000
>1 recurrence (baseline to 6 months)	12 (80.0)	9 (81.8)	3 (75.0)	

Note: Bold values indicate significant difference at $p < 0.05$.

[a]Acute symptomatic seizure.

[b]Unprovoked seizure.

[c]*p* Value for Fishers exact test.

[d]Classified as unprovoked (remote symptomatic) as the event occurred >7 days for structural and [e]for NCC no longer has active/transitional cysts.

[f]"Other" are detailed in the text.

insult (9%) are more common causes of ASyS.[8,23] Thus, the distribution of the causes of ASyS appears to differ between high- and LMICs,[24] demonstrating the dual challenges faced by LMICs, dealing with persistently high risk of infectious diseases while also facing increasing health threats from noncommunicable diseases, such as stroke. While stroke seems to be one of the most common causes of ASyS in high-, middle-, and low-income countries, other causes, especially infections, vary between high- and LMICs.

In our study, only 2.9% of the total cohort had evidence of neurocysticercosis (NCC). NCC is still described as the "most frequent cause of epilepsy worldwide," and 30%–40% of epilepsy cases in LMICs are attributed to NCC.[25]

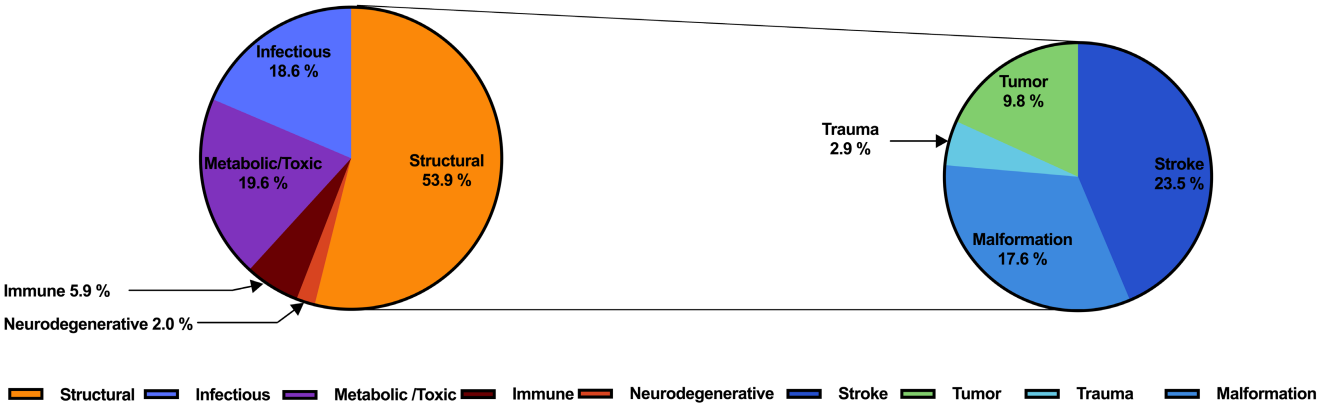

FIGURE 1 Etiology of 102 patients with symptomatic seizure.

However, our study suggests that NCC likely plays a smaller role in the development of seizures and even less in the development of epilepsy.

Overall, 58.8% of patients with ASyS and 30.7% of patients with UPS had abnormalities on neuroimaging, which is similar to previous studies regarding ASyS that found a range from 34% to 56% of imaging abnormalities.[26] We also found a greater frequency of generalized seizures, including those of unknown type (53.9%) than the 30%–35% expected based on previous research, while the expected proportion of focal seizures would be 65–70%.[27] In our study, tonic–clonic seizures included both focal to bilateral tonic–clonic seizures, as well as tonic–clonic seizures of unknown origin. This should be clarified as the EEG and CT imaging results become available, as well as patient follow-up on auras or focal symptoms. Additionally, 38.3% of patients reported a comorbidity. Multimorbidity has been reported in patients with the first seizure,[28,29] with a large cohort study of 1006 patients reporting that (26.4%) had at least one comorbidity. High rates of depression, up to 30%, have been reported in patients with UPS at their first presentation.[29]

In our study, 124 patients (69%) completed their 3-month follow-up assessment, in which seizure recurrence was similar among those with ASyS (23.9%) and UPS (29%). Eighty-two patients (45.5%) completed 6-month follow-up assessments, in which seizure recurrence was greater among those with ASyS (24%) than UPS (11.2%, $p = 1.0$) but the difference was not significant. These numbers are in accordance with previous published reports[9] and also with a recent of Cochrane's review[10] that reported 25% of seizures recurrence during a 6-month follow-up among adult patients with UPS. Longer follow-up is necessary to determine the risk of recurrence, as recommended for the ILAE's epilepsy definition criteria.

4.1 | Limitations

This study had several limitations. The non-significant findings may be attributed to type 2 errors due to the small sample size. There may have been measurement error in variables based on patient reports, such as the classification of seizure type. Variation in clinical data might have occurred due to differences among institutions and physicians. Finally, the participants were recruited from urban hospital EDs in five countries, and therefore, results may not be applicable to individuals who lack access to this level of care due to financial or transportation challenges, nor to residents of other countries.

4.2 | Clinical relevance or future directions

These findings suggest that there are differences in the distribution of causes of adult-onset first seizure by region, likely related to economic development. There are also differences in the clinical characteristics between patients with ASyS and UPS, which emphasizes the importance of distinguishing them to improve the comprehensive management of patients with epilepsy. Accurately identifying the underlying causes of first seizure in adulthood and the risk of recurrence is crucial for designing programs to address these causes and determining the appropriate treatment.

AUTHOR CONTRIBUTIONS

AC conceived of and managed the study implementation and wrote the manuscript. CS conducted the data management and analysis. EAK advised on study procedures and manuscript development. AC, DD, LN, NP-A, BG, AQ, LA, AF, RS, PH, LMP, MV, and CS-R implemented

participant recruitment, eligibility assessment, consent, and data collection. All authors were involved in the study design and manuscript development, providing feedback on, and approving the final manuscript.

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ACKNOWLEDGMENTS

The authors would like to thank the patients and hospital staff, without whom this study would not have been possible. This study was supported by a grant from the Vicerrectorado de Investigación, Universidad de Cuenca, Cuenca, Ecuador (Carpio, PI).

CONFLICT OF INTEREST STATEMENT

All authors report 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.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Carpio A, Salgado C, DiCapua D, Fleury A, Suastegui R, Giagante B, et al. Causes and prognosis of adults experiencing a first seizure in adulthood: A pilot cohort study conducted in five countries in Latin America. Epilepsia Open. 2024;00:1–9. https://doi.org/10.1002/epi4.12900