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**EMERGENCY PRESENTATION OF NEW ONSET VS RECURRENT
UNDIAGNOSED SEIZURES – A RETROSPECTIVE REVIEW**

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SH: Data collection, manuscript preparation, critical revision of manuscript for intellectual content.

EF: Study conception, data collection, manuscript preparation, critical revision of manuscript for intellectual content.

ZC: Statistical analysis, critical revision of manuscript for intellectual content.

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i. TITLE, ABSTRACT AND KEYWORDS

TITLE

EMERGENCY PRESENTATION OF NEW ONSET VS RECURRENT UNDIAGNOSED SEIZURES – A RETROSPECTIVE REVIEW

ABSTRACT

Objectives: To identify clinical factors that may assist emergency physicians to delineate between patients with new onset seizures (NOS) versus patients with recurrent undiagnosed seizures (RUS) among those presenting with apparent ‘first seizures’ to emergency departments (EDs). In addition, to provide a summary of current evidence-based guidelines regarding the workup of seizure presentations to ED.

Methods: This retrospective cohort study included patients aged over 17 who presented to a tertiary hospital ED between 1 January 2008 and 30 November 2016 with seizure-related ICD-10-AM discharge codes. Exclusion criteria included pre-existing epilepsy and non-seizure diagnoses. Medical records were reviewed and relevant data extracted.

Results: 75 patients had NOS (54.7% [41/75] female, median age 71 years) and 22 patients had RUS (59.1% [13/22] female, median age 64 years). Non-motor index seizures were more than four times as common among RUS patients (27.3% [6/22] RUS vs 6.7% (5/75) NOS; $p=0.015$). 95.5% (21/22) of RUS patients met epilepsy diagnostic criteria compared to

44.0% (33/75) of NOS patients ($p < 0.001$). No differences in patient demographics, seizure aetiology or seizure risk factors were identified.

Conclusions: Emergency physicians should be wary of patients presenting with non-motor 'first seizures': they are more likely to have experienced prior seizures (the 'recurrent untreated seizure' group), and thus meet epilepsy diagnostic criteria. Almost half of those with actual new-onset seizures may also meet epilepsy criteria, largely driven by abnormal neuroimaging. Distinguishing RUS from NOS patients in the ED allows accurate prognostication and timely initiation of appropriate therapy.

KEYWORDS

Antiepileptic drugs, Emergency department, Epilepsy, Neuroimaging, Seizure.

ii. TEXT

INTRODUCTION

A patient presenting with an apparent ‘first seizure’ poses an important diagnostic question: is this truly the patient’s first seizure (new onset seizure; NOS) or is this event the latest in a series of recurrent undiagnosed seizures (RUS) in a patient who should be diagnosed with epilepsy? Distinguishing RUS from NOS in the emergency department (ED) allows timely prognostication and treatment. This distinction relies on history; however, comprehensive history-taking is often not feasible in the ED due to patients being post-ictal, emotionally affected by their seizure, time constraints, and lack of readily available collateral history. Consequently, other patient or clinical factors in addition to history-taking would assist the emergency physician to determine which patients have a high pre-test probability for RUS versus those likely to have true NOS.

Diagnosing epilepsy by distinguishing RUS from NOS patients in the ED minimises future seizure risk by timely anti-epileptic drug (AED) initiation. Compared to NOS patients, RUS patients are much more likely to have further seizures.¹ A patient with unprovoked NOS has a 33% chance of another unprovoked seizure. But after a second unprovoked seizure (i.e. now a RUS patient), the risk of a third seizure is 73%. After a third unprovoked seizure, the risk of a fourth is 76%. The majority of recurrences happen in the year or two after the

second or third seizure. Appropriately commencing an AED in the ED, rather than waiting for outpatient follow-up, minimises future seizure risk.

Patients presenting with an apparent 'first seizure' need to undergo assessment to identify the underlying cause of their seizures and to determine the likelihood of seizure recurrence.

Acute symptomatic seizures (e.g. with fever or focal neurological signs) clearly require urgent investigation, such as neuroimaging and cerebrospinal fluid analysis, to rapidly identify and treat potentially life-threatening underlying conditions.² Unprovoked seizures, without an obvious precipitant, may not require urgent investigation. Here, distinguishing between NOS and RUS allows emergency physicians to prognosticate and manage patients accordingly. True unprovoked NOS patients who do not meet epilepsy diagnostic criteria (Box 1) may be suitable for early discharge and outpatient management without further investigation in ED.³⁻⁶ Patients with unprovoked RUS, however, fulfil epilepsy diagnostic criteria and should be considered for AED initiation.² These patients may benefit from inpatient neurology consultation prior to ED discharge, and more rapid outpatient follow-up.

Box 1: International League Against Epilepsy 2014 Practical Clinical Definition of Epilepsy³

1. Two or more unprovoked seizures more than 24 hours apart;

2. One unprovoked seizure plus an enduring risk of seizure occurrence >60% (includes epileptiform abnormalities on electroencephalogram (EEG) or epileptogenic lesion(s) on neuroimaging);
3. Identification of an epilepsy syndrome.

This study aimed to identify factors that may help emergency physicians distinguish RUS patients from NOS patients among those presenting with an apparent ‘first seizure’.

Furthermore, we provide a summary of current evidence-based guidelines regarding workup of seizure presentations to ED.

METHODS

The study was approved by the hospital’s human research ethics committee (study number 02-23-01-17). No funding was provided specifically for this study. Authors had full access to all of the data (including statistical reports and tables) in the study.

Patients

We included consecutive patients aged 18 years and over with an ICD- (International Classification of Diseases) 10-AM (Australian Modification) discharge code of G40-Epilepsy, G41-Status epilepticus or R56.8-Unspecified convulsions who presented to the ED of Cabrini Malvern, between 1 January 2008 and 30 November 2016. The hospital is a major metropolitan hospital in Melbourne, Australia with a 24/7 ED service, as well as in- and

outpatient neurology services. Patients were excluded if they had a pre-existing epilepsy diagnosis or a non-epileptic seizure final diagnosis.

Complete medical records, including all episodes prior to and following the index presentation, were reviewed. Using a standardised pro forma, researchers extracted data regarding demographics, comorbidities, seizure characteristics, investigation results and treatment plans.

Definitions

The 'index seizure' was defined as the episode captured by a relevant ICD-10-AM code.

NOS was defined as a seizure in a patient who had never experienced a seizure before, as documented by ED physicians and verified by review of the patient's entire medical record.

RUS was defined as a seizure in a patient who had experienced one or more previous seizures but had neither been diagnosed with epilepsy nor started on an AED because prior seizure(s) was/were:

1. Unrecognised until history-taking in the ED or at any future time (determined by chart review of that admission and all subsequent episodes);
2. Recognised, but did not meet epilepsy diagnostic criteria (see Box 1).

Both previous and index seizures were classified as either acute symptomatic seizures⁷ in the context of identifiable provoking factors, for example excessive alcohol intake or severe metabolic derangements,^{8,9} or unprovoked seizures without clear precipitants.² Semiology

was classified according to International League Against Epilepsy (ILAE) criteria.¹⁰ Motor seizures describe events with stiffening (tonic) and/or rhythmic jerking (clonic) movements, which can occur in a focal (single limb or unilateral) or generalised pattern; anatomically, these seizures originate from or spread to involve the motor cortex.^{11,12} Non-motor seizures may arise from different anatomical locations, and hence are associated with a variety of sensory and behavioural phenomena (see Box 2).

Statistical analysis

Comparisons between NOS and RUS groups were performed using Mann-Whitney test for continuous data and Fisher's exact test for categorical data. Post-hoc sensitivity analysis showed the sample size of 97 patients (NOS, n=75; and RUS, n=22) included in the analysis had 80% power to detect somewhat-large effect sizes of Cohen's $d=0.70$ or larger in Mann-Whitney test for mean ranks of continuous data or odds ratio of 4.08 or larger in Fisher's exact test for proportions of categorical data between the NOS and RUS groups. Unless otherwise specified, p -values of <0.05 were considered statistically significant.

All statistical analyses were performed using Stata 15 (College Station, TX, USA).

RESULTS

Of the 367 patients identified with a relevant ICD-10-AM seizure code during the study period, 97 attended the ED with either NOS (n=75/97, 77.3%) or RUS (n=22/97, 22.7%). The remaining 270 patients were excluded: 186 had a pre-existing epilepsy diagnosis, 30 had non-

seizure final diagnoses and 54 incidentally had seizures while an inpatient during an admission for a non-seizure indication. Figure 1 displays a flowchart of study methodology.

Patient characteristics

The median age of the cohort was 70 years and 55.7% were female. There were no significant differences in age and sex distribution between the two groups. Patient characteristics are displayed in Table 1.

Seizure characteristics

Significantly more NOS patients than RUS patients presented with motor seizures (93.3% [70/75] NOS vs 72.7% [16/22] RUS; $p=0.015$). Motor seizures include those with focal onset (formerly known as ‘partial’ seizures), generalised onset, and focal onset that progressed to bilateral tonic-clonic seizures (formerly known as ‘secondarily generalised’) (see Table 2). Non-motor index seizures were more than four times as common among RUS patients (27.3% [6/22] RUS vs 6.7% (5/75) NOS; $p=0.015$) and included symptoms such as déjà vu, depersonalisation and epigastric rising.

Prior to the index seizure, RUS patients had experienced a median of two (IQR 1-3) prior undiagnosed and/or untreated seizures. All prior seizures for any given patient were of a single semiology, most commonly (40.9% [9/22]) non-motor focal impaired awareness (formerly known as ‘partial complex’) seizures.

Seizure aetiology

Less than a third of patients in either group had acute symptomatic seizures (29.3% [22/75] NOS and 18.2% [4/22] RUS; $p=0.84$); the most common provoking factors were exposure to proconvulsant drugs in the former, and subdural haematoma at first identification and drug and/or alcohol intoxication/withdrawal in the latter. Epileptogenic lesions on neuroimaging were the most commonly identified remote seizure risk factor, identified in 36.0% (27/75) of NOS patients and 36.4% (8/22) of RUS patients. Epileptogenic lesions included primary and metastatic central nervous system tumours, cavernomas, gliosis and mesial temporal lobe sclerosis.¹⁴ Provoking and epileptogenic factors for each group are displayed in Table 1.

New-diagnosis epilepsy

95.5% (21/22) of RUS patients met epilepsy diagnostic criteria compared to 44.0% (33/75) of NOS patients ($p<0.001$). The majority of RUS patients' epilepsy diagnoses were based on two or more unprovoked seizures >24 hours apart (85.7% [18/21]). See Figure 2 for details of epilepsy diagnosis. One NOS patient was diagnosed with an epilepsy syndrome (3.0% [1/33]) while the remainder of the NOS group who met epilepsy criteria did so based on one unprovoked seizure and identification of an enduring seizure risk factor (97.0% [32/33]). Of this subgroup, the bulk of the enduring risk (84.4% [27/32]) was based on epileptogenic lesions identified on neuroimaging (total 36.0% NOS patients with abnormal computer tomography (CT) [27/75]) while 15.6% [5/32] had epileptiform abnormalities on EEG. Figure 2 displays a flowchart demonstrating the proportion of patients in each group meeting epilepsy diagnostic criteria.

Management

Neurologist input was obtained for 68% (51/75) NOS and 90.9% (20/22) of RUS patients. A minority of patients received AED loading in the ED (41.3% [31/75] NOS and 9.1% [6/22] RUS). CT scanning occurred within four hours for 68.0% (51/75) of NOS patients and 54.6% (12/22) of RUS patients. Ultimately, most patients received cerebral CT during their admission (82.7% [62/75] NOS and 77.3% [17/22] RUS). Admission to the ward, rather than discharge home, was the norm in both groups (90.7% [68/75] NOS and 86.4% [19/22] RUS patients admitted).

Prognosis

Seizure control was good among both groups who were admitted to the inpatient ward. All RUS patients remained seizure-free for their admission, as did 90.7% (68/75) of NOS patients. Median length of stay was similar: four days (IQR 3-9) and three days (IQR 2-8) for NOS and RUS groups, respectively.

DISCUSSION

Seizures are common presentations to hospitals, accounting for approximately 1-2% of all ED visits.^{15,16} Establishing whether these events represent a new onset seizure versus an underlying, undiagnosed epilepsy is critical as it carries important management and prognostic implications. Early distinction between NOS and RUS in the ED allows accurate

prognostication, risk-stratification and management. Failure to appropriately diagnose RUS patients with epilepsy delays treatment and exposes the patient to risks associated with future seizures. This study reveals that, in addition to targeted history-taking, other clinical factors, including seizure semiology and neuroimaging, may be important considerations when working up 'first seizure' patients and identifying those with epilepsy.

While non-motor seizures were more common among RUS patients, overall across both groups, most index seizures were motor seizures. Previous studies reveal a similar preponderance: one cohort of 368 seizure presentations to EDs found 86% were classified as 'generalised convulsions'.¹⁶ Work by Tafuro et al mirrored these findings: patients with disruptive seizures, that is, seizures with obvious motor features, were more likely to present to the ED after their first seizure than patients with subtle seizures such as non-motor events.¹⁷ The higher incidence of motor seizure events presenting to the ED may be due to selection bias: these events are usually concerning to patients and/or bystanders and prompt people to urgently seek medical attention.

Patients with RUS are four times more likely to present with non-motor seizures compared to patients with NOS; history-taking for prior seizures should be particularly rigorous when assessing patients presenting with non-motor seizures. In our study, RUS patients had experienced a median of two prior seizures, usually non-motor focal impaired awareness seizures. This is consistent with an Australian study of newly-diagnosed seizures which identified non-motor, low-impact first events to be strongly associated with diagnostic delay;

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this may be because patients may not recognise these events as seizures.¹⁸ Even if medical attention is sought, seizures may be misdiagnosed for a wide range of differentials including syncope or transient cerebral ischaemia.⁴ Patient factors, such as socioeconomic disadvantage, have further been identified as a risk factor for delayed presentation.¹⁸ Emergency physicians should familiarise themselves with key questions (Box 2)¹⁹ to identify previous undiagnosed seizures of this semiology and should also enquire about more ‘obvious’ prior convulsive seizures. One-third of RUS patients in our study had experienced one or more previous motor seizures. This figure is in keeping with previous research which found 28% of RUS patients had experienced at least one convulsive event before the index seizure.¹⁸

Box 2: Targeted screening questions to elicit previous focal seizures (adapted from Wilkinson¹⁹)

Ask the patient

Sense of intense déjà vu?

Racing memories?

Smelt or tasted things that others did not (particularly unpleasant, metallic taste)?

‘Rollercoaster’ rising sensation, or ‘stomach dropping’ sensation?

Sudden, intense anxiety, fear, or other emotions?

Tingling in one arm, leg, or half your face?

Ask the witness

Repeating words or sounds?

Sudden blank staring?

Purposeless movements like picking, fumbling, lip-smacking, chewing?

Convulsive head turning or eye movements to one side?

Bent one arm and straightened the other?

Strong convulsive movements of one arm, leg, or half the face?

While many new onset seizure patients ultimately undergo cerebral magnetic resonance imaging (MRI), in the ED setting a CT is adequate to exclude catastrophic pathologies requiring urgent intervention. The American Academy of Neurology (AAN) endorses CT as an acceptable initial alternative to MRI, acknowledging its speed, ease of performance and effectiveness.² Among NOS patients ultimately diagnosed with epilepsy, abnormal cerebral CT imaging identified the bulk (84.4%) of enduring seizure risk which informed this diagnosis. In our study, 36% of NOS patients had abnormal cerebral CT imaging: this rate is higher than the average yield of 15% cited by the AAN guidelines for first seizure management.² Our higher rate of CT-identified abnormalities likely reflects higher disease burden in our relatively old cohort. An Australian study of over 1,000 NOS patients revealed CT imaging to be a high-yield investigation, with only 12% of patients with normal CT imaging going on to have abnormal MRI.²⁰ Our findings support the utility of CT as a high-yield investigation in the ED, particularly among older NOS patients. Figure 3 provides a

flowchart outlining the management of apparent 'first seizure' patients in ED, including when to request CT imaging.

LIMITATIONS

Patient and clinical characteristics, including prior seizure details, were obtained from ED and other notes, which may have been incomplete. This limitation was addressed by reviewing all available medical records for patients as held by the study hospital including all notes by medical, nursing and allied health staff, and all correspondence from external facilities. Requesting further records from patients, their family doctors or other facilities was beyond the scope of this study, and so study authors may have been unaware of previous seizures treated elsewhere.

Only patients presenting to the ED were included in this study, rather than patients who attended a primary care provider. Consequently, there may be a selection bias in this study towards more obvious seizure presentations. Seizure-related ICD-10 codes were used to identify patients, and coding errors or omissions would potentially introduce a bias; however we do note that regular audits of ICD-10 coding take place to ensure consistency and accuracy, and ICD-10 codes are a widely-accepted method used for identifying morbidity in medical and epidemiological studies. Our study population was older than seen in other

studies of apparent first seizure presentations. The hospital catchment's older demographic, as revealed by the most recent Australian Bureau of Statistical Data, may account for this.²³

CONCLUSION

Differentiating NOS from RUS is reliant on history-taking; however, this is not always feasible in the ED setting due to factors such as patients' post-ictal state and absence of collateral history. Beyond history-taking, our study identifies that patients with a non-motor seizure presentation are more likely to have experienced prior seizure events, and thus meet epilepsy diagnostic criteria. These criteria may also be met among NOS patients via identification of epileptogenic abnormalities on neuroimaging, with rapid CT imaging in the ED proving a high-yield diagnostic investigation. Emergency physicians play a crucial role in the evaluation of seizure patients; skilful management, including appropriate epilepsy diagnosis, AED initiation and timely involvement of Neurology services may substantially alter patient outcomes by reducing the probability of further seizures.

iii. REFERENCES

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iv. TABLES

Table 1: Baseline patient and clinical characteristics

NOS = new onset seizure

RUS = recurrent undiagnosed seizure

IQR = interquartile range

EEG = electroencephalogram

	NOS (n=75)	RUS (n=22)	p-value
Median age (IQR)	71 (55-83)	64 (33-79)	0.091
Females	41 (54.7%)	13 (59.1%)	0.81
Acute symptomatic seizure risk factors			
None	53 (70.7%)	18 (81.8%)	0.84
Subdural haematoma (first identification)	2 (2.7%)	2 (9.1%)	
Drug / alcohol intoxication / withdrawal	3 (4.0%)	2 (9.1%)	
Exposure to proconvulsant drugs	4 (5.3%)	0	
Stroke (within one week)	3 (4.0%)	0	
Anoxic encephalopathy (within one week)	2 (2.7%)	0	
Active central nervous system infection	2 (2.7%)	0	

Severe metabolic derangement (within 24 hours)	2 (2.7%)	0	
Acute intracranial haemorrhage	2 (2.7%)	0	
Intracranial surgery (within one week)	1 (1.3%)	0	
Acute flare autoimmune disease	1 (1.3%)	0	
Meeting epilepsy diagnostic criteria			
1 unprovoked seizure and probability of further seizures >60%	32 (42.7%)	2 (9.1%)	<0.001
<i>Based on epileptogenic lesion on neuroimaging</i>	<i>27 (36.0%)</i>	<i>2 (9.1%)</i>	
<i>Based on epileptiform EEG</i>	<i>5 (6.7%)</i>	<i>0</i>	
≥2 unprovoked seizures occurring >24 hours apart	0	18 (81.8%)	
Diagnosis of an epilepsy syndrome	1 (1.3%)	1 (4.5%)	

Table 2: Comparison of previous and modern terminology for describing seizures

(adapted from ILEA 1981¹³, Scheffer¹⁰)

Type of onset	Previous terminology	Modern terminology
Focal onset seizures	Simple partial seizure with motor signs	Focal aware seizure, motor (automatisms, atonic, clonic, epileptic spasms, hyperkinetic, myoclonic, tonic)
	Simple partial seizure with somatosensory, autonomic, or psychic symptoms	Focal aware seizure, non-motor (autonomic, behaviour arrest, cognitive, emotional, sensory)
	Complex partial seizure, with or without automatisms	Focal impaired awareness seizure, motor or non-motor
	Secondarily generalised seizure	Focal to bilateral tonic-clonic seizure
Generalised onset seizures	Absence seizure ('petit mal'), typical or atypical	Generalised non-motor seizure (additional

		subcategories: myoclonic, eyelid myoclonia)
	Convulsive seizure (tonic-clonic ['grand mal'], tonic, clonic, atonic, myoclonic)	Generalised motor seizure (additional subcategories: myotonic-atic, myotonic-tonic-clonic, epileptic spasms)
Unclassified (inadequate or incomplete date)	Unclassified epileptic seizure	Unclassified seizure

v. FIGURE LEGENDS

Figure 1: Flowchart of study methodology

ICD-10-AM = International Classification of Diseases 10 Australian Modification

ED = emergency department

Figure 2: Flowchart of patients meeting epilepsy criteria

EEG = electroencephalogram

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Figure 3: Management of apparent ‘first seizure’ patients in ED (adapted from Huff²¹, Turner²², Krumholz²)

† Drugs with high epileptogenic potential include meperidine, sevoflurane, clozapine, phenothiazines and cyclosporine. Drugs with intermediate epileptogenic potential include propofol, maprotiline, tricyclic antidepressants and chlorambucil. Drugs with low epileptogenic potential include fluoroquinolones, carbapenems, bupropion and iodinated contrast media. Drugs with minimal or inconclusive epileptogenic potential include interferon alpha.⁷

TIA = transient ischaemic attack

HIV = human immunodeficiency virus

CT = computed tomography

ECG = electrocardiogram

AED = antiepileptic drug

ED = emergency department

EEG = electroencephalogram

MRI = magnetic resonance imaging

Figure 1: Flowchart of study methodology

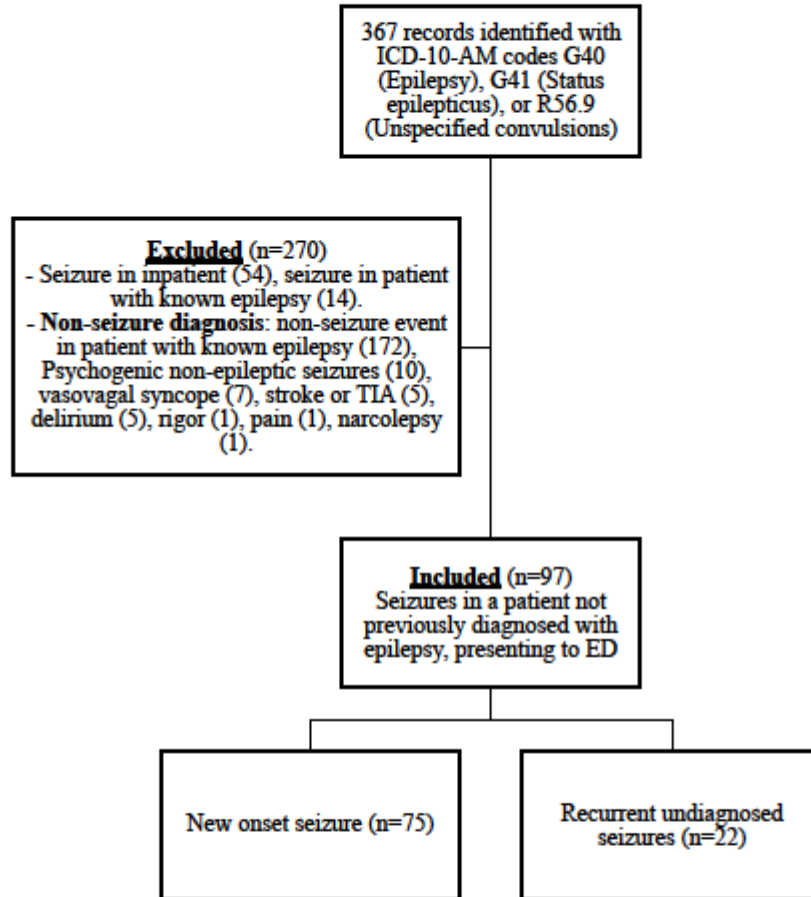


Figure 2: Flowchart of patients meeting epilepsy criteria

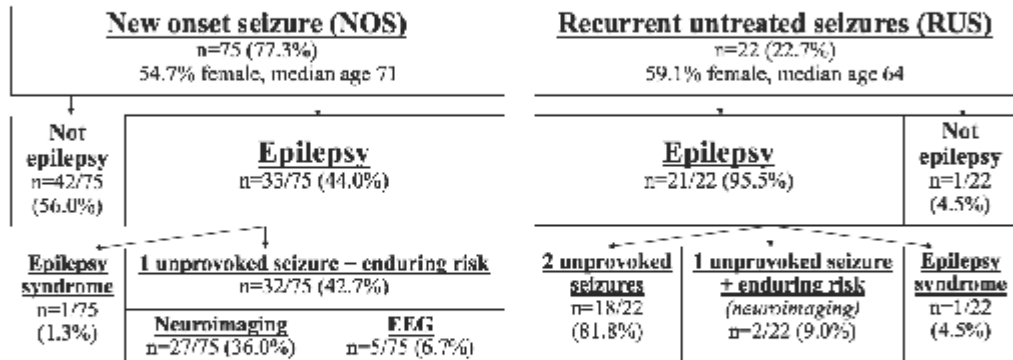


Figure 3: Management of apparent ‘first seizure’ patients in ED (adapted from Huff²¹, Turner²², Krumholz²³)

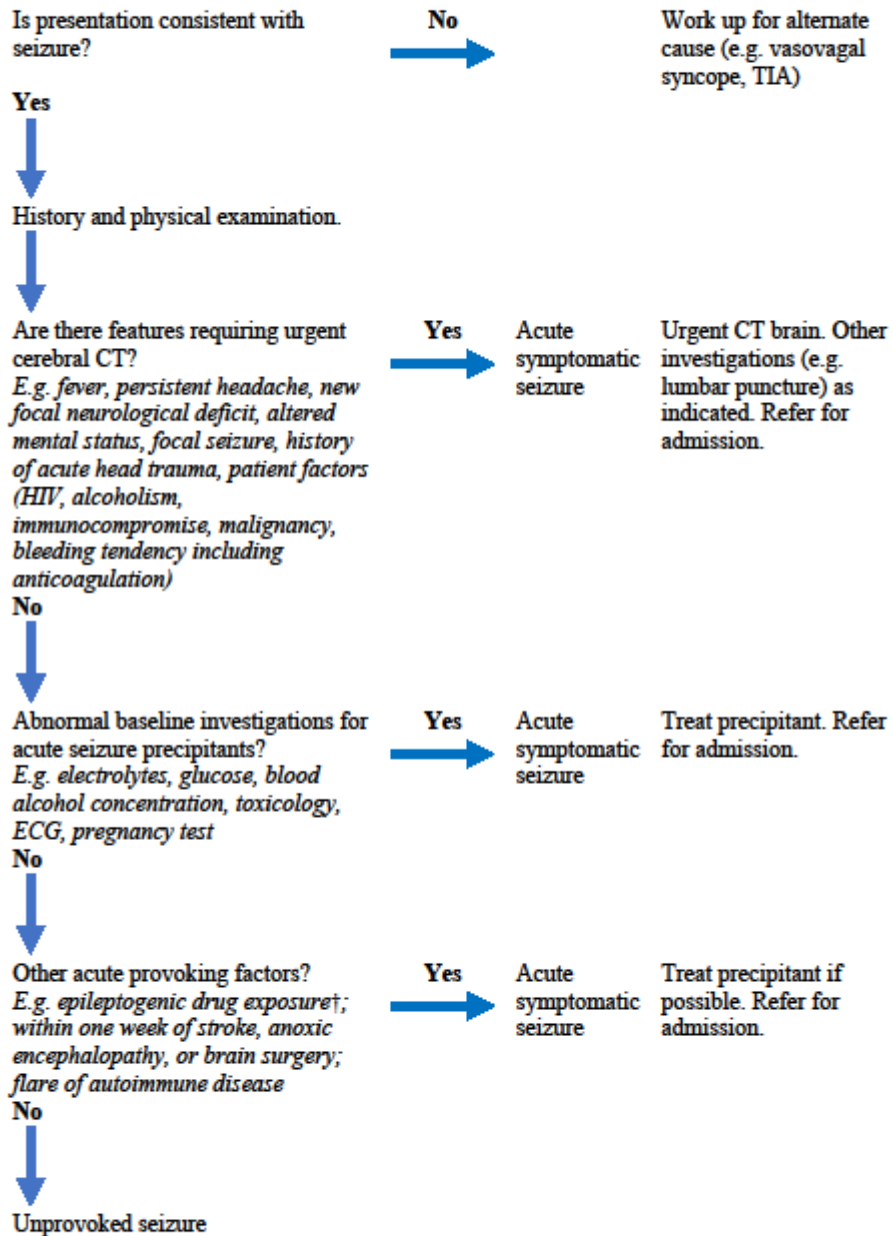


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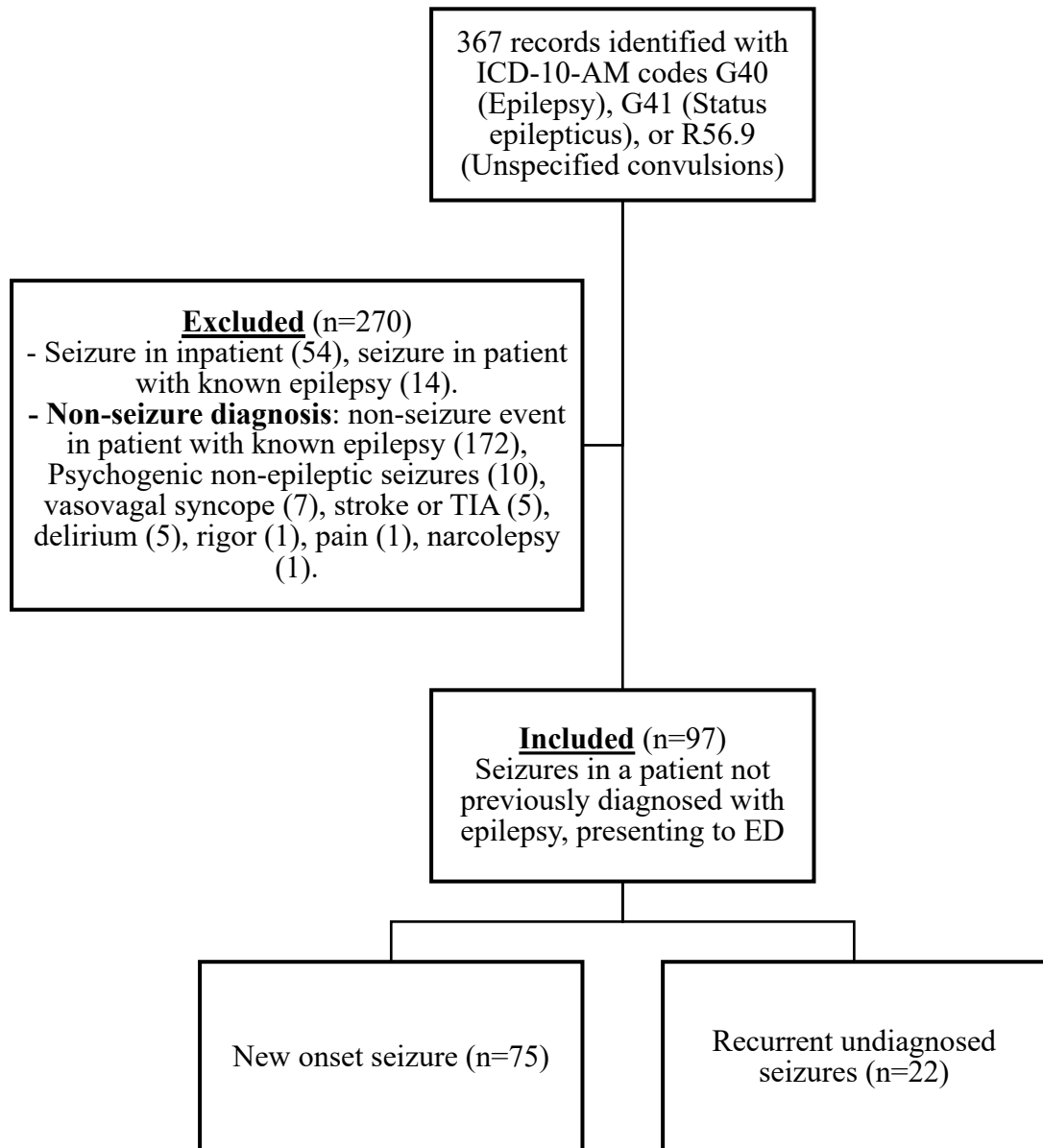
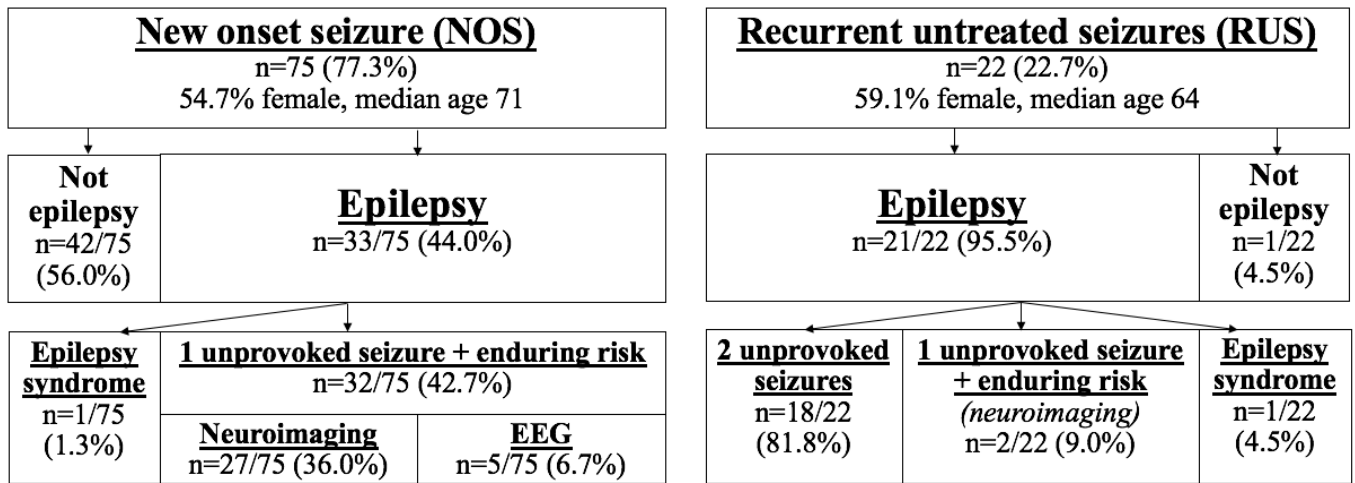


Figure 2: Flowchart of patients meeting epilepsy criteria



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Figure 3: Management of apparent ‘first seizure’ patients in ED (adapted from Huff²¹, Turner²², Krumholz²)

