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NEUROLOGIA

Risk of epilepsy after a first seizure: a retrospective observational study of patients evaluated in 2023 at the emergency department

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1. INTRODUCTION

1.1 EPILEPSY

1.1.1 DEFINITION OF EPILEPSY AND DIAGNOSTIC CRITERIA

CONCEPTUAL DEFINITION

Epilepsy is a common neurological disorder affecting ≈ 0.7% of the general population. However, the lifetime prevalence of an isolated epileptic seizure is much higher (8–10%) (1,2).

In 2005, the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) have reached consensus conceptual definitions for the terms epilepsy and epileptic seizure.

An **epileptic seizure** is "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" (3).

This abnormal activity can affect sensory, motor, and autonomic function, consciousness, emotional state, memory, cognition, or behavior (3).

Epileptic seizures are defined as "transient," meaning they are limited in time, with a clear start and finish. However, even though they usually have a short duration, lasting less than 5 minutes, they can be preceded by a prodromal phase, and they are usually followed by a postictal phase, during which return to baseline is gradual (4).

Epilepsy is "a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition" (3). The definition of epilepsy requires the occurrence of at least one epileptic seizure.

In simpler words, "epilepsy exists in a patient who has had a seizure and whose brain, for whatever reason, demonstrates a pathological and enduring tendency to have recurrent seizures. This

tendency can be imagined as a pathological lowering of the seizure threshold, when compared to persons without the condition" (5).

Not everyone who experiences an epileptic seizure suffers from epilepsy. A seizure can be caused by a transient factor (e.g. an acute brain insults or a temporary alteration in the brain metabolism) acting on an otherwise normal brain, which temporarily lowers the seizure threshold. In this case, that seizure does not count for a diagnosis of epilepsy (5,6).

Epileptic seizures occurring in people with an acute brain insult but without epilepsy are defined as "**acute symptomatic seizures**". In clinical practice, several terms such as "provoked seizure" and "reactive seizure", are frequently used as synonyms. The opposite term "**unprovoked**" indicates that the epileptic seizure occurs in the absence of any apparent provocative factors (6).

Etiology must not be confused with provocative factors, because some brain lesions (e.g. a brain tumor) can produce an enduring tendency to have seizures, so they do act as a provocative factor, but not as a transient insult, at least as long as the lesion is present (5).

For this reason, seizures that are caused by most brain tumors or neurodegenerative diseases (e.g. Alzheimer's dementia, which is neither transient nor reversible but a persistent and progressive condition) may be referred to as **progressive symptomatic seizures** (6).

Acute symptomatic seizures are defined as occurring "in close temporal relationship with an acute CNS insult, which may be metabolic, toxic, structural, infectious, or due to inflammation". They show notable distinction from unprovoked seizures, and are consequently excluded from the definition of epilepsy (6).

First, unlike in unprovoked seizures, "there should always be a clearly identifiable, concomitant, acute, causal condition that has occurred close to the time of the seizure".

In adults, the most common etiologies of acute symptomatic seizures include: cerebrovascular diseases, traumatic brain injuries, medications/drugs of abuse and alcohol withdrawal, and central nervous system (CNS) infections. Less common causes of acute symptomatic seizures include: metabolic disorders (e.g. hyponatremia, hypoglycemia), intoxication, eclampsia, and other disorders. The situation is less defined about sleep deprivation: if extensive, it can provoke a seizure in an individual without any enduring predisposition to generate seizures, but is also known as a typical provocative factor in certain epilepsies such as idiopathic generalized epilepsy (6).

The "close temporal relationship" between the brain insult and the seizure is different according to the underlying pathology. For strokes or traumatic brain injuries, a seizure is considered acute

symptomatic if it occurs within the first 7 days after such events. The required time interval can be longer if there is evidence of a continued active brain disease (e.g. CNS infections, autoimmune encephalitis) or shorter (e.g. metabolic disturbances such as hypothermia, where there must be evidence of low serum sodium level within 24 hours of the seizure) (6).

Unprovoked seizures can be caused by a CNS insult in the remote past. The extensive length of time between the brain insult and the seizure, in the absence of ongoing active disruption of CNS integrity, classifies this kind of unprovoked seizure as "**remote symptomatic**" (6).

Secondly, the distinction between acute symptomatic seizure and unprovoked seizure has important implication in terms of recurrence risk. In fact, acute symptomatic seizures usually do not recur once the underlying cause has been resolved, and the CNS has been restored to its functional integrity. This is in contrast to the epilepsy definition, which requires an enduring predisposition to develop subsequent seizures (6).

The distinction between acute symptomatic seizures and epilepsy is easier when the precipitating factor is a metabolic disorder, intoxication or withdrawal, but it might be more complicated when the seizure is caused by destructive brain pathologies such as stroke or head trauma, because they carry an increased risk for the later development of epilepsy (6). Some pathologies causing acute symptomatic seizures are associated with a minimal risk of being followed by unprovoked seizures, whereas with others this risk may be consistent (7).

The distinction between provoked and unprovoked can be even more challenging considering that a provocative factor can hardly be absolutely excluded even if a seizure appears to be unprovoked (6) and that the identification of a provocative factor does not necessarily exclude the presence of an enduring epileptogenic abnormality (a borderline provocation might trigger a seizure in an person with an enduring predisposition to have seizures, but not in a non-predisposed individual) (5).

For all these reasons, even though acute symptomatic seizures do not allow an epilepsy diagnosis, the increased risk for the later development of epilepsy must be considered.

As an example of this subtle distinction, **reflex epilepsies** (specific syndromes in which all epileptic seizures are precipitated by sensory stimuli, e.g. flashing lights or reading (8)) fulfill the conceptual definition of epilepsy even though all seizures are provoked, because the tendency to respond repeatedly to such stimuli with seizures indicates an enduring abnormality of the brain and an enduring predisposition to develop such seizures (5,6).

OPERATIONAL DEFINITION AND DIAGNOSTIC CRITERIA

Before 2014, the conceptual definition of epilepsy was practically applied as requiring 2 unprovoked seizures occurring at least 24 hours apart. In fact, while after a single unprovoked seizure the risk for another is 40–52%, with two unprovoked seizures, the chance by 4 years of having another rises to 73% (5).

However, many epileptologists observed that after the first seizure event (FSE), some patients have a risk of a second unprovoked seizure that is comparable to the risk for further seizures after two unprovoked seizures, and used to manage patients as if epilepsy was present, even though those patients didn't meet the diagnostic criteria. Such examples may include patients who present with a single unprovoked seizure after a remote brain insult, such as a stroke, CNS infection, or trauma (remote symptomatic seizures) or a child with a single seizure whose evaluation showed a structural etiology and an epileptiform activity in the electroencephalography (EEG) (5).

In order to bring the practical clinical definition of epilepsy into concordance with how epileptologists think about epilepsy, in 2014 ILAE commissioned a Task Force to formulate an operational definition of epilepsy including these particular circumstances.

The task force proposed the following definition:

"Epilepsy is a disease of the brain defined by any of the following conditions (5):

1) **At least two unprovoked seizures occurring >24 h apart.**
2) **One unprovoked seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years.**
3) **Diagnosis of an epilepsy syndrome.**"

The first criterion refers to the previous practical definition, which remains valid, even though it is not the only case in which epilepsy can now be diagnosed.

The second criterion addresses the fact that, in some patients, a high risk of recurrence can be assessed even after a single seizure. If after the FSE the patient is known to suffer from a condition which causes an enduring predisposition for unprovoked seizures with a risk comparable to those who have had two unprovoked seizures, then that person too should be diagnosed with epilepsy.

Fisher et al. identified the presence of epileptogenic lesions on MRI and interictal epileptiform discharges in the EEG as two factors leading to a higher risk for recurrent seizures after a first seizure. The threshold level of 60% was chosen because it appropriately exceeds the 50% level of recurrence risk found at 5 years after a single seizure in the Multicenter Epilepsy and Single Seizure study (MESS) study (5,9).

Data vary among different studies and different clinical circumstances, so no formula can be applied for deciding whether this second criterion is met. In the absence of clear information about recurrence risk, the diagnosis of epilepsy must be made at the second unprovoked seizure (5).

The third criterion addresses the possibility to diagnose epilepsy in patients who don’t meet the previous criteria, but who meet the clinic-electroencephalographic criteria for a clearly defined epilepsy syndrome: in this case, epilepsy may be presumed to be present, even if the risk of subsequent seizures may not be as high as the previous criteria would require (5).

ETIOLOGY

ILAE has defined 6 etiologic categories for epilepsy (10):

1) **Structural etiology**: a lesions detected by neuroimaging, which is concordant with seizure semiology and EEG findings, and is therefore reasonably inferred to cause the patient's seizures.

2) **Genetic etiology**: a disease-causing variant in a gene or copy number variant, believed to be pathogenic for epilepsy. The classification of a patient's epilepsy as genetic doesn't need a molecular analysis, but having a relevant family history and typical features (EEG, seizure semiology) is enough. However, genetic disease-causing variants can also arise de novo and are not always inherited, so a family history of epilepsy might not be present.

3) **Infectious etiology**: a patient with an acute infection and seizures does not have epilepsy, because these kind of seizures are provoked, but patients with seizures due to brain alteration by a resolved CNS infection (e.g. meningitis, neurocysticercosis, HIV, CMV, cerebral toxoplasmosis) would be classified as having an infectious cause of their epilepsy. Many of these cases could also be considered of structural etiology.

4) **Metabolic etiology**: acquired (not genetic) metabolic derangement, e.g. pyridoxine-dependent seizures, cerebral folate deficiency. Such metabolic disturbance must not be transient, as this would result in acute-symptomatic seizures and would not be considered to be epilepsy.

5) **Immune etiology**: auto-immune diseases (e.g. Antibody mediated limbic encephalitis).

6) **Unknown category:** this category is used when etiology is unclear.

1.1.2 SEIZURE CLASSIFICATION

Seizures were traditionally categorized as grand mal seizures (convulsive seizures) or petit mal seizures (staring without convulsive movements), but this is not an accurate terminology anymore, because seizures can include a much wider spectrum of symptoms (4).

In 2017, the ILAE has revised the classification of seizure types. The Task Force established for this purpose chose to develop an operational classification, not based on anatomy (like some previous ones) or on fundamental mechanisms (because although our understanding of seizure networks is evolving, it is not yet sufficient to serve as a basis for seizure classification) (11).

The classification begins with clinical history and observation of the most common signs and symptoms that are known to be associated with seizures. However, it is not based exclusively on observed behavior, but it allows the use of additional data to classify seizure types, such as EEG patterns, lesions detected by neuroimaging, laboratory results (e.g. detection of antineuronal antibodies), gene mutations, or an epilepsy syndrome diagnosis known to be associated with a specific type of seizures (11).

Signs and symptoms cannot be matched in one-to-one relationships with seizure types, because some symptoms associates with more than one seizure type, and seizure type are often characterized by multiple symptoms (12).

The classification has a basic version (Figure 1) and an expanded one (Figure 2). Both reflect the same classification framework, with the simplified version resulting from the merging of subcategories. Use of one versus the other depends on the desired degree of detail (11).

BASIC CLASSIFICATION

Seizures are first categorized by type of onset, evaluating whether the initial manifestations of the seizure are focal or generalized (11,12).

Focal onset seizures are defined as “originating within networks limited to one hemisphere”. They may be discretely localized or more widely distributed (12).

Generalized onset seizures are defined as “originating at some point within, and rapidly engaging, bilaterally distributed networks” (12).

The words “focal” and “generalized” at the start of a seizure name are assumed to mean of focal or generalized onset, so the term “onset” can be omitted (11).

"Focal to bilateral tonic–clonic" is a distinct seizure type, corresponding to the 1981 term "partial onset with secondary generalization." This terminology reflects a propagation pattern, rather than a specific seizure type, but it is such a diffuse and relevant presentation that the Task Force decided to keep this separate categorization. In this seizure type the onset is focal, so the term "to bilateral" instead of "secondary generalized" was used to better differentiate it from a generalized-onset seizure (11).

The onset may be unwitnessed or not clear (e.g. the patient was asleep, alone, or observers did not notice the presence of focal features) in which case the seizure is categorized as "**of unknown onset"** (11).

Sometimes it's impossible to classify a seizure at all, either because of insufficient information or because of the atypical nature of the seizure, in which case it is categorized as "**unclassified**." This term includes both seizures with features that do not fit into the other categories and seizures described with insufficient detail to allow classification (11,12).

Further classification is optional.

The next level of focal seizure classification is by level of awareness. The Task Force adopted state of awareness as a measurable surrogate marker for consciousness (consciousness is a complex phenomenon, its surrogate markers usually include awareness, responsiveness, memory, and a sense of self as distinct from others). In this context, awareness refers to "perception or knowledge of events occurring during a seizure", not to knowledge of whether a seizure occurred. Retained awareness means that the person is aware of self and environment during the seizure, even if immobile (11).

If awareness of the event is impaired for any portion of the seizure, then the seizure is classified as a **focal seizure with impaired awareness**. Conversely, if the patients is aware during the whole duration of the seizure, it is classified as **focal aware seizure** (12).

Focal seizures can be additionally subgrouped as **motor** or **nonmotor** seizures, basing the classification on motor and nonmotor signs (e.g. sensory) and symptoms at the onset. If both motor and nonmotor signs are present, the motor signs will usually dominate, so the seizure is classified as motor (11). Further specification of the motor or nonmotor signs and symptoms requires referring to the extended classification.

The vertical organization of the focal-onset class is not hierarchical, so seizures can be categorized referring to motor or nonmotor signs without mentioning the awareness level (12).

Generalized seizures are divided into **motor** and **nonmotor (absence)** seizures. By definition of the generalized branch of the classification, motor activity should be bilateral from the onset in order to classify the event as a generalized motor seizure (11,12).

Level of awareness is not used as a classifier for generalized seizures, since awareness is impaired in the large majority of generalized seizures.

Absence seizures (the prefix "generalized" may be omitted) are characterized by a sudden cessation of activity and awareness. They tend to occur in younger persons, have more sudden start and termination, and usually display less complex automatisms than do focal seizures with impaired awareness, but these differences are not absolute, so EEG may be required for the classification (focal epileptiform activity may indicate a focal type, and bilaterally synchronous spike-waves may point to an absence seizure) (12).

A **seizure of unknown onset** may still present some relevant motor or nonmotor feature, so they can be classified as motor or nonmotor too (11,12).

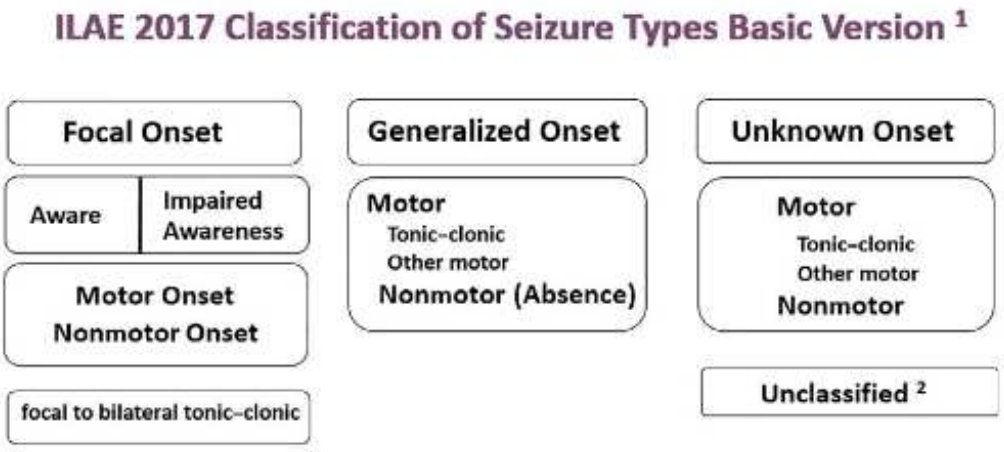


Figure 1: From "Instruction manual for the ILAE 2017 operational classification of seizure types" – Fisher et al. 2017

EXPANDED CLASSIFICATION

The expanded classification (Fig. 2) provides another level of seizure subgrouping, built on the framework of the basic classification (12). Focal and generalized seizures may be further characterized by one of the listed motor or nonmotor symptoms. Additional classifiers are encouraged, but optional, and their use depend on the experience and purposes of the person classifying the seizure (11).

Focal motor onset behaviors include: atonic (focal loss of tone), tonic (sustained focal stiffening), clonic (focal rhythmic jerking), myoclonic (irregular, brief focal jerking), or epileptic spasms (focal flexion or extension of arms and flexion of trunk). Other less obviously focal motor behaviors include hyperkinetic (e.g. pedaling, thrashing, etc.) activity and automatisms (12).

The same terms can be used in subgroping generalized motor seizures (12).

The term **atonic** indicates a loss of tone. When leg tone is lost during a generalized atonic seizure, the patient can fall on the buttocks or sometimes forward onto the knees and face (12).

Generalized **tonic** seizures presents as bilateral limb stiffening or elevation, often associated with neck stiffening or a sustained abnormal posture, either in extension or flexion. The classification implies that the tonic activity is not followed by clonic movements, otherwise it would be classified as tonic-clonic (12).

Generalized **clonic** seizures are characterized by sustained rhythmic jerking of limbs on *both* sides of the body and often head, neck, face, and trunk (12).

Generalized **myoclonic** activity can occur in isolation or in conjunction with tonic or atonic activity. Myoclonus differs from clonus by being briefer and not regularly repetitive (12).

An **epileptic spasm** manifests as a sudden flexion, extension, or mixed extension–flexion of predominantly proximal and truncal muscles. They commonly occur in clusters (12).

Tonic–clonic is the term replacing the “grand mal” seizure type, although popular usage of the old term still persists today. During a tonic-clonic seizure, awareness is lost before or contemporaneously with the stiffening and jerking movements. Given that a new seizure type characterized by myoclonic movements preceding tonic and clonic movements was defined, documenting the early movements of a tonic–clonic seizure as being tonic is crucial for the correct classification of these seizure types (12).

Generalized **myoclonic–tonic–clonic** seizures begin with a few myoclonic jerks followed by tonic–clonic activity (12).

A **myoclonic–atonic** seizure involves brief jerking of limbs or trunk, followed by a limp drop (12).

The classification of generalized nonmotor seizure distinguishes between **typical** and **atypical** absence. Absence seizures are considered atypical when they are associated with changes in tone that are more pronounced than in typical absence and the onset and cessation are not abrupt. The two types of seizures usually are associated with different EEG findings, epilepsy syndromes, therapies, and prognoses. An EEG may be required to secure the distinction between typical and atypical absence seizures (12).

A **myoclonic absence seizure** refers to an absence seizure with myoclonic movements, causing ratcheting abduction of the upper limbs leading to progressive arm elevation, and associated with three-per-second generalized spike-wave discharges (12).

Eyelid myoclonia are myoclonic jerks of the eyelids and upward deviation of the eyes, often precipitated by eyes closure or by light (12).

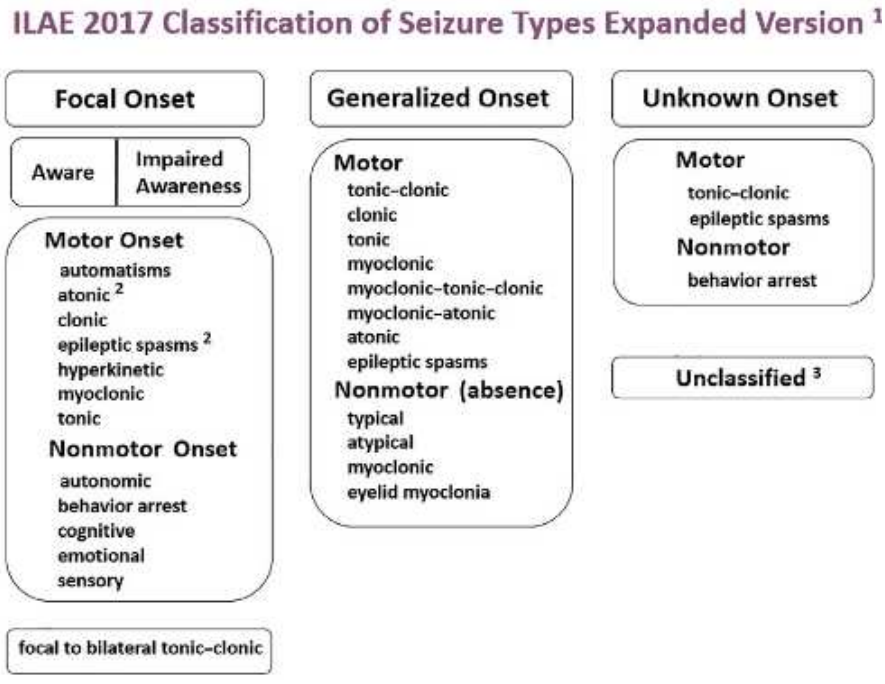


Figure 2: From "Instruction manual for the ILAE 2017 operational classification of seizure types" – Fisher et al. 2017

1.1.3 EPILEPSY CLASSIFICATION

The ILAE classification of the epilepsies is more extensive than the seizure classification: it considers the possibility for a patient to have multiple seizure types, and includes information about the overall clinical profile, imaging, genetics, laboratory tests, and prognosis (10).

Epilepsy types are classified as:

1) **Focal epilepsy**: patients who only experienced focal seizure have focal epilepsy. The diagnosis can be supported by focal EEG findings (such as focal slowing or epileptiform discharges) and concordant focal MRI findings (13).
2) **Generalized epilepsy**: patients who only experienced generalized seizure have generalized epilepsy. Their EEGs typically reveal generalized spike-wave activity (13).
3) **Combined generalized and focal epilepsy**: epilepsy syndromes, such as Dravet syndrome and Lennox-Gastaut syndrome, in which it is usual to have both generalized and focal seizures (10). EEG may display both focal and generalized electrographic findings (13).
4) **Unknown**: used when a patient meets the diagnostic criteria for epilepsy but it remains undetermined whether it is a focal or generalized epilepsy, either because of unavailable or indeterminate EEG, MRI and family history (13).

EPILEPSY SYNDROMES

An epilepsy type is a separate designation than an epilepsy syndrome (10).

Epileptic syndromes are defined by many factors, including not only the type of seizure, but also age at onset, family history, clinical features, ictal and interictal EEG patterns, and neuroimaging. Each epileptic syndrome is associated to a typical natural history, prognosis, and medications to which it is more likely to respond (4).

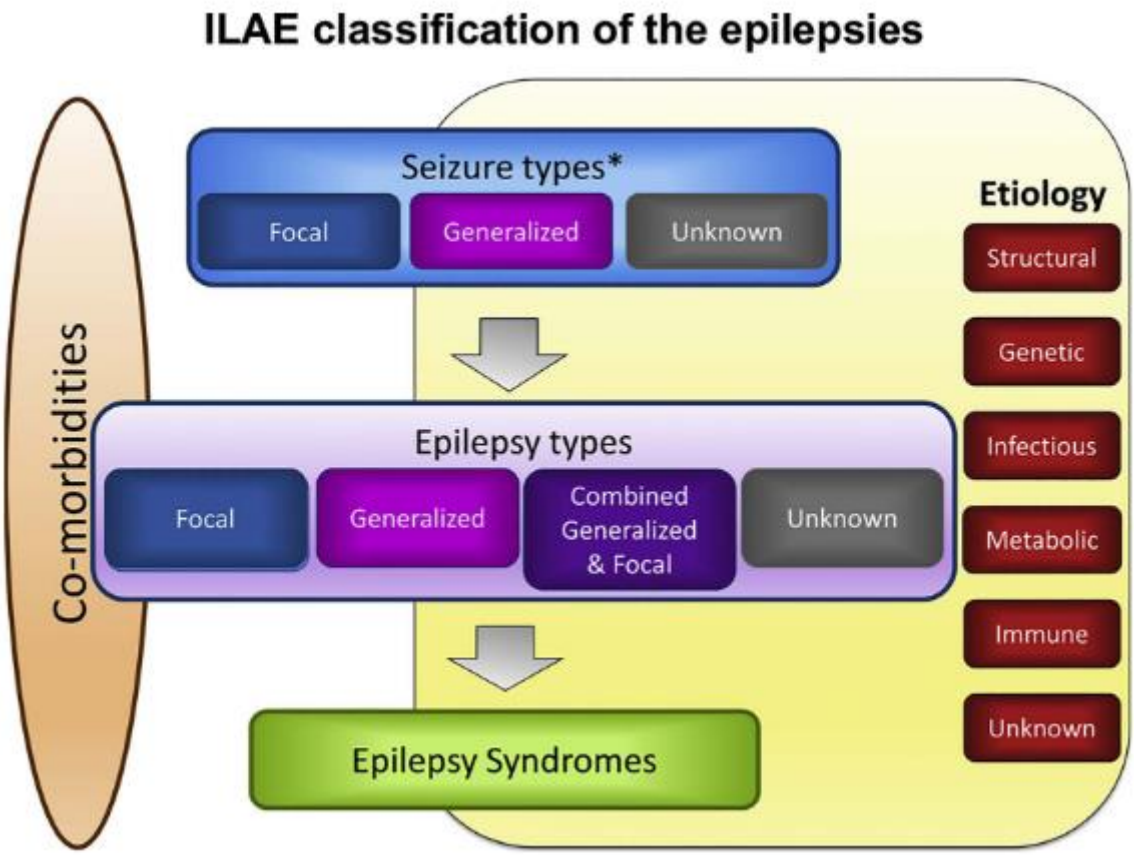


Figure 3: ILAE 2017 classification of the epilepsies. From "The new definition and classification of seizures and epilepsy. Falco-Walter et al. 2018

1.1.4 SEIZURE CLUSTERING AND STATUS EPILEPTICUS

SEIZURE CLUSTERING

There is no consensus in terms of definition of seizure clusters, but different definitions are used in different studies and contexts. A seizures' cluster is generally defined as a series of grouped seizures that have short interictal periods, but the number of such seizures and the length of the interictal period is a subject of controversy (14).

Another common approach is to define clusters as more than one seizure occurring within a specific time interval, but again not everyone proposes the same seizure number and time period. A broad definition could include any 24-hour period or calendar day during which two or more seizures occurred (15).

Many studies define seizure clusters as 3 or more seizure in 24 h (which means that the interictal period is 8 h or less) since seizures with an interictal period of less than 8 h has been proven to be more likely to come from the same hemisphere than seizures with longer interictal intervals (14).

Other clinical definitions include: 2 or more seizures in 6 hours, 2 or more seizures in 24 h, 2 to 4 seizures in 48 h, 2 generalized tonic clonic or 3 focal impaired awareness seizures in 4 h, multiple focal impaired awareness seizures or generalized seizures occurring within a 24-h period in adults or a 12-h period in children (14).

These clinical definitions do not consider the variability in the baseline seizure frequency among different patients. For this reason, some studies have proposed statistical definitions that require an increase in seizure occurrence compared with the patient's average seizure frequency: a threefold or fourfold increase in seizure frequency within a 3-day period has been considered as seizure clustering. However, clinical definitions are easier to use and probably more relevant in the acute settings (14).

Prevalence of seizure clusters varies significantly in different studies depending on the chosen definition. Prevalence is lower if a statistical definition is used, since clinical definitions tend to overestimate the occurrence of seizure clusters in patients who regularly have high frequencies of seizures (14).

STATUS EPILEPTICUS

In the first ILAE Classification of Seizures (1970) status epilepticus (SE) was defined as a "seizure that persists for a sufficient length of time or is repeated frequently enough to produce a fixed and enduring condition". In the 1981 revision, the definition was minimally changed into a "seizure that persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur". These definitions were imprecise, because they did not provide a defined duration of the seizure (16).

In 2015, the ILAE has charged a Task Force to revise concepts, definition, and classification of status epilepticus. The proposed new definition of SE is as follows: "Status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (after time point t1). It is a condition which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures (16).

This definition is conceptual, with two operational dimensions:

- The first (**t1**) is "the length of the seizure and the time point beyond which the seizure should be regarded as an abnormally prolonged seizure." This time point determines the moment at which treatment should be started (16).
- The second time point (**t2**) is "the time of ongoing seizure activity after which there is a risk of long-term consequences". This dimension determines how aggressive the treatment should be (16).

Most seizures are brief and unlikely to last more than 1–2 min before spontaneously resolving (17).

The required duration for defining a seizure as SE varies between different forms of seizures.

- **Tonic-clonic SE**: evidence suggests that most convulsive seizures last < 5 min, and seizure lasting > 7 min are likely to be prolonged and require acute treatment. These findings led the Task Force to set the time of t1 at 5 min. Available data indicate that seizures lasting more than 30 min are less likely to terminate spontaneously and are more likely associated with irreversible brain damage and mortality, so the Task Force set the time of t2 at 30 min (16).
- **Focal SE and absence SE**: there is limited information to define t1 and t2 in focal SE and absence SE. In these seizures, the likelihood of damage is dependent on the location of the

epileptic focus, the intensity of the status, the age of the patient and other factors. Further research is needed to better define these aspects (16).

The Task Force provided time limits for each type of SE (Figure 3), but it is important to note that such limits are only general approximations, meant primarily for operational purposes. As knowledge and understanding increase, these time points can be revised (16).

Table 1. Operational dimensions with t_1 indicating the time that emergency treatment of SE should be started and t_2 indicating the time at which long-term consequences may be expected

Type of SE	Operational dimension 1 Time (t_1), when a seizure is likely to be prolonged leading to continuous seizure activity	Operational dimension 2 Time (t_2), when a seizure may cause long term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)
Tonic–clonic SE	5 min	30 min
Focal SE with impaired consciousness	10 min	>60 min
Absence status epilepticus	10–15 min[a]	Unknown

[a]Evidence for the time frame is currently limited and future data may lead to modifications.

Figure 4: From "A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus" - Trinka et al. 2015

For research purposes in epidemiology, status epilepticus is usually defined as “a continuous seizure lasting at least 30 min or intermittent seizures without full return to baseline occurring over the course of at least 30 min” (18).

1.1.5 DIFFERENTIAL DIAGNOSIS

Multiple nonepileptic paroxysmal events can mimic seizures.

Common seizure mimics in adults include (19):

- **Transient ischemic attacks (TIA)**: "sudden onset of focal neurologic symptoms that resolve completely within 24 hours, usually within 30-60 minutes". The semiology of the event can guide in the differential diagnosis between seizures and TIA: seizures more commonly present with positive symptoms due to an excess of neuronal discharge (e.g. flashing lights, pain, paresthesia, motor features), while signs and symptoms in TIA typically reflect loss of function (e.g. paresis, aphasia) (19).
- **Vasovagal syncope**: "sudden loss of consciousness typically triggered by prolonged standing, dehydration, change in posture or emotional factors". This event can be confused with a seizure because the patient experiences a loss of muscular tone, which may be followed by brief myoclonic jerks or tonic posturing. Prodromal and postictal symptoms can indicate the vasovagal nature of the event and distinguish it from a seizure: patients usually experience typical prodromal symptoms, such as lightheadedness, sweating, blurred vision, ringing in the ears, pallor, and they rapidly regain awareness after the syncope, even though lightheadedness may remain for a brief period (19).
- **Cardiac syncope – long QT**: sudden loss of consciousness often triggered by fear, physical exercise, surprise, and immersion in water. Signs can include pallor, atonia, or tonic posturing, leading to misdiagnose this event as a seizure. Electrocardiogram (ECG) can help in discriminating between the two (19).
- **Migraine with aura**: prodromal symptoms (commonly visual, e.g. a scintillating scotoma) followed by a migraine headache. Seizures can manifest with visual symptoms as well, so these two events can be confused (19).
- **Psychogenic nonepileptic spells**: "paroxysmal psychogenic events that can consist in unresponsive periods without motor phenomena or motor phenomena with bizarre, irregular jerking and thrashing". They differ from seizure because they are often prolonged >15-30 minutes and followed by a minimal postictal phase. EEG is useful in distinguish these psychogenic events from real seizures (19).
- **Narcolepsy**: disease characterized by cataplexy (loss of tone in response to strong emotion), excessive daytime sleepiness, hypnagogic hallucinations, and sleep paralysis (19).

- **Tics**: “involuntary, sudden, repetitive, nonrhythmic, simple or complex movements or vocalizations, that often occur multiple times per day and last only a few seconds”. As opposed to seizure, they are interruptible and can be suppressed (19).
- **REM sleep disorders**: “abnormal motor activity typically in the later third of sleep, when the individual acts out their dreams”. The events are not as stereotypical as seizures, and the patient can recall them (19).

The differentiation of a seizure from a nonepileptic event is sometimes difficult, especially in the initial diagnostic workup due to lack of specificity in the clinical description and the absence of other informative data. Careful follow-up is recommended in order to confirm the diagnosis before initiation of antiseizure medication (19).

1.2 FIRST SEIZURE EVENT

1.2.1 DIAGNOSTIC WORKUP

When evaluating a patient who had a possible first seizure event (FSE), the physician must assess whether the episode is an actual seizure or one of its common mimics (e.g. syncope, TIA, PNES) and, if it is a seizure, whether it is an acute symptomatic seizure or an unprovoked seizure.

In order to do so, the first and most important step is a careful **clinical history**, taken from both the patient and eventual witnesses.

The patient and the observers should be asked to describe the event from its onset, including (19):

- Any prodromal or postictal symptoms (e.g. confusion, sleepiness, focal weakness, or language difficulties)
- What the patient was doing at the onset
- Possible triggers, intercurrent illnesses, medications. A special relevance must be given to any condition that could provoke an acute symptomatic seizure (e.g. chronic diseases that could lead to metabolic disturbances, such as diabetes or kidney diseases), use or abrupt cessation of any prescription medication (e.g. benzodiazepines) or drug of abuse, including alcohol.
- Motor findings (e.g. abnormal limp, stiffness), abnormal movements (e.g. rhythmic clonic movements, irregular shaking)
- Response to voice or touch during the event
- Any previous similar episode. Given that several studies have shown that a significant amount of patients presenting with an alleged first, unprovoked seizure have actually experienced prior seizures, typically with less intense symptoms (e.g. absence, myoclonic seizures, or focal seizures) patients and their families should also be questioned about any previous episode of unresponsive staring, isolated quick body jerks, and signs of nocturnal seizures, such as unexplained tongue biting or incontinence.

Subjective descriptions by patients and witnesses can be limited in detail, inaccurate, or ambiguous. In these cases, smartphone videography can be a useful adjunctive tool in the diagnosis of seizure-like events. Modern smartphones have become ubiquitous, they are portable and allow to instantly

share media files, so they have an increasingly important role in epilepsy diagnosis. A prospective study demonstrated 94% diagnostic concordance between expert-reviewed smartphone and video-EEG footage of events for the same affected individuals (20,21). Nevertheless, this aspect is very important in the epilepsy diagnostic work-up while it is very unlikely used in the first seizure event one.

Physical examination is another important element of the evaluation, if done immediately after the seizure it may show evidence of a previous convulsive activity (e.g. signs of incontinence, lateral tongue bites) or a Todd paralysis that can disclose a focal seizure onset. Moreover, since seizures can cause the patients to fall, bruises or other traumatic injuries can be observed. The physical examination should also include the assessment of vital signs and other eventual clinical findings (19).

Research about first seizure-related accidents and injuries is lacking, but existing data may provide some relevant observations (22). A retrospective study from Kirby et al. in 1995 reviewed injuries and deaths associated with all-cause seizure presentations across 4 EDs over a 1 year period. Injuries or deaths occurred in 15% of the seizures, but most of them were minor, involving cranial soft tissue contusions or lacerations, and required little or no treatment (22). In 2004, Lawn et al. (23) studied an established epilepsy population and found seizure-related injuries in 16% of the patients. Most injuries involved cranial soft tissue contusions or lacerations (79%) and the majority (82%) of seizure-related injuries occurred during generalized convulsive seizures. In 2017, Pellinen et al. studied a new-onset focal epilepsy cohort and found that both subtle seizure semiology (including motor arrest) and disruptive semiology (including convulsive seizures) are associated with accidents and injuries (22). More studies of first seizure-related accidents and injuries are needed to better understand the consequences of these events.

In case of acute symptomatic seizures, clinical history and physical examination often provide hints to the underlying cause, such as fever, abnormal vital signs, or neurologic findings consistent with the patient's brain injury. Moreover, seizures are usually focal, and seizure symptomatology reflects the location of the acute brain process (19).

Instrumental and laboratory tests that can be used to further evaluate the patient, in order to better distinguish epileptic seizures from non-epileptic events and, after confirming the epileptic nature, investigate the seizure type and etiology.

Such tests include:

- **Electroencephalogram (EEG)**: the Scottish Intercollegiate Guidelines Network (SIGN) and the National Institute for Health and Care Excellence (NICE) concur that a routine EEG should be conducted as soon as possible after a suspected FSE. (6) The diagnostic efficacy appears highest if the EEG is performed in the first 24 hours after the seizure, but if the patient fully recovers to neurologic baseline and is otherwise well, the EEG can be delayed to the next days, on an outpatient basis (19). An EEG has to be always acquired as soon as possible whenever there is not a full recovery, in order to rule out a nonconvulsive status epilepticus.

The EEG assists with determination of (19,24,25):

- Differential diagnosis between seizure and nonepileptic seizure-like events, therefore confirming or excluding a diagnosis.
- Seizure type and epilepsy type: focal epilepsy is suggested if the EEG shows focal epileptiform discharges or focal slowing, while generalized spike-and-wave discharges would suggest generalized epilepsy.
- Epilepsy syndrome: for those epilepsy syndromes that have a unique EEG signature.
- Choice of further investigations: for instance, in most cases, focal epileptiform discharges and/or focal slowing may suggest the presence of an underlying lesion thus a neuroimaging examination should be performed as soon as possible.
- Prognosis and risk for seizure recurrence.
- Clinical management (medications initiations, dose change or discontinuation)
- Discharge from the ED or hospital wards, and the diagnosis at discharge.

An abnormal EEG does not equate to epilepsy, because approximately 3% of people without epilepsy may show epileptiform discharges, so the interpretation must be done in the context of the clinical history. The routine EEG may include activation parameters such as hyperventilation and photic stimulation (19).

The 2022 NICE guidelines (26) (last updated on 30/01/2025) cite as follows: if an EEG is requested after a first seizure, perform it as soon as possible (ideally within 72 hours after the seizure). If agreed with the patients and his family or carers, include provoking manoeuvres (such as hyperventilation and photic stimulation) during routine EEG to assess a suspected first seizure. If routine EEG is normal, consider a sleep-deprived EEG if agreed with the person, and their family or

carers. If routine and sleep-deprived EEG results are normal and diagnostic uncertainty persists, consider ambulatory holter-EEG (for up to 48 hours).

- **NEUROIMAGING**: neuroimaging can identify underlying structural causes of epilepsy, so it can help with the determination of the epilepsy etiology, type and prognosis (21). Every patient presenting with a FSE must undergo a neurodiagnostic exam (especially patients with associated focal neurological deficits, fever, persistent headache, cognitive changes, or a recent history of head trauma) which is more commonly done by computed tomography (CT), given its greater accessibility if compared to magnetic resonance imaging (MRI). However, imaging with MRI is preferable to CT, because of its higher sensitivity for detecting many small cortical epileptogenic lesions (e.g. focal cortical dysplasia, mesial temporal sclerosis, gliomas, cavernomas) which significantly increases the diagnostic yield (19,21). The superiority of MRI over CT in the FSE context has been shown in several studies (27) so the ILAE has recommended that all patients with epilepsy should undergo MRI, except those with a clearly defined, drug-responsive idiopathic generalized epilepsy syndrome or self-limited focal epilepsy of childhood. In patients who have returned to their neurologic baseline, who have no focal neurologic deficits and for whom no other concern is present, MRI can be postponed to the following days, on an outpatient basis (19).

  If a lesion is found on MRI, it is not necessarily the cause of the seizure, but such finding must be associated with clinical and electrophysiological data in order to established whether it is indeed the underlying cause of the seizure (19).

- **ROUTINE BLOOD AND URINE STUDIES**: routine laboratory screening (including complete blood cell count, glucose, electrolytes, blood urea nitrogen, and creatinine) of patients with new-onset seizures is commonly done in order to exclude provoked seizures.

  Postictal blood test can also include creatine phosphokinase (CPK) levels, which might be useful in the differential diagnosis of epileptic seizures and non-epileptic events (28,29). A review about this topic found conflicting information about the utility of this test as an indicator of a preceding epileptic seizure: despite high specificity (85-100%) the diagnostic yield is limited by a low sensitivity (14.6–87.5%) (28).

- **TOXICOLOGY**: toxicology screening is not done in all cases, but it's considered if the clinical findings are suggestive of a possible substance abuse or toxin exposure (19).

- **LUMBAR PUNCTURE**: lumbar puncture should be considered if the clinical profile is suggestive of a possible meningitis, encephalitis, or subarachnoid hemorrhage (e.g. unexplained fever, nuchal rigidity or other meningeal signs) (19).

- **AUTOIMMUNE TESTING**: serum and cerebro-spinal fluid (CSF) autoimmune studies should only be considered in the presence of suggestive clinical features of an autoimmune etiology, such as: characteristic onset (frequent, drug-resistant seizures), specific seizure types (e.g. faciobrachial dystonic seizures), and other associated features (e.g. cognitive and/or behavioral dysfunction, dysautonomia, movement disorders such as orofacial dyskinesias) (19).

- **GENETIC TESTING**: genetic testing is not recommended for most patients with new-onset epilepsy. It should only be considered if a genetic etiology is suspected. This might be the case with patients with findings on neuroimaging suggestive of a genetic structural cause (e.g. tuberous sclerosis complex) or those with imaging or laboratory findings suggestive of a genetic-metabolic disease (e.g. mitochondrial disorders, glucose transporter deficiency) or in the presence of a positive family history of epilepsy (19).

After confirmation of the epileptic nature of the event, the ILAE criteria for a diagnosis of epilepsy must be considered. If the patient meets such criteria, then the diagnosis can be made, and if possible, the type of epilepsy should be assessed, according to the ILAE classification of epilepsies.

If the seizure proves to be acute symptomatic, treatment of the underlying cause should be organized (e.g. i.v. thrombolysis and mechanical thrombectomy for ischemic stroke, acyclovir for herpes encephalitis, anticoagulation for cerebral venous thrombosis, etc.) (6).

COUNSELLING ON LIFESTYLE AND SAFETY

Any patient presenting with a first unprovoked seizure or receiving a new epilepsy diagnosis should be given lifestyle advice, covering several aspects:

- **Safety at home and work**: patients with new-onset unprovoked seizures need to be safe around water (showers are generally safe, but being in a bathtub or swimming alone is not recommended). Other potential restrictions may be required based on their occupation (first seizures limit potentially dangerous workplace activities such as operating heavy machinery) or participation in certain sports (19,22).
- **Driving restrictions**: people who have had seizure with impaired awareness are subject to driving restrictions, which varies depending on the place of residence. Many countries have a minimum 6-month driving restriction after a first seizure, but restrictions might be far stricter for operators of commercial vehicles and public transport (19,22).
- **Factors that may reduce seizure threshold in people with unprovoked seizures**, such as sleep deprivation, alcohol and recreational drugs. Sleep deprivation and fever are common triggers for many epilepsy types, so it's important for patients to regulate their sleep hygiene and to treat fever. Certain epilepsies are associated with other specific triggers, such as flashing lights, eating or reading (19).
- **What to do if further seizures occur**: physicians should provide patients and their families information about when and how to administer therapy and other aspects of seizure first aid, such as the need to roll the patient on their side, the danger in placing hands or objects in the patient's mouth during the seizure, and when to call emergency medical services (19).
- **Potential risks of recurrent seizures**, including status epilepticus, aspiration, and sudden unexpected death in epilepsy (SUDEP) that are extremely variable in relation to epilepsy type and seizures frequency (19).

ADDED VALUTE OF AND ADVANCED DIAGNOSTIC WORKUP

In 2016, Fisch et al. (30) compared two different managing protocol after a FSE:

- **Standard patient care (SPC)**: neurology consultation in the ED, routine EEG and CT scan. No follow up was scheduled, but the patient was advised to make an appointment with his general practitioner or with a neurologist of his choice. MRI and/or long-term monitoring EEG (LTM-EEG) were recommended in the discharge report whenever they were considered to be necessary for the diagnosis.
- **Early comprehensive patient care (ECPC)**: consultation by an epileptologist in the ED, routine EEG and CT scan. If CT and routine EEG were not informative, MRI and LTM-EEG were scheduled within 72 h. The protocol ended with scheduling three follow-up consultations (3 weeks, 3 months, 12 months).

The ECPC protocol proved to be better than SPC in terms of diagnostic accuracy (more patients were correctly diagnosed after the FSE), follow-up adherence, and seizure recurrence (the seizure relapse rate did not differ between the two groups, but the delay between the first event and the next ED re-admission was significantly longer in the ECPC group, which suggests that these patients better understood their condition and the importance of treatment compliance and lifestyle adjustments, e.g. avoiding precipitating factors).

In 2023, they took the study a step further (10) and investigated the sensibility and specificity of routine EEG, LTM-EEG, brain CT, and brain MRI and the added value of advanced workup (MRI and LTM-EEG) to diagnose new onset epilepsy. LTM-EEG proved to have higher sensitivity than routine EEG (54.39% vs. 25.5%) and MRI had a higher sensitivity than CT (67.98% vs. 54.72%). LTM-EEG resulted in an additional yield of 46% compared to routine EEG, and brain MRI showed epileptogenic lesions in an additional 32% compared to brain CT. In patients with all four examinations, advanced workup provided an overall additional yield of 50% compared to routine workup. These results prove that starting an advanced workup already in the ED has a significant added value for the diagnosis of new onset epilepsy. De Stefano et al. recognize that many hospitals and EDs don’t have access to LTM-EEG or MRI in a short period of time, but based on their findings, identifying resources to make such diagnostic examinations available in the acute setting should be strongly encouraged.

OPPORTUNITY FOR ADVANCED WORKUP: FIRST SEIZURE CLINICS

In the light of their findings, De Stefano et al. (27) encourage the creation of "First Seizure Units", allowing brief hospitalizations, or at least first-seizure networks (i.e. dedicated neurophysiologists, neurologists, neuroradiologists, etc. working in collaboration on an outpatient level), active upon patient admission to the ED, similar to stroke units and centers, in order to avoid unnecessary delay in diagnosis.

Several countries (such as USA, UK, Canada, and Australia) have now established First Seizure Clinics (FSC). In these clinics patients who have experienced a first seizure are promptly seen by an experienced epileptologist, and they can undergo an appropriate diagnostic workup, including EEG and neuroimaging, hoping that this early expert assessment will more appropriately guide treatment. Diagnosis of the epileptic or nonepileptic event is made at the first appointment or during follow up, depending on investigation results. After diagnosis and, if appropriate, prescription of antiseizure medications, patients are referred to their general practitioner or to a neurologist (31–33).

In 2024, Li et al. (31) conducted a study aiming to investigate the association between FSC attendance and subsequent health care utilization (measured by ED presentations and hospitalization), morbidity, and mortality. FSC attendance, particularly within a short time after the seizure event (< 2 weeks, as recommended by international guidelines) was associated with reduced subsequent all-cause ED presentations and all-cause hospital admission. Conversely, attendance was also associated with an increased seizure-related ED presentation and hospitalization. Their suggested explanation for this finding is that attendees had more opportunity for an epilepsy diagnosis to be made and recorded - and therefore noted at subsequent epilepsy-related presentations - whereas nonattendees' subsequent presentations may have been more likely to receive non–epilepsy-related codes, such as syncope, transient ischemic attack, or fall.

Their findings suggest that early epileptologist care for patients with suspected new-onset epilepsy can influence the course their prognosis, and support the potential role for FSCs in delivering such care.

1.2.2 RISK OF RECURRENCE AFTER A FIRST SEIZURE AND ITS ROLE IN DECIDING WHETER TO START TREATMENT

The decision to initiate anti-seizure medications (ASM) treatment is relatively straightforward in patients who experience two or more unprovoked seizures, and hence have a diagnosis of epilepsy. The decision to treat a patient after a single unprovoked seizure is more complex: it must consider the recurrence risk for further seizures, the seizure severity, the potential impact of further seizures on the individual patient, and balance this against potential adverse effects (AEs) of medication (33,34).

Risk of recurrence after a FSE and factors associated with recurrence have been the focus of extensive research for many years. Classic epidemiological studies regarding this topic are now more than twenty years old and predate the widespread use of MRI, but they still have relevance today, and were crucial in designing more recent guidelines (32).

A landmark study about this theme was conducted by Hauser et al. (35) going back to 1982. They studied ~ 250 patients of all ages presenting with a first unprovoked seizure, following them for over 36 months in order to determine the risk of subsequent seizures. The cumulative risks of recurrence were 16% at 12 months, 21% at 24 months, and 27% at 36 months after the FSE. The cumulative risk of recurrence was higher (34% within the first 20 months, and no more after that time) in patients with a history of remote symptomatic seizure. Patients without a history of a prior neurologic insult, which were classified as idiopathic, had a cumulative recurrence risk of only 17% by 20 months and 26% by 36 months. Among idiopathic cases, a sibling with epilepsy and a generalized spike and wave EEG increased risk for recurrence, while age at first seizure, sex, seizure type, onset with status epilepticus, or abnormality on neurologic examination did not affect the risk of recurrence.

Hauser et al. extended this study to longer follow-up (36) confirming a higher risk of recurrence in patients whose FSE was a remote symptomatic seizure (2.5-fold increased risk). Overall, risk factors for seizure recurrence in patients with idiopathic seizures were: a sibling with epilepsy, generalized spike-wave discharges on EEG, and a history of acute symptomatic seizures. Treatment with ASMs was not associated with a decrease in recurrence risks, but their study was admittedly limited: “the data available were inadequate to determine whether the results were real or artifacts attributable to irregular medication use, inadequate or inappropriate ASM, or ASM withdrawal” (36).

The role of ASM treatment in decreasing the recurrence risk was then studied by two high-quality randomized trials: a 1993 multicenter study from Italy, FIR.S.T. (First Seizure Trial group) by Musicco et al, (37) and the 2005 European-wide Multicenter Epilepsy and Single Seizure study (MESS) by Marson et al. (9)

In the FIR.S.T. trial, patients with a first unprovoked primarily or secondarily generalized seizure were randomized to immediate treatment or to treatment only after another seizure. Compared to the deferred (untreated) group, the risk of recurrence in the immediate treatment group was substantially lower: at 3, 6, 12, and 24 months after randomization, the cumulative risk in the immediate treatment group was 7%, 8%, 17%, and 25% versus 18%, 28%, 41%, and 51% in the deferred group, suggesting that treatment does lead to significant reduction of risk in the first 2 years after the FSE. However, patients treated after the first seizure and those treated after seizure relapse had the same time-dependent probability of achieving 1 and 2 seizure-free years, suggesting that the probability of long-term remission is not influenced by treatment of the first seizure (18,32,37).

Some variables were found to be significant predictors of relapse in the first 2 years (age, acute treatment of the seizure with benzodiazepines, remote etiologic factors, and EEG abnormalities) but none of these was significantly associated with the probability of having 1 or 2 years of seizure control (37).

The European Multicenter Epilepsy and Single Seizure Study (MESS) was an unmasked multicenter randomized study of immediate versus deferred ASM treatment in 1847 patients with single seizures or newly diagnosed epilepsy. The cumulative risk of recurrence in the immediate treatment group was 18%, 32%, 42%, and 46% at 6 months, 2, 5, and 8 years after randomization versus 26%, 39%, 51%, and 52% in the deferred treatment group. This study showed that although immediate versus delayed treatment with the commonly used antiseizure drugs (carbamazepine and valproic acid) reduced the risk of further seizures in the first 2 years after the FSE (it increased the time to first seizure, second seizure, and first tonic-clonic seizure, as well as the time to achieve a 2-year remission of seizures), there was no evidence of an effect on long-term remission rates: the proportion of patients in each group who were seizure free between 3 and 5 years after randomization was almost identical (76% vs 77%), indicating that immediate ASM treatment did not influence the long term prognosis of epilepsy (9,18,32).

Both of the randomized trials demonstrate a pattern seen in most of the long-term observational studies of first seizures: the risk of recurrence is highest during the period immediately after the FSE (18).

In 2006, Kim et al. (34) further analyzed the MESS patient cohort, in order to assess the role of patient characteristics and treatment in the prediction of seizure recurrence. Their study resulted in the identification of 3 potentially important prognostic factors: number of seizures of all types at presentation, presence of a neurological disorder, and an abnormal EEG. They calculated a prognostic index based on the presence of these factors, and developed a prognostic model for seizure recurrence based on such index.

- **Low risk group** (prognostic index score = 0): it includes patients who had a single seizure, a normal EEG, and no neurological disorder.
- **Medium risk group** (prognostic index score = 1): patients who had two to three seizures, a normal EEG, and no neurological abnormality, or patients with a single seizure and an abnormal EEG or a neurological disorder.
- **High risk group** (prognostic index score 2-4): those with a single seizure, abnormal EEG, and a neurological disorder; those with two to three seizures, an abnormal EEG, or neurological disorder; and any individual with four or more seizures.

Their study shows that there is little benefit to immediate treatment in patients at low risk of seizure recurrence (an individual in the low-risk category has around a 30% chance of seizure recurrence by 3 years and 35% by 5 years under both treatment policies) but potentially useful for those at medium and high risk (an individual in the high-risk category has around a 50% chance of seizure recurrence within both 3 and 5 years if antiepileptic drug treatment is started immediately, compared with around a 65% chance of seizures within 3 years and 70% within 5 years if treatment is delayed).

In 2015, the American Academy of Neurology (AAN) published an evidence-based guideline for the management of an unprovoked first seizure in adults (38). They conducted an exhaustive review, including the studies that have been discussed above and many others, and provided the following conclusions:

- "Adults with an unprovoked first seizure should be informed that their seizure recurrence risk is greatest early within the first 2 years (21%–45%)". Although cumulative risk of seizure recurrence increases over time, most recurrences happen within the first year. Such risk appears to be lower for patients treated with ASMs, and higher in presence of some other factors (listed below).
- "The most consistently noted factors associated with an increased risk of seizure recurrence following an unprovoked first seizure include: a prior brain lesion or insult causing the seizure, an EEG with epileptiform abnormalities (characterized by spikes or sharp waves), a significant brain-imaging abnormality (judged the cause of the seizure) and a nocturnal seizure. In contrast, clinical variables that were not consistently associated with an increased seizure recurrence risk after an unprovoked first seizure in adults include: age, sex, family history of seizures, seizure type, and presentation with status epilepticus or multiple (2 or more) seizures within 24 hours with recovery between them."
- "Immediate therapy with an ASM after an unprovoked first seizure in adults significantly reduces seizure risk in the short term (which we define as within 2 years) but is unlikely to improve the chance of attaining sustained seizure remission over the longer term (> 3 years)"
- "Patients should be advised that risk of ASM adverse events may range from 7% to 31%, but these AEs are likely predominantly mild and reversible.
- "Clinicians' recommendations whether to initiate immediate ASM treatment after a first seizure should be based on individualized assessments that weigh the risk of recurrence against the AEs of ASM therapy, and consider educated patient preferences."

Similar conclusions were reached by reviews by Rizvi et al. In 2016 (33) and by Jiménez-Villegas et al. in 2021 (39) :

- Factors that appear to be associated with a high risk of recurrence include: remote symptomatic etiology, epileptiform activity on EEG, potentially epileptogenic lesions on brain imaging, abnormal neurological exam, and nocturnal seizures.
- ASM treatment reduces the seizure recurrence risk in the short term, but not in the long term (so it does not prevent progression to epilepsy). At present, there is no general rule for studying and treating people with a first epileptic seizure, the decision must be made

considering individual's patient's clinical, demographic, and socioeconomic characteristics (33).

A recent research about this topic was published by Ménétre et al. (40) in 2023. They conducted a retrospective study aiming to assess whether immediate ASM therapy (i.e. within 48 h) was associated with better prognosis up to 5 years after the index event. Immediate therapy was associated with a significantly higher percentage of seizure-free patients compared with treatment at a later time point, proving once again that delaying treatment until after the second or further seizure leads to a lower chance of subsequent seizure control.

The 2022 NICE guidelines (26), which were last updated on 30/01/2025, cite as follows:

"Start treatment with an antiseizure medication once the diagnosis of epilepsy is confirmed."

"Consider starting treatment after a first unprovoked seizure if any of the following apply:

- An examination identifies signs of neurological deficit
- The EEG shows unequivocal epileptic activity
- Brain imaging shows a structural abnormality
- After a discussion of the risk of further seizures, the person or their family or carers consider the risk unacceptable".

STATUS EPILEPTICUS AND SEIZURE CLUSTERS

The 2021 review by Jiménez-Villegas et al. in 2021 addresses the issue about whether presentation with status epilepticus or seizure clusters is associated with a high risk of recurrence: "it remained unclear if the first event as status epilepticus implied a major risk of recurrence. Many studies excluded patients with status epilepticus, so the evidence in the subject is scarce. The majority of available studies did not show any additional risk of recurrence in this group of patients. Some studies in teenagers found an elevated risk of recurrence in patients with a first status epilepticus or those with multiple seizures on the same day. It is important to recognize that status epilepticus is considered a life-threatening event and thus it is probably treated more often with ongoing ASMs (39)."

TREATMENT AFTER ACUTE SYMPTOMATIC FSE

Theoretically, acute symptomatic seizures should not recur once the precipitating factor is resolved, so there might be uncertainty about whether to initiate a treatment with ASMs (41).

However, patients with acute symptomatic seizures can develop further seizures soon after the first event, so it is reasonable to treat them with ASMs during the acute phase of the underlying disease, or as long as the precipitating factor is present (6).

As explained by Maurtiz et al. (6) the risk of subsequent seizures after an acute symptomatic seizure is particularly high for some seizure etiologies, such as stroke, traumatic brain injury and CNS infection. These higher risks are probably related to the destructive nature of these three brain pathologies, and similar recurrence risks would not be expected following acute symptomatic seizures from causes such as hyponatremia. For this reason, etiology might be a criterion that can guide the decision about whether to start a secondary prophylaxis with ASMs.

Mauritz et al. also addresses the duration of such treatment: "Data on how long to treat patients with acute symptomatic seizures with ASMs is largely lacking. The duration of treatment with ASMs needs probably to be individualized for every patient and will depend on factors such as the underlying etiology (e.g. fully resolved hyponatremia versus an ongoing autoimmune encephalitis), the risk of further seizures, the severity of the acute symptomatic seizure (e.g. status epilepticus, seizure-related injuries), the overall clinical situation (i.e. is the patient awake and doing well or is the patient still critically ill/ comatose in intensive care? Are there severe comorbidities?), and patient preference."

In 2022, Punia et al. (41) conducted an international, cross-sectional survey of health care providers who manage patients with acute symptomatic seizures in order to understand the current management: nearly a quarter of respondents prescribe them for longer than 6 months, and one-third each prescribe them for 3–6 months and less than 3 months.

In 2024, Yardi et al. (7) proposed a practical system to determine treatment duration of acute symptomatic seizures (ASyS) based on hyperexcitability and the subsequent risk of epilepsy associated to the underlying cause. They divide AsYS into the following groups:

1) **ASyS with acute hyperexcitability**: caused by medication, alcohol, drugs of abuse, electrolyte disturbances, eclampsia. The subsequent risk of epilepsy is very low, so ASM may not be required.
2) **ASyS with subacute hyperexcitability**: caused by Posterior reversible encephalopathy syndrome, sepsis, and some autoimmune pathologies. The subsequent risk of epilepsy is low

in these patients, so treatment with ASM is demanded only if seizures are complex to control or recur, and should be limited to the duration of the hospitalization.

3) **ASyS with prolonged hyperexcitability**: caused by cerebrovascular causes, traumatic brain injury, CNS infections, and some autoimmune pathologies. The risk for recurrence and development of epilepsy is higher in these patients due to lack of reversibility of the underlying pathologies, so they may need treatment for a longer duration, which may range up to 3–6 months.

1.2.3 IS THE FIRST SEIZURE ACTUALLY THE FIRST SEIZURE?

Several studies have shown that a significant amount of patients presenting with an alleged first, unprovoked seizure have actually experienced prior seizures (19,21,32,33,42–44).

Typically, patients tend to ignore seizures without motor manifestations or with less intense symptoms (e.g. absence, myoclonic seizures, or focal seizures), and it is only the first generalized tonic-clonic seizure that brings them to seek medical attention, resulting in a significant diagnostic delay. Moreover, such episodes may be brought to medical attention but not recognized as seizures.

To avoid missing information about possible past seizures, patients and their families should be questioned not only about prior similar episodes, but also about any episodes of unresponsive staring, isolated quick body jerks, signs of nocturnal seizures (such as unexplained tongue biting or incontinence) or subtle dyscognitive features (19,32,33).

In 2020, Parviainen et al. (42) conducted a study aiming to assess the diagnostic delay and the impact of diagnostic delay on seizure outcome in a cohort of newly diagnosed patients with focal epilepsy. They analyzed the time from first seizure to diagnosis, the number of seizures before diagnosis, and the response to treatment at five years. No statistically significant association was observed between diagnostic delay and treatment response, however, a large number of seizures before diagnosis was associated with poor response to treatment.

Several studies showed that multiple seizure before treatment initiation is a risk factor for seizure recurrence (9,40,42) so this tendency to ignore subtle signs and symptoms must be fought, and information about this issue must be provided to both the general population and not-neurologist physicians.

2. PURPOSE OF THE STUDY

The present study pursued the following aims:

1) To define the demographic and clinical characteristics of a cohort of adult patients evaluated at the Emergency Department of Baggiovara Civil Hospital (Ospedale Civile Baggiovara, OCB) for a first epileptic seizure during the year 2023.

2) To assess the short-term (< 48 h) and long term (follow-up up to 21 months) risk of seizure recurrence and the risk of developing epilepsy after the FSE, and to evaluate its relation with demographic and clinical characteristics of the FSE.

3. MATERIALS AND METHODS

3.1 INCLUSION AND EXCLUSION CRITERIA

All adult patients (aged >14 years) who presented to the Emergency Department (ED) of Baggiovara Civil Hospital with a first epileptic seizure between January 1 and December 31, 2023, were included in the study. Patients younger than 14 years are not admitted in this ED but to the pediatric ED of the Modena University Hospital, thus they were excluded.

Patients with a pre-existing diagnosis of epilepsy who presented with a recurrent seizure were excluded, as were those whose clinical presentation was ambiguous and could not be definitively classified as an epileptic seizure and those diagnosed with a seizure mimic at the end of the diagnostic process.

3.2 STUDY DESIGN

This is a retrospective cohort study. Data about the FSE were retrospectively obtained by reviewing the hospital information system (SIO) and the emergency department software (Emergency). Data about the follow up were prospectively collected by using the same softwares.

3.3 ANALYZED VARIABLES

The following demographic and clinical variables were collected:

- **Demographics**: sex (M/F) and age.
- **Clinical presentation**:
    - Seizure pattern: single seizure / seizure cluster (defined as ≥ 2 seizures within 24 hours) / status epilepticus (as described by the ILAE clinical definition)
    - Seizure type: unprovoked / acute symptomatic.
    - Seizure semiology: focal / generalized; motor / non-motor.

- Seizure-related injuries (yes/no), including injury type:
  - Head trauma with cranium fractures
  - Head trauma without cranium fractures
  - Uncomplicated thoracic trauma
  - Complicated thoracic trauma (with fractures, contusions, pneumothorax etc.)
  - Uncomplicated abdominal trauma
  - Complicated abdominal trauma (with fractures, contusions etc.)
  - Complicated limb trauma (with fractures, dislocations etc.). Uncomplicated limb trauma is very common with seizures, especially when the patient loses consciousness and falls to the ground, and does not indicate that the event is more severe than a seizure which is not associated to such trauma, so it was not considered in this study as a possible traumatic complication.
- Cardiorespiratory complications (yes/no).

- **Pre-hospital management**:
  - Administration of antiseizure medications (ASM) (yes/no), including drug type: intramuscular midazolam (MZM IM), intranasal midazolam (MZM IN), intravenous midazolam (MZM IV), intravenous diazepam (DZP IV), intravenous lorazepam (LZP IV), Propofol (PRO), ketamine (KETA).
  - Orotracheal intubation (OTI) prior to hospital arrival (yes/no).
- **In-hospital management in the ED**:
  - Need for OTI (yes/no).
  - ASM administration (yes/no), including type: MZM IM, MZM IN, MZM IV, DZP IV, LZP IV, PRO, KETA.
  - Management of seizure-related injuries: none / conservative treatment / surgical treatment.
  - Neurology consultation (yes/no).
  - EEG: performed (yes/no) and findings: normal / generalized slowing / focal slowing / focal epileptiform activity / generalized epileptiform activity.

- Brain CT scan: performed (yes/no) and findings: normal / space-occupying lesion / acute ischemic or hemorrhagic stroke / post-stroke sequelae / post-traumatic findings / post-surgical findings / congenital or malformative lesions.
- Brain MRI: scheduled (yes/no) and findings: normal / space-occupying lesion.
- Sleep-deprived EEG: scheduled (yes/no) and findings: normal / generalized slowing / focal slowing / focal epileptiform activity / generalized epileptiform activity.
- Laboratory tests: leukocyte count (total and percentage), neutrophil count (total and percentage), creatine phosphokinase (CPK), and C-reactive protein (CRP).
- Body temperature (fever: yes/no). We considered fever to be present if the ED discharge paper mentioned it explicitly or if a body temperature > 37,5 °C was reported.
- Diagnosis of epilepsy if already possible after the FSE according to the ILAE diagnostic criteria (yes/no), including epilepsy type: focal / generalized / unknown.
- Initiation of long-term ASM therapy (yes/no), including drug type.
- Need for observation in the dedicated ED unit (Osservazione Breve Intensiva, OBI)
- Hospital admission status: hospitalization vs. discharge; and department of admission: internal medicine / neurology / neurosurgery / semi-intensive care / postoperative intensive care.
- Occurrence of further seizures during observation in the ED or in the OBI unit (yes/no). These subsequent seizures, occurring in the first 48 h after the FSE, were classified as “early recurrences”.
- Scheduling of a follow-up appointment at the Neurology outpatient clinic (yes/no).

In recognition of the fact that many patients presenting with a presumed first unprovoked seizure may have experienced previous undiagnosed episodes, any self-reported history of prior seizure-like events was also recorded (yes/no).

- **Follow-up (FU)**

  Follow-up data were collected up to May 2025 (ensuring a minimum 1-year follow-up for all patients). The following information was recorded:

  - Time in FU (measured in months)

- Seizure recurrence (yes/no) and time to recurrence (measured in months). Seizures occurring > 48 h after the FSE were classified as “long term recurrences”.
- Diagnosis of epilepsy during FU (yes/no)
- Death (yes/no) and time to death (measured in months).

The following variables were evaluated as potential risk factors:

- **Age and sex:** assessed in order to provide a demographic analysis of the phenomenon. Different age groups may be associated with distinct etiologies, and thus with varying risks of recurrence. A difference in recurrence risk between males and females could suggest a role for hormonal, genetic, or environmental factors influencing seizure recurrence.
- **Structural lesions, epileptiform EEG activity, history of previously unrecognized seizures:** well-established risk factors for epilepsy.
- **Presentation as seizure cluster or status epilepticus:** more severe clinical presentations may reflect a higher epileptic activity and greater neurological instability. Moreover, some studies in the literature have identified these types of presentations as risk factors for increased seizure recurrence rates; however, the evidence is not consistent across studies, as will be discussed later (18,32,35,39).
- **Seizure semiology:** different seizure types may be associated with different etiologies, and thus with varying risks of recurrence (e.g., focal seizures are more likely to be caused by structural brain lesions). Additionally, seizure semiology has been investigated in the literature as a potential predictor of seizure recurrence, as will be discussed later (18,35).
- **Initiation of ASM therapy:** according to scientific literature, early initiation of ASM therapy has been associated with a reduced risk of recurrence (as discussed later) (2,9,32–34,37,40). Conversely, the need for immediate initiation of antiseizure medication may reflect greater clinical severity or a strong suspicion of epilepsy, which could in turn correlate with an increased risk of recurrence.
- **Prior unrecognized seizures:** numerous studies have demonstrated a higher risk of recurrence in patients with a history of prior seizures (9,18,34).
- **Fever:** ever is a known triggering factor or it could be as a sign of an underlying infectious etiology.

- **Laboratory tests:**
    - **White blood cell count and C-Reactive Protein:** markers of systemic inflammation, which may indicate an underlying infectious or autoimmune etiology, and predispose to neuronal instability (45).
    - **CPK:** elevated serum CPK levels may result from prolonged or repeated seizures (motor manifestations during seizures may lead to muscle overuse, causing muscle cell damage and thus elevated CPK levels) (46), potentially indicating more severe clinical presentations.

3.4 STATISTICAL ANALYSIS

Descriptive statistics were reported as mean ± standard deviation or median, range and IQR depending on the variables distribution. Statistical significance for intergroup differences was assessed with Pearson $\chi 2$ test and Fisher exact tests for dichotomous or nominal variables. The Mann-Whitney U test was used for continuous variables when they did not follow a normal distribution (Kolmogorov-Smirnov test). To evaluate time to seizures' recurrence Kaplan-Meier analysis and Univariate Cox Regression analysis were performed.

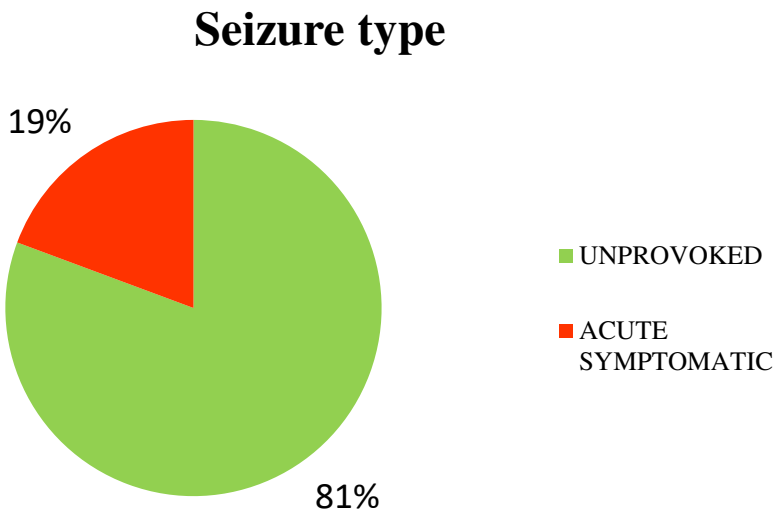
The level of significance was set at $p < 0.05$. The statistical analysis was performed with Statistical Package for Social Science (SPSS-IBM software, version 29).

4. RESULTS

4.1 DESCRIPTIVE ANALYSIS OF THE ENTIRE POPULATION

A total of 150 patients met the inclusion criteria for the study. Of these, 91 (60.7%) were male and 59 (39.3%) were female. The median age was 61 years (min 14, max 92, IQR 42). Unprovoked seizures were found to be markedly more frequent than acute symptomatic seizures (121 patients, 80.7%, vs. 29 patients, 19.3%).

All data are reported in Table 1.



Since the question about whether to make an epilepsy diagnosis after a first seizure applies only to patients with unprovoked seizures, we further analyzed this subgroup in detail.

4.2 DESCRIPTIVE ANALYSIS OF THE POPULATION WITH UNPROVOKED SEIZURES

All data are reported in Table 2.

4.2.1 DEMOGRAPHIC CHARACTERISTICS

The subgroup with unprovoked seizures included 121 patients. Among them, 74 (61.2%) were male and 47 (38.8%) were female. The proportions are comparable to those observed in the whole cohort.

Likewise, median age (63 years), minimum (14 years), and maximum (92 years) ages and IQR (42) showed little to no difference if compared to the overall population of the study.

4.2.2 PRE-HOSPITAL AND IN-HOSPITAL MANAGEMENT OF THE SEIZURE

Pharmacological therapy was administered to interrupt the seizure in 21 cases (17.4%) in the pre-hospital setting, and in 21 cases (17.4%) in the ED.

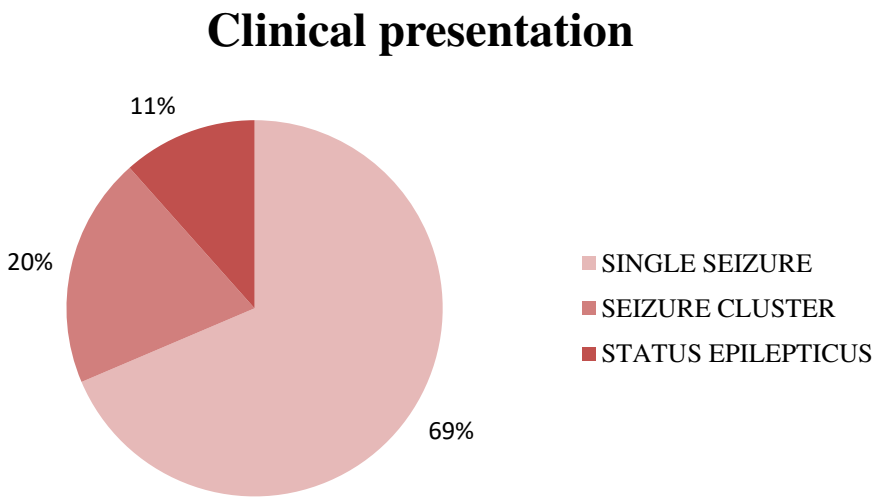
Orotracheal intubation (OTI) was required in only 1 case (0.8%) before hospital arrival and in 2 cases (1.7%) at the hospital.

All patients underwent brain CT scan, nearly all underwent EEG (118 patients, 97.4%) and a neurological consultation (115 patients, 95,0 %).

A total of 56 patients (46.3%) were hospitalized, while the remaining 65 (53.7%) were discharged after the initial diagnostic workup. A total number of 46 patients (38.0%) was admitted for observation in the emergency department unit (OBI) before a final decision regarding whether hospitalization or discharge was the most appropriate.

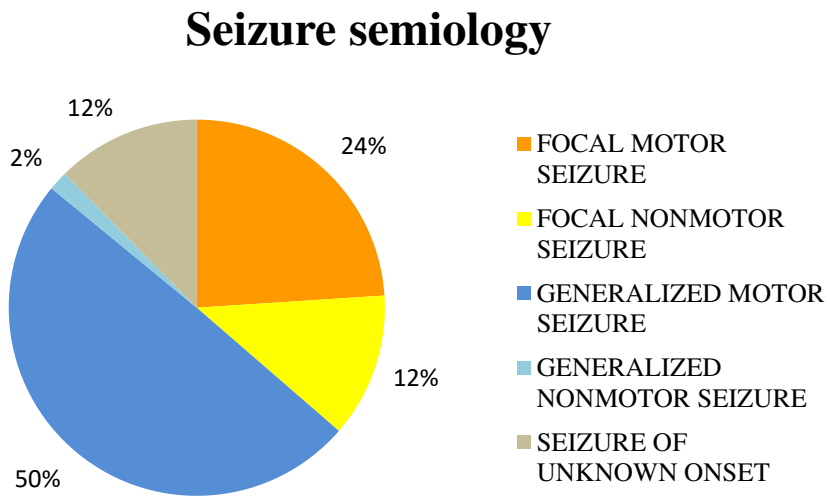
4.2.3 CLINICAL CHARACTERISTICS OF THE FSE

The most common clinical presentation was a single seizure (83 patients, 68.6%). However, in a notable proportion, the FSE occurred as a seizure cluster (24 patients, 19.8%) or as status epilepticus (14 patients, 11.6%).

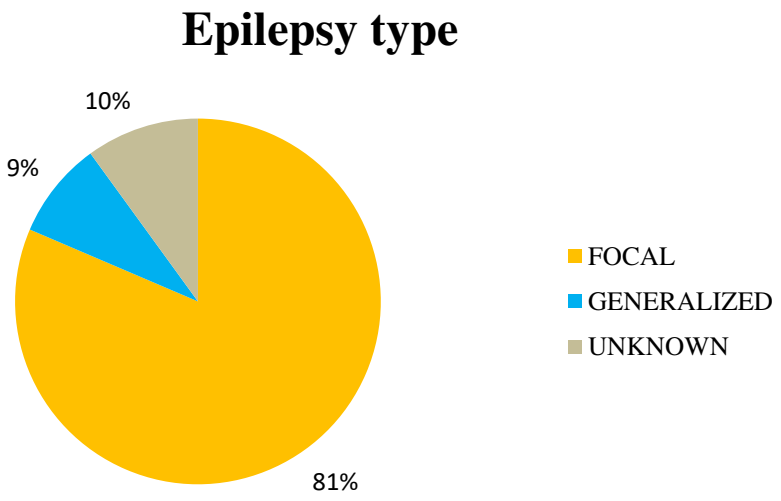


The seizure semiology was distributed as follows:

- Focal motor seizure: 29 cases (24,0 %)
- Focal non-motor seizure: 15 cases (12.4 %)
- Generalized motor seizure: 60 cases (49.6 %)
- Generalized non-motor seizure: 2 cases (1.6 %)
- Seizure of unknown onset: 15 cases (12.4 %)



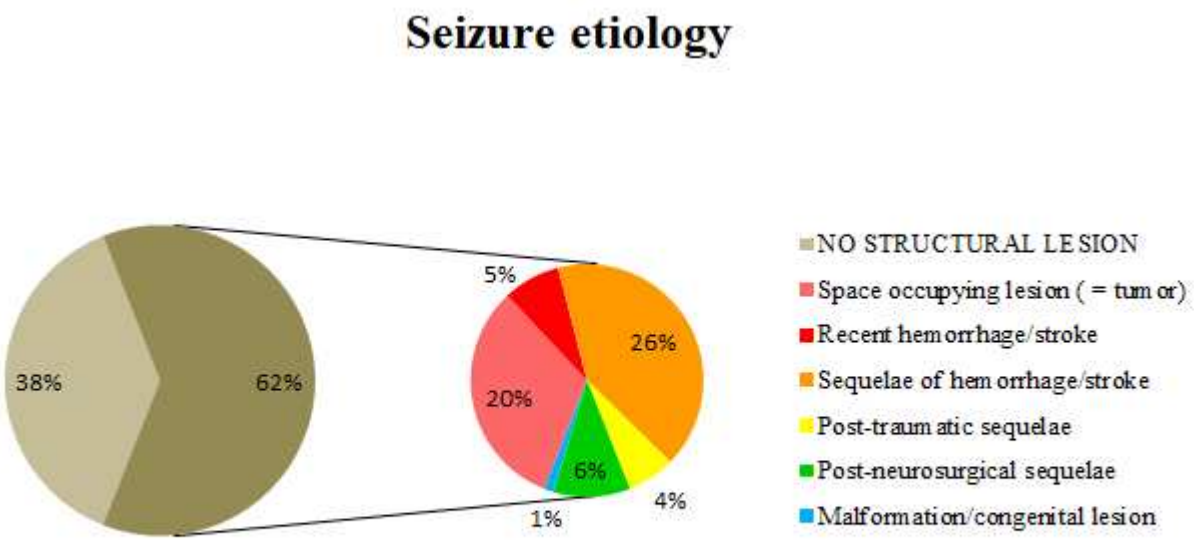
A diagnosis of epilepsy was made after the FSE in over half of the patients (70 individuals, 57.9%). Among these, the great majority (81%) were diagnosed with focal epilepsy, while generalized epilepsy and epilepsy of unknown type accounted for 9% and 10% respectively.



Chronic ASM therapy was initiated in 83 patients (68.6%).

In more than half of the cases (75 patients, 62%), the etiology of the unprovoked seizure was identified in a structural brain lesion. The lesions could be classified into the following categories:

- Space-occupying lesion (= brain tumor): 24 cases (32%)
- Recent hemorrhage/stroke: 6 cases (8%)
- Sequelae of hemorrhage/stroke: 31 cases (41%)
- Post-traumatic sequelae: 5 cases (7%)
- Post-neurosurgical sequelae: 8 cases (11%)
- Malformation/congenital lesion: 1 case (~1%)

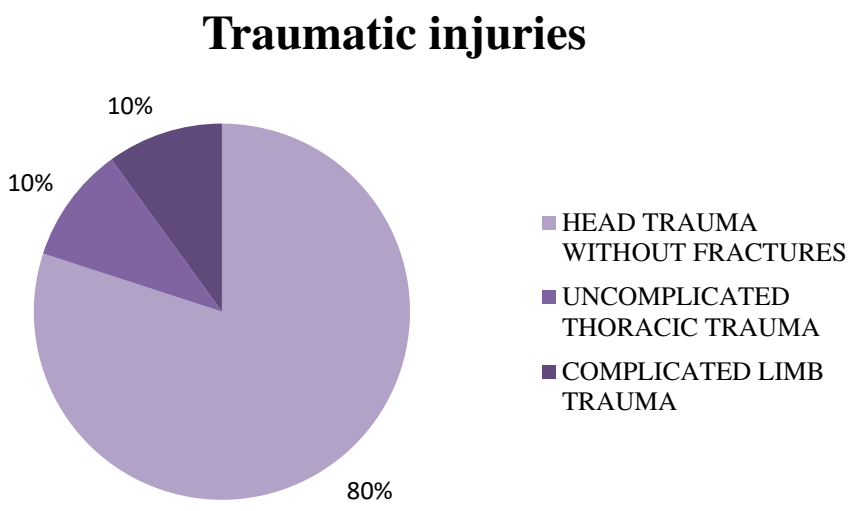


A notable proportion of patients (26 cases, 21.5%) reported previous episodes which might be suggestive of unrecognized minor seizure events prior to the index event.

Traumatic consequences from the seizure occurred in 8.3% of patients. However, the majority of these cases did not require medical intervention (70%), some required conservative treatment (30%) while none required surgical treatment.

The types of traumatic injuries did not fall within the broad range of possibilities we had assumed possible, but were instead limited to the following three categories:

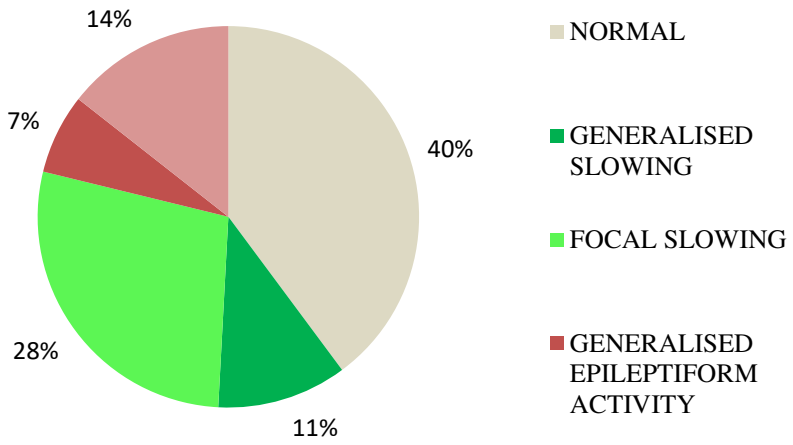
- Head trauma without fractures: 8 cases (80%)
- Complicated thoracic trauma: 1 case (10%)
- Complicated limb trauma: 1 case (10%)



Only 1 patient (0.8%) developed cardiorespiratory complications after the seizure (aspiration pneumonia).

EEG findings (available for 118 out of 121 patients) were as follows:

- Normal: 47 cases (38.8%)
- Generalized slowing: 13 cases (10.7%)
- Focal slowing: 33 cases (27.3%)
- Focal epileptiform activity: 17 cases (14.0%)
- Generalized epileptiform activity: 8 cases (6.6%)



As for body temperature measured in the ED, data was unavailable in 51 cases (42%). Among the 70 patients with available temperature data, fever was present in only 6 cases (5%).

A considerable number of patients experienced early recurrent seizures during observation in the ED or during the short intensive observation in OBI (18 cases, 14.9%).

4.2.4 FOLLOW-UP

The cohort was followed for a median of 21.67 months (min 0.03 – max 29.37, IQR 8.45). During follow-up, approximately one-third of the patients (38 cases, 31.4%) experienced seizure recurrence, while about two-thirds (81 cases, 66.9%) remained seizure-free. Data was unavailable for 2 patients (1.7%).

The median time to recurrence was 1.98 months, ranging from 0 to 27 months (IQR 4).

A diagnosis of epilepsy was ultimately established in 88 of the 121 patients (72.7%) with a first unprovoked seizure, including diagnoses made both in the emergency setting and during follow-up.

Up to May 31, 2025, a total of 27 patients (22.3%) had died. The median time to death was 6.20 months, with a range from 0 to 24 months (IQR 10).

Table 1: Descriptive analysis of the total population				
	Median	**Min**	**Max**	**IQR**
Age	61	14	92	42
	Num.		**%**	
Gender				
Male	91		60,7	
Female	59		39,3	
Seizure type				
Unprovoked	121		80,7	
Acute symptomatic	29		19,3	

Table 2: Descriptive analysis of the population with unprovoked seizures (N = 121)				
DEMOGRAPHICS				
	Median	**Min**	**Max**	**IQR**
Age	63	14	92	42
	Num.		**%**	
Gender				
Male	74		61,2	
Female	47		38,8	
CHARACTERISTICS OF THE FSE				
	Num.		**%**	
Clinical presentation				
Single seizure	83		68,6	
Seizure cluster	24		19,8	
Status epilepticus	14		11,6	
Seizure semiology				
Focal motor seizure	29		24,0	
Focal nonmotor seizure	15		12,4	
Generalized motor seizure	60		49,6	
Generalized nonmotor seizure	2		1,6	
Seizure of unknown onset	15		12,4	
Epilepsy diagnosis after the FSE				
No	51		42,1	
Yes	70		57,9	
Diagnosed epilepsy type (N = 70)				
Focal epilepsy	57		81	
Generalized epilepsy	6		9	
Unknown epilepsy	7		10	
Chronic AED therapy				
No	38		31,4	
Yes	83		68,6	

Seizure etiology		
No structural lesion	46	38
Structural lesion	75	62
Type of structural lesion (N = 75)		
Space occupying lesion (= tumor)	24	32
Acute hemorrhage/stroke	6	8
Sequelae of hemorrhage/stroke	31	41
Post-traumatic sequelae	5	7
Post-neurosurgical sequelae	8	11
Malformation/congenital lesion	1	1
Previous episodes suggestive of unrecognized seizures prior to the FSE		
No	95	78,5
Yes	26	21,5
Traumatic injuries		
No	111	91,7
Yes	10	8,3
Type of traumatic injuries (N = 10)		
Head trauma without fractures	8	80
Head trauma with fractures	0	0
Uncomplicated thoracic trauma	0	0
Complicated thoracic trauma	1	10
Uncomplicated abdominal trauma	0	0
Complicated abdominal trauma	0	0
Complicated limb trauma	1	10
Treatment of the traumatic injuries (N = 10)		
None	7	70
Conservative treatment	3	30
Surgical treatment	0	0
Cardiorespiratory complications		
No	120	99,2
Yes	1	0,8
EEG findings (N = 118)		
Normal	47	38,8
Generalized slowing	13	10,7
Focal slowing	33	27,3
Generalized epileptiform activity	8	6,6
Focal epileptiform activity	17	14,0
Fever		
No	64	53
Yes	6	5
Unavailable data	51	42
Early recurrence (in ED/OBI)		
No	103	85,1
Yes	18	14,9

PRE-HOSPITAL AND IN-HOSPITAL MANAGEMENT				
	Num.		**%**	
Pre-hospital therapy				
No	100		82,6	
Yes	21		17,4	
In-hospital therapy				
No	100		82,6	
Yes	21		17,4	
Pre-hospital IOT				
No	120		99,2	
Yes	1		0,8	
In-hospital IOT				
No	119		98,3	
Yes	2		1,7	
Neurological consultation				
No	6		5,0	
Yes	115		95,0	
Brain CT				
No	0		0,0	
Yes	121		100,0	
EEG				
No	3		2,5	
Yes	118		97,5	
Short intense observation (OBI)				
No	75		62,0	
Yes	46		38,0	
Hospitalization				
No (immediate discharge)	65		53,7	
Yes	56		46,3	
FOLLOW UP				
	Num.		**%**	
Recurrent seizures				
No	81		66,9	
Yes	38		31,4	
Unknown	2		1,7	
Epilepsy diagnosis (ED+FU)				
No	31		25,6	
Yes	88		72,7	
Unknown	2		1,7	
Death (up to 31/05/2025)				
No	94		77,7	
Yes	27		22,3	
	Median	**Min**	**Max**	**IQR**

Time in follow up	21,67	0,03	29,37	8,45
Time to recurrence	1,98	0	27	4
Time to death	6,20	0	24	10

4.3 RISK OF SHORT-TERM RECURRENCE (< 48 h, during ED or OBI observation)

Patients who experienced an unprovoked seizure were categorized into two groups: those who developed an early recurrence (N = 18) and those who did not (N = 103). Based on the available literature data and clinical importance, several variables were analyzed as potential predictors of early recurrence. The incidence of these variables was compared between the two groups in order to determine whether significant differences could be identified.

The results are displayed in Table 3.

Table 3: Risk of early recurrence (< 48 h)

	Recurrence-free patients (N=103), n (%)	**Relapsing patients (N=18), n (%)**	**p**
Gender (M)	63 (61.2)	11 (61.1)	0.997
Seizure semiology			
Focal motor seizure	21 (20.4)	8 (44.4)	0.113
Focal nonmotor seizure	15 (14.6)	0 (0)	
Generalized motor seizure	51 (49.5)	9 (50)	
Generalized nonmotor seizure	2 (1.9)	0 (0)	
Seizure of unknown onset	14 (13.6)	1 (5.6)	
Clinical presentation as seizure cluster or SE	27 (26.2)	11 (61.1)	**0.003**
Fever	3 (5.2)	3 (25)	**0.026**
History of previous undiagnosed seizures	24 (23.3)	2 (11.1)	0.356
Structural lesion detected by TC/MRI	62 (60.2)	13 (72.2)	0.434
Epileptiform activity detected by EEG	19 (19.4)	4 (23.5)	0.744
Age (median)	63	66.5	0.657
Blood test performed at the ED			
Leukocyte total count (median)	8.92	8.26	0.212
Leukocyte % (median)	6.12	5.04	0.06
Neutrophil % (median)	74.7	65.9	0.122
CPR (median)	0.5	0.5	0.205
CPK (median)	153	105	0.264

A statistically significant association with early recurrence was observed for two variables only: clinical presentation in the form of seizure cluster or status epilepticus (considered collectively, as opposed to a single seizure), and the presence of fever detected by the clinical evaluation performed at the emergency department. These two variables may therefore represent risk factors associated with an increased likelihood of early seizure recurrence.

Given the small sample size (information about fever was available only for 70 patients) a multivariate regression analysis was not performed.

4.4 RISK OF LONG-TERM RECURRENCE

For 119 patients with a first unprovoked seizure we had an available clinical follow-up.

These patients were categorized into two groups: those who developed long-term recurrence (N = 38) and those who did not (N = 81). As for the analysis of the risk of short term recurrence, based on the available literature data and clinical importance, several variables were analyzed as potential predictors of early recurrence. The incidence of these variables was compared between the two groups to assess whether significant differences could be established.

The results are reported in Table 4.

Table 4: Risk of long term recurrence (N = 119)			
	Recurrence-free patients (N=81), n (%)	**Relapsing patients (N=38), n (%)**	**p**
Gender (M)	50 (61.7)	23 (60.5)	0.900
Seizure semiology			
Focal motor seizure	17 (21)	12 (31.6)	0.442
Focal nonmotor seizure	9 (11.1)	6 (15.8)	
Generalized motor seizure	41 (50.6)	17 (44.7)	
Generalized nonmotor seizure	2 (2.5)	0 (0)	
Seizure of unknown onset	12 (14.8)	3 (7.9)	
Clinical presentation as seizure cluster or SE	30 (37)	8 (21.1)	0.081
Immediate administration of ASM	58 (71.6)	25 (65.8)	0,52
Fever (N = 69)	6 (13)	0 (0)	0,168
History of previous undiagnosed seizures	14 (17.3)	12 (31.6)	0,079
Structural lesion detected by TC/MRI	48 (59.3)	27 (71.1)	0,214
Epileptiform activity detected by EEG (N = 113)	18 (19.4)	4 (23.5)	0.130
Age (median)	63 (37)	62.5 (21.1)	0.857
Blood test performed at the ED			
Leukocyte total count (median)	8.92	8.66	0.555
Leukocyte % (median)	6.12	5.77	0.957
Neutrophil % (median)	73.8	72.10	0.791
CPR (median)	0.5	0.5	0.903
CPK (median)	155	128	0.553

No associations reached statistical significance, suggesting that none of the examined variables act as a risk or protective factor for long-term recurrence.

Subsequently, time to recurrence was analyzed. Three variables were evaluated as potential factors influencing the timing of recurrence (clinical presentation as a seizure cluster or status epilepticus, immediate administration of ASMs, and the presence of a structural lesion detected by neuroimaging).

The results are shown in Table 5 and in the following graphs.

Table 5: Time to recurrence			
Cox Regression			
	Exp(B)	**95%CI**	**p**
SE or Seizure cluster	0.553	0.253-1.206	0.137
Immediate administration of ASM	0.842	0.429-1.651	0.617
Structural lesion detected by TC/MRI	1.586	0.784-3.208	0.199

The univariate Cox regression models did not demonstrate any association with time to recurrence that reached statistical significance. These variables therefore do not appear to significantly influence the timing of recurrence.

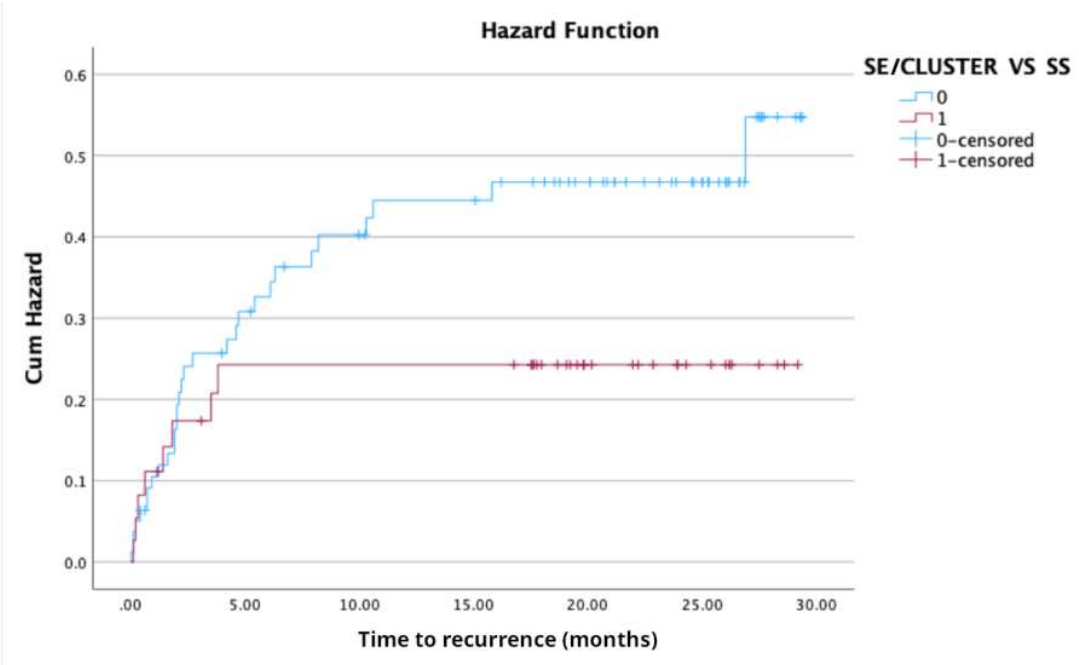


Figure 5

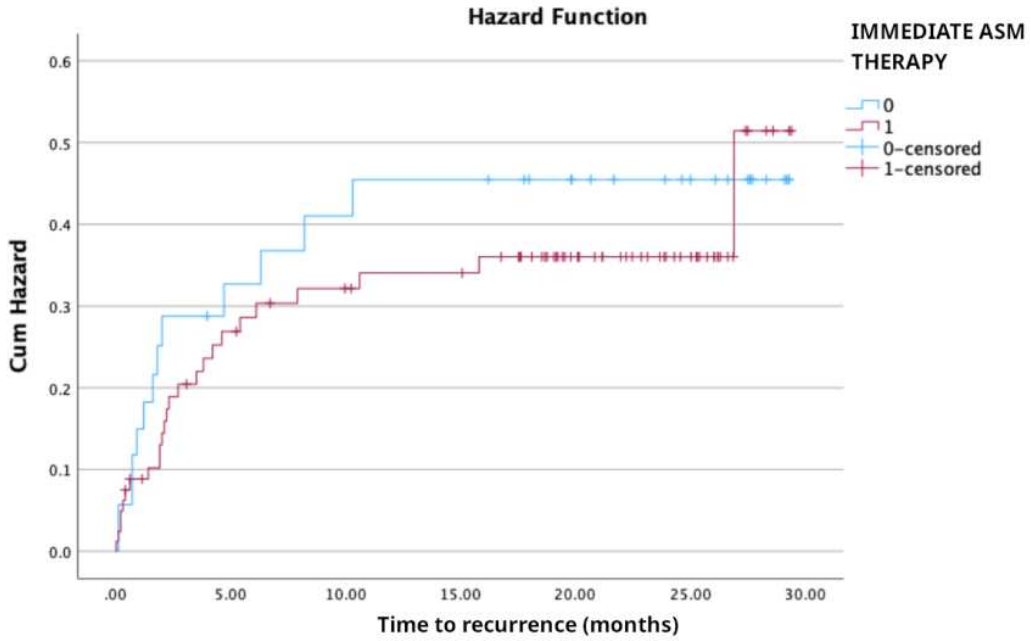


Figure 6

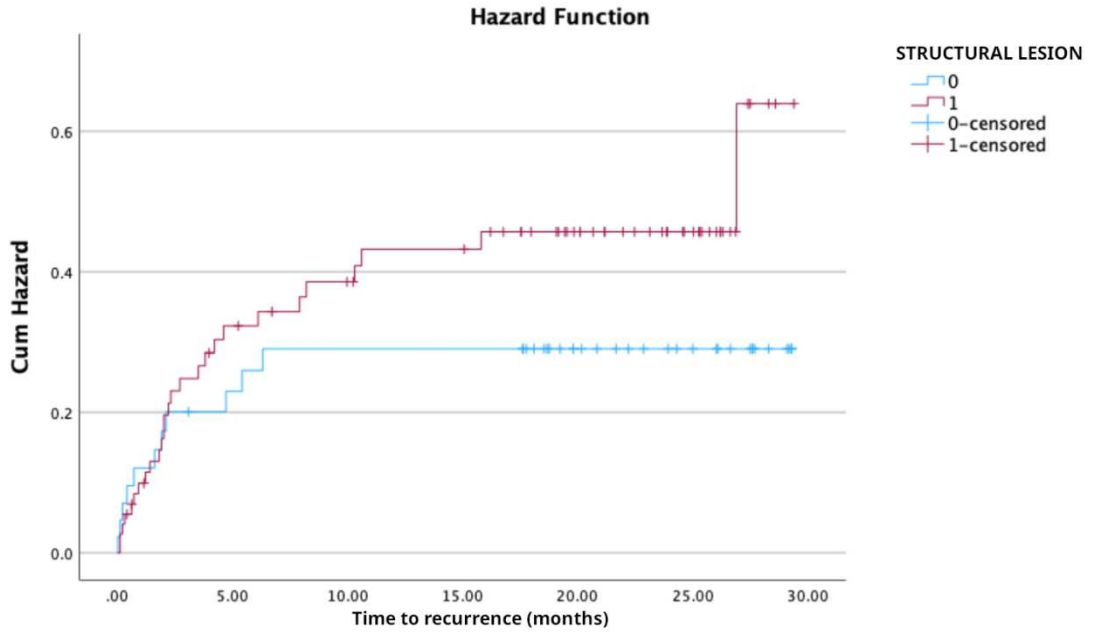


Figure 7

5. DISCUSSION

5.1 DEMOGRAPHIC PROFILE

Descriptive analysis of the cohort reveals a predominance of male patients (60%) and a median age of 61 years, which is closer to the upper end of the age range (14–92 years). This suggests that, once pediatric patients are excluded, a first epileptic seizure is a phenomenon that primarily affects older adults (in line with previous literature reports (1)). Considering patients with ASyS and Unprovoked Seizures, they showed similar demographic characteristics, indicating that they do not represent distinct subpopulations.

5.2 CLINICAL PROFILE IN PATIENTS WITH A FIRST UNPROVOKED SEIZURE

The most common clinical presentation was with an isolated seizure, occurring in approximately two thirds of cases. However, the FSE manifested as seizure clusters or status epilepticus in a considerable proportion of patients— considered together, they represent nearly one third of the total events. These findings suggest that FSE could be more than a mere “first seizure” and may include cases of variable complexity and severity, some of which warrant intensified diagnostic and therapeutic efforts. This conclusion is further supported by the high rate of hospitalization (46.3%).

Moreover, immediate complications of the FSE, although not severe, happened in 11 patients (seizure-related traumatic injuries: 8.3%, with 30% of these requiring immediate treatment, cardio-respiratory complications: 0.8%) and 3 patients needed OTI.

As for seizure semiology, generalized motor seizures represented the most common type (49.6%), followed by focal motor seizures (24%). Motor seizures were therefore markedly more frequent than non-motor seizures.

This observation, along with the significant proportion of patients (21.5%) reporting prior episodes suggestive of undiagnosed seizures, aligns with previous literature findings (2–8): many patients come to medical attention only after the first seizure with major motor manifestations, whereas subtler episodes often go unrecognized by both patients and physicians.

This highlights the importance of conducting a thorough medical history during the evaluation of a patient presenting with a FSE.

The diagnostic investigations performed in the emergency department enabled a diagnosis of epilepsy in more than half of the patients with a first unprovoked seizure (57.9%). This finding highlights the improved diagnostic yield of the current epilepsy definition compared to the previous one (9).

The diagnostic workup also frequently allowed identification of the seizure etiology, which in over half of the cases (62%) was attributable to a structural lesion. In this study, therefore, most unprovoked seizures can be classified as remote symptomatic seizures or progressive symptomatic seizures.

Overall, these findings advocate for the development of a clearly defined diagnostic and therapeutic pathway targeted at individuals presenting with a FSE, to allow rapid and accurate patient management.

5.3 FOLLOW-UP OF THE POPULATION WITH A FIRST UNPROVOKED SEIZURE

Follow-up enabled an epilepsy diagnosis in 18 additional patients (14.8%) beyond those diagnosed during the initial emergency department workup.

More than half of the patients did not experience seizure recurrence during follow-up.

Patients experiencing a recurrence after the first seizure still account for a substantial proportion (approximately one third). The median time to recurrence was 1.98 months, indicating that most recurrences occur within the first few months after the initial event. This finding is concordant with previous studies, which showed that the risk of seizure recurrence is highest within the first few months following the FSE, with the critical period typically ranging from 3 to 6 months, depending on the specific study (9–12).

5.4 SHORT-TERM RECURRENCE

Two variables were identified as risk factors for early seizure recurrence: clinical presentation as a seizure cluster or status epilepticus (considered together, in contrast to a single seizure), and the presence of fever detected at the ED.

Identification of these features in a patient presenting with a FSE may help clinicians recognize individuals at higher short-term recurrence risk, and guide decisions regarding the initiation of ASM treatment, the need for in-hospital observation for 24–48 hours prior to discharge or hospital admission.

However, the association between fever and increased risk of recurrence should be interpreted with caution: the retrospective design of the study allowed us to retrieve the information on body temperature for nearly half of the patients with a first unprovoked seizure, potentially introducing bias into the findings. Thus, further studies are needed to clarify the validity of this association.

The availability of studies in the literature that have analyzed seizure recurrence within the first 48 hours following a first unprovoked seizure in adult patients is extremely limited.

The study that most closely aligns with the objectives of our research is that conducted by Magliola et al. (13), which aimed to characterize the risk of early seizure recurrence (ESR) in patients over 14 years of age who were evaluated in the emergency department for any type of seizure, including both unprovoked and acute symptomatic seizures. The authors also sought to identify potential predictive factors for ESR, with the goal of proposing a reliable observation time threshold to guide safe ED discharge practices. In their cohort, 21% of patients experienced a recurrent seizure within 24 hours. Among the analyzed variables, the presence of EEG abnormalities and alcohol withdrawal emerged as the strongest predictors of increased ESR risk, whereas structural brain lesions identified on CT scans and seizure semiology were not associated with ESR. Based on the observation that 68% of subsequent seizures occurred within the first 6 hours after ED arrival, the authors propose this time frame as a reasonable observation window for patients presenting to the ED with an epileptic seizure.

Other studies analyzing the role of fever and clinical presentation as clusters/SE in influencing the recurrence risk after an unprovoked FSE in adult patients were unavailable for comparison.

5.5 LONG-TERM RECURRENCE

Several variables were analyzed as potential predictors of long-term recurrence, but none reached statistical significance. This suggests that, in the present study, none of the evaluated factors reliably predict long-term seizure recurrence or time to recurrence.

However, the analyzed sample is small. This limitation must be considered, and precludes reaching conclusions. This topic must be evaluated in the future and with a larger population.

Our results are only partially consistent with previous literature data.

Gender

Although male sex was more common, it was not associated with a different risk of seizure recurrence, either in the short or long term (the proportion of male patients was identical in both recurrence and non-recurrence groups and reflected the overall distribution).

Age

Age was not found to be a significant factor influencing the risk of seizure recurrence over either time frame.

The majority of the studies compare pediatric and adult populations, while few have explored differences among various adult age groups. In general, within individual studies, age appears to have minimal, if any, influence on the risk of seizure recurrence (10), which is consistent with our findings.

It is important to note that age is closely linked to etiology, as unprovoked seizures in older adults are more frequently caused by remote symptomatic rather than idiopathic etiologies. Bergey et al. (5) suggested that seizures of unknown etiology in elderly patients should be interpreted as having an undefined cause rather than being truly idiopathic.

Seizure clusters and Status epilepticus

It remains uncertain whether an initial presentation as status epilepticus or a seizure cluster implies a higher risk of recurrence. These clinical scenarios are often perceived as high-risk events, so they are more likely to be treated promptly, and they are unlikely included in randomized trials in which they might risk being assigned to the untreated arm. Consequently, the evidence regarding their prognostic value is limited (10,12).

Most available studies have not demonstrated a significantly increased recurrence risk in this subgroup (5,10,12,14), which aligns with our findings.

However, some studies coming to the opposite conclusion do exists (12). Therefore, this topic remains open to further investigation.

Seizure semiology

As for seizure semiology, our findings are in agreement with existing literature (10,14). Focal seizures may appear to be associated with a higher recurrence risk, although this is likely due to their correlation with symptomatic etiologies and abnormal EEG findings. There is currently no robust evidence supporting the notion that specific seizure types independently influence the risk of recurrence (10).

Prior unrecognized seizures

Our results diverge from previous literature concerning the presence of potentially unrecognized prior seizures. Numerous studies have demonstrated a higher risk of recurrence in patients with a history of prior seizures (10,15,16).

However, in our study, the occurrence of seizures prior to the index event remains a hypothesis, primarily based on patient self-reports and on the medical history retrieved by relatives. The uncertainty of these data may explain the discrepancy between our findings and those of previous research.

Structural lesions and EEG findings

As for the presence of potentially epileptogenic lesions on neuroimaging and epileptiform abnormalities on EEG, our findings are not consistent with much of the existing literature, which has shown that both factors are associated with an increased risk of recurrence (5,12,16,17). However, a few rare studies that failed to demonstrate these factors as reliable predictors of seizure recurrence do exist (9,11,18). It is therefore plausible that, while an association exists, it may not be sufficiently strong to yield consistent statistical significance across studies, regardless of sample size or study design.

An interesting interpretive framework is offered by Beretta et al., who did not find these individual risk factors to be predictive on their own, but observed that the combination of abnormal EEG findings, imaging abnormalities, and neurological deficits was associated with a higher risk of seizure recurrence.

Early treatment with ASM

The effectiveness of early initiation of ASM treatment is another area where our results differ from the existing literature. Several studies have reported a reduction in seizure recurrence within the first two years when ASM is administered immediately following a first unprovoked seizure (5,6,9,11,15,16,19). However, among these studies, the one by Marson et al. (9) showed that despite the effectiveness of early treatment in the first 2 years after the FSE, it did not influence the long term prognosis of epilepsy.

Obviously, a prominent role on the recurrence risk is played by the seizure's etiology, and the case mix of the etiologies of the analyzed population could have influenced this result.

Fever and laboratory tests

Current literature offers limited data on the association between recurrence risk after a first epileptic event and clinical parameters such as fever or laboratory findings. While several studies have explored inflammatory markers—such as leukocyte count, neutrophil-to-lymphocyte ratio (NLR), and C-reactive protein (CRP) — and CPK, these investigations primarily focus on the diagnostic differentiation between epileptic and non-epileptic events, rather than long-term prognostic outcomes.

Moreover, the presence of fever in the postictal period has been scarcely studied in adult populations (research on febrile seizures is predominantly focused on the pediatric population, where febrile episodes are a well-known and more frequent seizure trigger).

At present, this lack of robust studies in adults limits the clinical utility of laboratory and systemic inflammatory markers in guiding decisions about treatment initiation or follow-up after a first unprovoked seizure, and advocates for future studies focusing on these aspects.

Time to recurrence

The majority of the studies analyzes the factors influencing seizure recurrence as a dichotomous outcome (recurrence: yes/no) within a defined time interval, but few have investigated the factors affecting the shortening or lengthening of the time to recurrence. However, when this parameter has been evaluated, the findings appear to contrast with the lack of correlation with early administration of ASM observed in our study: in the landmark study by Marson et al. (MESS trial) (15), immediate ASM therapy was shown to prolong the time to the second seizure. It should be noted that the population of the MESS trial was slightly different from our cohort: in their study, they included patients aged at least 1 month, with a history of one or more unprovoked epileptic seizures (early epilepsy). These differences could be responsible for the discrepancy between our results and those of their study.

6. CONCLUSIONS

The present study has shown that the FSE is a more complex phenomenon than just a "first seizure", given the high incidence of cases presenting as seizure clustering/status epilepticus, the frequent need for hospitalization or observation, and the not negligible portion of patients developing complications such as seizure-related traumatic injuries, cardio-respiratory complications, and need for OTI. Moreover, a significant amount of patients presenting with an alleged first seizure have actually experienced prior episodes that are suggestive of unrecognized seizures.

These findings highlights the need for dedicated diagnostic and therapeutic workups for patients presenting to EDs for a FSE, including an accurate questioning about the patient's medical history (patients and their families should be asked not only about any previous similar episode, but also about minor symptoms that might have been underestimated).

Two variables were identified as risk factors for early seizure recurrence (during the first 48 h): clinical presentation as a seizure cluster or status epilepticus, and the presence of fever detected by the clinical evaluation at the ED. Conversely, these factors did not show any influence on long-term recurrence. These results are poorly explored by previous studies and need future confirmation.

Age, gender, seizure semiology, early ASM treatment, history of previous undiagnosed seizures, structural lesions, epileptiform activity, leukocyte count, CPR and CPK appeared to have no influence on either short-term and long-term recurrence in this study. These findings are only partially concordant with previous literature, so further research is needed to clarify the role of these variables in predicting seizure recurrence.

BIBLIOGRAPHY

1. Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohamed M, Chaudhuri AR, Zalutsky R. How common are the "common" neurologic disorders? Neurology. 2007 Jan 30;68(5):326–37.

2. Habermehl L, Linka L, Krause K, Fuchs A, Weil J, Gurschi M, et al. The impact of the new definition of epilepsy on diagnosis, treatment, and short-term outcomes—A prospective study. Front Neurol. 2025 Mar 24;16:1564680.

3. Fisher RS, Boas WVE, Blume W, Elger C, Genton P, Lee P, et al. Epileptic Seizures and Epilepsy: Definitions Proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005 Apr;46(4):470–2.

4. Shneker BF, Fountain NB. Epilepsy. Dis Mon. 2003 Jul;49(7):426–78.

5. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE Official Report: A practical clinical definition of epilepsy. Epilepsia. 2014 Apr;55(4):475–82.

6. Mauritz M, Hirsch LJ, Camfield P, Chin R, Nardone R, Lattanzi S, et al. Acute symptomatic seizures: an educational, evidence-based review. Epileptic Disorders2022 Feb;24(1):26–49.

7. Yardi R, Vasireddy RP, Galovic M, Punia V. Antiseizure medication use in acute symptomatic seizures: A narrative review. Epilepsia. 2025 Apr;66(4):955–69.

8. Engel J. A Proposed Diagnostic Scheme for People with Epileptic Seizures and with Epilepsy: Report of the ILAE Task Force on Classification and Terminology. Epilepsia. 2001 Jun;42(6):796–803.

9. Marson A, Jacoby A, Johnson A, Kim L, Gamble C, Chadwick D. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomized controlled trial. The Lancet. 2005 Jun;365(9476):2007–13.

10. Falco-Walter JJ, Scheffer IE, Fisher RS. The new definition and classification of seizures and epilepsy. Epilepsy Res. 2018 Jan;139:73–9.

11. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017 Apr;58(4):522–30.

12. Fisher RS, Cross JH, D'Souza C, French JA, Haut SR, Higurashi N, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia. 2017 Apr;58(4):531–42.

13. Pack AM. Epilepsy Overview and Revised Classification of Seizures and Epilepsies. Contin Lifelong Learn Neurol. 2019 Apr;25(2):306–21.

14. Jafarpour S, Hirsch LJ, Gaínza-Lein M, Kellinghaus C, Detyniecki K. Seizure cluster: Definition, prevalence, consequences, and management. Seizure. 2019 May;68:9–15.

15. Fisher RS, Bartfeld E, Cramer JA. Use of an online epilepsy diary to characterize repetitive seizures. Epilepsy Behav. 2015 Jun;47:66–71.

16. Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, et al. A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia. 2015 Oct;56(10):1515–23.

17. Betjemann JP, Lowenstein DH. Status epilepticus in adults. Lancet Neurol. 2015 Jun;14(6):615–24.

18. Berg AT. Risk of recurrence after a first unprovoked seizure. Epilepsia. 2008 Jan;49(s1):13–8.

19. Wirrell E. Evaluation of First Seizure and Newly Diagnosed Epilepsy. Contin Lifelong Learn Neurol. 2022 Apr;28(2):230–60.

20. Amin U, Primiani CT, MacIver S, Rivera-Cruz A, Frontera AT, Benbadis SR. Value of smartphone videos for diagnosis of seizures: Everyone owns half an epilepsy monitoring unit. Epilepsia [Internet]. 2021 Sep [cited 2025 Apr 24];62(9). Available from: https://onlinelibrary.wiley.com/doi/10.1111/epi.17001

21. Pellinen J, Foster EC, Wilmshurst JM, Zuberi SM, French J. Improving epilepsy diagnosis across the lifespan: approaches and innovations. Lancet Neurol. 2024 May;23(5):511–21.

22. Foster E, Carney P, Liew D, Ademi Z, O'Brien T, Kwan P. First seizure presentations in adults: beyond assessment and treatment. J Neurol Neurosurg Psychiatry. 2019 Sep;90(9):1039–45.

23. Lawn ND, Bamlet WR, Radhakrishnan K, O'Brien PC, So EL. Injuries due to seizures in persons with epilepsy: A population-based study. Neurology. 2004 Nov 9;63(9):1565–70.

24. Rodríguez Quintana JH, Bueno SJ, Zuleta-Motta JL, Ramos MF, Vélez-van-Meerbeke A, , the Neuroscience Research Group (NeuRos). Utility of Routine EEG in Emergency Department and Inpatient Service. Neurol Clin Pract [Internet]. 2021 Oct [cited 2025 Apr 22];11(5). Available from: https://www.neurology.org/doi/10.1212/CPJ.0000000000000961

25. Scarpino M, Verna MT, Grippo A, Lolli F, Piccardi B, Nazerian P, et al. The role of EEG in the emergency department: Its contribution to the patient's diagnostic–therapeutic pathway. The EMINENCE study. Clin Neurophysiol Pract. 2025;10:70–7.

26. Jones KEA, Howells R, Mallick AA, Paul SP, Dey I. NICE guideline review: Epilepsies in children, young people and adults NG217. Arch Dis Child - Educ Amp Pract Ed. 2023 Jun 20;108(6):416–21.

27. De Stefano P, Ménétré E, Stancu P, Mégevand P, Vargas MI, Kleinschmidt A, et al. Added value of advanced workup after the first seizure: A 7-year cohort study. Epilepsia. 2023 Dec;64(12):3246–56.

28. Brigo F, Igwe SC, Erro R, Bongiovanni LG, Marangi A, Nardone R, et al. Postictal serum creatine kinase for the differential diagnosis of epileptic seizures and psychogenic non-epileptic seizures: a systematic review. J Neurol. 2015 Feb;262(2):251–7.

29. Masoumi B, Mozafari S, Golshani K, Heydari F, Nasr-Esfahani M. Differential Diagnosis of Seizure and Syncope by the Means of Biochemical Markers in Emergency Department Patients. Int J Prev Med. 2022 Jan;13(1):58.

30. Fisch L, Lascano AM, Vernaz Hegi N, Girardin F, Kapina V, Heydrich L, et al. Early specialized care after a first unprovoked epileptic seizure. J Neurol. 2016 Dec;263(12):2386–94.

31. Li Y, Ren T, Burgess M, Chen Z, Carney PW, O'Brien TJ, et al. Early Access to First-Seizure Clinics, Subsequent Outcomes, and Factors Associated With Attendance. JAMA Neurol. 2024 Jul 1;81(7):732.

32. Bergey GK. Management of a First Seizure. Contin Lifelong Learn Neurol. 2016 Feb;22(1, Epilepsy):38–50.

33. Rizvi S, Ladino LD, Hernandez-Ronquillo L, Téllez-Zenteno JF. Epidemiology of early stages of epilepsy: Risk of seizure recurrence after a first seizure. Seizure. 2017 Jul;49:46–53.

34. Kim LG, Johnson TL, Marson AG, Chadwick DW. Prediction of risk of seizure recurrence after a single seizure and early epilepsy: further results from the MESS trial. Lancet Neurol. 2006 Apr;5(4):317–22.

35. Hauser WA, Anderson VE, Loewenson RB, McRoberts SM. Seizure Recurrence after a First Unprovoked Seizure. N Engl J Med. 1982 Aug 26;307(9):522–8.

36. Hauser WA, Rich SS, Annegers JF, Anderson VE. Seizure recurrence after a 1st unprovoked seizure: An extended follow-up. Neurology. 1990 Aug;40(8):1163–1163.

37. Musicco M, Beghi E, Solari A, Viani F, First Seizure Trial Group (FIRST Group). Treatment of first tonic-clonic seizure does not improve the prognosis of epilepsy. Neurology. 1997 Oct;49(4):991–8.

38. Krumholz A, Wiebe S, Gronseth GS, Gloss DS, Sanchez AM, Kabir AA, et al. Evidence-based guideline: Management of an unprovoked first seizure in adults: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2015 Apr 21;84(16):1705–13.

39. Jiménez-Villegas MJ, Lozano-García L, Carrizosa-Moog J. Update on first unprovoked seizure in children and adults: A narrative review. Seizure. 2021 Aug;90:28–33.

40. Ménétré E, De Stefano P, Megevand P, Sarasin FP, Vargas MI, Kleinschmidt A, et al. Antiseizure medication ≤48 hours portends better prognosis in new-onset epilepsy. Eur J Neurol. 2024 Feb;31(2):e16107.

41. Punia V, Daruvala S, Dhakar MB, Zafar SF, Rubinos C, Ayub N, et al. Immediate and long-term management practices of acute symptomatic seizures and epileptiform abnormalities: A CROSS-SECTIONAL international survey. Epilepsia. 2024 Apr;65(4):909–19.

42. Parviainen L, Kälviäinen R, Jutila L. Impact of diagnostic delay on seizure outcome in newly diagnosed focal epilepsy. Epilepsia Open. 2020 Dec;5(4):605–10.

43. Firkin AL, Marco DJT, Saya S, Newton MR, O'Brien TJ, Berkovic SF, et al. Mind the gap: Multiple events and lengthy delays before presentation with a "first seizure." Epilepsia. 2015 Oct;56(10):1534–41.

44. Jackson A, Teo L, Seneviratne U. Challenges in the first seizure clinic for adult patients with epilepsy. Epileptic Disord. 2016 Sep;18(3):305–14.

45. Van Vliet EA, Aronica E, Vezzani A, Ravizza T. Review: Neuroinflammatory pathways as treatment targets and biomarker candidates in epilepsy: emerging evidence from preclinical and clinical studies. Neuropathol Appl Neurobiol. 2018 Feb;44(1):91–111.

46. Wang K, Yang J, Xu W, Wang L, Wang Y. Characteristics and treatments of patients with significantly elevated creatine kinase levels induced by seizures: Case report and literature review. Clin Case Rep. 2023 Aug;11(8):e7788.

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