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Acute symptomatic seizures and epileptiform abnormalities: Management and outcomes

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Acute symptomatic seizures and epileptiform abnormalities: Management and outcomes

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Table of contents

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Editorial: Acute symptomatic seizures and epileptiform abnormalities: Management and outcomes

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Editorial on the Research Topic
Acute symptomatic seizures and epileptiform abnormalities: Management and outcomes

Every brain can produce an epileptic seizure. A key distinction is whether it is provoked or unprovoked. This dichotomy alludes to the identification of a temporally-associated etiology. When it is present at the time of, or immediately preceding, a seizure, they are called acute symptomatic seizures (ASyS). The insult-to-ASyS time window is etiology-dependent, ranging from 24 h to 7 days and longer (1). Conceptually, the idea of seizure risk reduction after reversing underlying etiology is quite appealing. However, most ASyS are secondary to a non-reversible etiology, such as acute brain injuries (2), and exert a far more significant impact than traditionally appreciated. Assumptions and assertions about these "transitory" events have prevented systematic investigations into ASyS management, outcomes, and its natural history determination. The most glaring example underlies its fundamental defining feature—seizures within 7 days of acute brain injuries—proposed initially for "epidemiological studies" (1), which now pervades clinical practice. While seizures after the arbitrarily chosen 7 days have different outcomes than ASyS (3), emerging data suggest that ASyS after 3 days of injuries like stroke have similar implications (4). Needless to say, it is time to rethink ASySs and their standing in clinical epileptology.

Convulsive ASyS are ubiquitous in clinical practice and, depending on geographical location, account for 40–50% of all afebrile seizures (5). Convulsive ASyS, including ones from metabolic insults, undoubtedly increases the risk of epilepsy development (epileptogenesis) (5, 6). Prognostic models for symptomatic epilepsy development find ASyS contributing the highest risk among predictors of epileptogenesis (7, 8). As a corollary to the classic dictum of *seizure begets seizure* (9), if a brain can generate a seizure (ASyS) once, it is easier for it to produce an unprovoked, remote symptomatic seizure as well, i.e.,

remote symptomatic epilepsy (10). In other words, ASyS may be a marker of a lower seizure threshold in an individual.

The risk of symptomatic epilepsy after ASyS in stroke patients is 33% (3), precisely similar to the risk of developing epilepsy after a first unprovoked seizure (11). The SeLECT score, a prognostic model for ischemic stroke, predicts more than 60% risk of epilepsy development within a year of ASyS in patients with MCA cortical stroke and more than 3 NIHSS (7), suggesting that epilepsy can be diagnosed at the time of ASyS in some patients (10). These high seizure recurrence risk predictions can have socio-economic ramifications for patients, including driving restrictions.

Convulsive ASyS represents only "*the tip of the iceberg*" when it comes to acute epileptogenic activity after brain injuries. ASyS prevalence is higher in the era of continuous EEG (cEEG) monitoring because most are non-convulsive, i.e., electrographic seizures, during hospitalization (12, 13). In addition, epileptiform abnormalities (EAs) such as lateralized periodic discharges (LPDs), lateralized rhythmic delta activity (LRDA), etc., which significantly increase ASyS risk, are present in 25–40% of patients undergoing acute EEG (14, 15). Like convulsive ASyS, these electrographic findings also increase epilepsy development risk (14, 16–18). Based on this evidence, it is no exaggeration that ASyS and acute EAs may represent the earliest stage of epileptogenesis. Hence, ignoring ASyS and EAs as an epiphenomenon of acute injury is a heavy loss of opportunity for enhancing our understanding of epileptogenesis biomarkers and targets for testing anti-epileptogenic therapies—the holy grail of epilepsy care.

Mortality after ASyS is nine times higher than unprovoked seizures, with a 30-day case fatality of 20% (3, 19). Primary ASyS prophylaxis using anti-seizure medications (ASMs) is recommended after brain injuries, like trauma (20), but not stroke and hemorrhages (21, 22). Some experts recommend ASM prophylaxis after ASyS in intracerebral hemorrhage (ICH) (22) or after "recurrent" ASyS in ischemic stroke (21). In contrast, some organizations recommend against secondary ASM prophylaxis after ischemic stroke (23), and we lack data to support its use after infections (24). Nonetheless, real-world data shows that ASyS and EAs are frequently treated with ASMs during hospitalization, and patients are discharged on them (25–27). While 20% ASyS present as status epilepticus (6), 100% are treated with a status epilepticus management algorithm. The costs and benefits of this treatment strategy for ASyS remain unknown. The *unknowns* abound in this sphere—convulsive vs. electrographic ASyS management, wisdom of prophylactically treating EAs to prevent ASyS, duration of inpatient therapy, and need for discharging patients on ASMs after ASyS—are all unknowns. The latter does not show any benefit in neonates (28). Due to a lack of data guiding optimal ASM duration in adults, a majority continue ASMs several months to years after hospital discharge (29, 30). There is a large variability of expert recommendation on the duration of ASM continuation after ASyS and EAs ranging from months to years (31, 32). In the absence of anti-epileptogenic therapies, there is an acute need for developing evidence-based management strategies in this patient population.

This research collection aims to collate the latest research and review articles concerning ASyS and EAs, their implications, and management. Fatima et al. found that the evolution of LPD's amplitude over time in a patient correlates with seizure risk. Martinez et al. found that nearly a quarter of suspected ASyS patients undergoing cEEG monitoring have the poorly understood phenomenon of stimulus-induced, rhythmic, periodic, or ictal discharges (SIRPIDs), especially common in acute systemic illness, and may correlate with poor outcomes. Pan et al. report that a lower partial pressure of carbon dioxide ($PaCO_2$) in intracerebral hemorrhage patients could be associated with an increased risk of hyperacute (<24 h) ASyS. Yu et al. found that late symptomatic seizures (>12 months), rather than ASyS after moderate to severe traumatic brain injury, are associated with unfavorable long-term (5 years) functional outcomes. Tako et al. report that the severity of large arterial vessel occlusion ischemic stroke, based on the NIHSS at 24 h after admission, has a small but significant association with subsequent ASyS. Germeraad et al. explore the age-old question of primary ASyS prophylaxis in the unique setting of hematopoietic stem cell transplantation with busulfan conditioning and report that phenytoin use may cause more harm than benefit and hence recommend against it. Asnakew et al. report that in a specific Ethiopian region and community, illiteracy is the primary driver of people's attitude and care toward people with seizures, ASyS, or otherwise. Sharma et al. provide a comprehensive, concise, and clinically helpful review of the role of cEEG in managing patients with suspected ASyS, including challenges and new opportunities for its widespread use. Kong and Marawar address the knowledge gap about the often ignored, highest-risk for ASyS demographical segment—the older adults. Yoo reviews the current literature on BIRDs (Brief Potentially Ictal Rhythmic Discharges) that have a high degree of association with ASyS and status epilepticus and subsequent outcomes.

We will be remiss not to point out the lack of articles that can guide us on ASyS and EA management in the collection. However, it merely reflects the malaise toward ASyS management research in the neurological community. A phenomenal boost to help overcome this apathy would be to define etiology-specific ASyS using multimodal biomarkers, which will be a big step toward improving management, prognosis, and understanding epileptogenesis.

Author contributions

VP, MG, ZC, and CB contributed to the conception of the editorial. VP wrote the first draft of the manuscript. All authors contributed to the manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Association Between Lateralized Periodic Discharge Amplitude and Seizure on Continuous EEG Monitoring in Patients With Structural Brain Abnormality in Critical Illness

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Objective: To investigate the association between lateralized periodic discharge (LPD) amplitude and seizure risk on an individual level in patients with structural brain abnormality.

Methods: Retrospective case–control study of patients with structural brain abnormality undergoing continuous EEG monitoring was performed. We included 10 patients with LPDs and seizures as cases and 10 controls, patients with LPDs without seizure. Analysis was performed with a mixed-effects model with primary outcome measure of number of seizures per 8-h EEG epoch with fixed effects being variables of interest and random effect being subject ID.

Results: Epochs with seizures showed a higher absolute amplitude (corrected $p = 0.04$) and a higher relative amplitude (corrected $p = 0.04$) of LPDs. Additionally, the number of seizures was higher in epochs that had LPDs with plus features (uncorrected $p = 0.002$) and LPDs with higher relative amplitude (uncorrected $p = 0.005$).

Conclusion: Higher LPD amplitude is associated with increased risk of seizures on an individual patient level. A decreasing amplitude is suggestive of decreasing seizure risk, and may in fact be suggestive of decreasing ictal character of LPDs.

Keywords: LPD, seizure, amplitude, PLEDs, lateralized periodic discharge

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HIGHLIGHTS

- Lateralized periodic discharges (LPDs, also known as PLEDs) are a common EEG pattern in critically ill patients and associated with increased risk of seizures.
- On an individual patient level, decreasing LPD amplitude reflects decreasing seizure risk.
- Lateralized periodic discharge plus features are associated with increased risk of seizure.

INTRODUCTION

Lateralized periodic discharges (LPDs), formerly known as periodic lateralized epileptiform discharges (PLEDs) were first described by Chatrain et al. as periodic or quasi-periodic unilateral

focal spikes or sharp waves, occurring at a rate of 1–2 Hz (1). LPDs are commonly found in association with focal acute or subacute cerebral lesions like subdural hematoma, intracerebral hemorrhage, infectious etiologies, tumor, autoimmune conditions, metabolic disorders, and cerebrovascular disease (2). LPDs are a common EEG pattern in critically ill patients, with prevalence of ∼6.2–8.6% (3). From LPDs' first description, there has been controversy whether these patterns are ictal or interictal in nature, or whether they should be viewed as a part of ictal–interictal continuum (4).

Lateralized periodic discharges are found to be associated with an increased risk of discrete seizures (5, 6). Certain electrographic features of LPDs portend a greater risk of seizures. These features associated with an increased risk of seizures may also suggest a more "ictal" nature of the LPDs, placing them closer to the ictal end of the ictal–interictal continuum (7, 8). This remains true for LPD frequency on at least superficial level. LPDs with a higher frequency are associated with both higher risk of discrete seizures and increased markers of metabolic distress (9, 10). Studies in the past have established direct correlation between LPD frequency and metabolic activity (11).

In this study, we primarily aimed to determine a relationship between LPD amplitude with seizure on an individual level. The study of LPD amplitude is difficult as there are other factors that contribute to amplitude other than spatial extent of the source generating the discharge and degree of synchrony. These are primarily the spatial orientation of the underlying dipole, variation in skull thickness, prevalence of skull defects, and the distance from the LPD-generating region to the skull (12). These confounding factors hamper group-wise comparisons. To overcome this barrier, we used a mixed-effect model using the individual patient as a random variable and compared 8-h epochs to see the association between LPD amplitude and number of seizures on an individual patient level. We also evaluated other electrographic features of LPDs beyond amplitude to explore their association with risk of seizure.

METHODS

Study Design

This is a case–control study of 10 patients with LPDs and electrographic seizures compared with 10 patients with LPDs and no seizures. Groups were matched for age and patients with structural brain abnormality were selected. This study was approved by the University of Wisconsin-Madison institutional review board (IRB) and a waiver of consent was granted.

Study Sample

We maintain a retrospective database of all patients undergoing continuous EEG (cEEG) monitoring at our institution. The inpatient monitoring is done using 10–20 standard electrode placement system. For this study, we reviewed our database for the patients who underwent cEEG monitoring between October 2018 and February 2020. Starting from October 2018, we selected the first 10 consecutive patients with structural brain abnormality who had LPDs and seizures on cEEG. After establishing the cases, the same database was reviewed to identify controls, i.e., consecutive patients with LPDs without seizures, who were monitored during the same period ($N = 10$), starting at October 2018 until 10 matched controls were found. Matching was done based on similar age range (±3 years) between the two groups and we coarsened the etiology to include only the patients with structural brain abnormality in the two groups.

Abbreviations: ACNS, American Clinical Neurophysiology Society; AEDs, Antiepileptic drugs; AVM, Arteriovenous malformations; cEEG, continuous EEG; CNS, central nervous system; IV, Intravenous; LPD, lateralized periodic discharge; PRES, Posterior reversible encephalopathy syndrome; SDH, subdural hemorrhage; TBI, Traumatic Brain Injury; h, hour; s, second.

Definitions

Lateralized periodic discharges were defined according to the American Clinical Neurophysiology Society's (ACNS) standardized critical care EEG terminology as repetition of a waveform that is unilateral or bilateral but clearly and consistently with higher amplitude in one hemisphere and with relatively uniform morphology and duration, as well as with a clearly discernible inter-discharge interval between consecutive waveforms and recurrence of the waveform at nearly regular intervals (13). Electrographic seizures were defined as epileptiform discharges averaging >2.5 Hz for ≥10 s (>25 discharges in 10 s), or any pattern with definite evolution as defined above and lasting ≥10 s (13). LPD burden was defined as number of discharges in a specific period of time. Absolute amplitude was defined as typical voltage measured in standard longitudinal bipolar 10–20 recording in the channel in which the pattern is most readily appreciated measured from peak to trough and relative amplitude as typical ratio of voltage of the highest voltage component of the typical discharge to the voltage of the typical background between discharges, measured in the same channel and montage as absolute voltage (13). Relative amplitude was made into a binary variable with categories of <10 and ≥10.

Data Acquisition

Electroencephalographic recordings of the seizure group and control group were reviewed. Total duration of EEG monitoring in the seizure group was 1,213 h and in control group was 461 h. Each raw EEG data record was notch-filtered at 60 Hz, a bandpass filter (1–70 Hz) was applied and reviewed in a longitudinal bipolar montage using CURRY 8 software (Compumedics Neuroscan, Charlotte, NC, USA). LPDs and seizures were initially marked by our investigators (S.F.) and (M.S.) and confirmed by board-certified neurophysiologist (A.S.). In both the groups, LPDs were marked manually for a period of 60 s every 10 min consistently for 1-h duration (i.e., marking was done starting at 1st, 11th, 21st, 31st, 41st, and 51st min of an hour, each for a duration of 60 s). This process was repeated every 8 h until the recording ended. Each record was abstracted into a set of variables for each of these 60-s periods based on the ACNS nomenclature "modifiers" that characterized specific electrographic features of the LPDs. These include frequency, prevalence, sharpness, absolute amplitude, relative amplitude, polarity, number of phases, and plus feature (shown in **Table 1**). These measures were scored semi-quantitatively for each 60-s period and for a discharge that looked prevalent in terms of

TABLE 1 | Electrographic features of LPDs that were abstracted for each epoch.

LPD feature	Method of abstraction of LPD feature
Frequency	Rate per second. Highest value of the range is recorded
Prevalence	Percent of epoch that includes the pattern Categorized as following based on that percent: Continuous ≥90%; Abundant 50-89%; Frequent 10–49%; Occasional 1–9%; Rare <1%
Sharpness	Measured as the duration of the sharpest discharge at the baseline in milliseconds (ms) specified for predominant phase. Categorized as: Spiky = duration of the component <70 ms; Sharp = duration of the component 70–200 ms; Blunt = duration of the component >200 ms
Absolute amplitude	Measured in standard longitudinal bipolar montage in the channel in which the pattern is most appreciated. It is measured from peak to trough. Units of measurement in microvolts
Relative amplitude	Measured as ratio of amplitude of the highest amplitude component to the amplitude of the typical background between the discharges, measured in the same channel and montage as Absolute Amplitude
Number of phases	Number of baseline crossings of a typical discharge counted in longitudinal bipolar montage. Categorize as 1/2/3
Polarity	Dominant phase judged in standard longitudinal bipolar montage, classified as positive or negative or unclear
Plus feature	Presence of superimposed fast activity or superimposed rhythmic or quasi-rhythmic delta activity with each discharge

LPD, lateralized periodic discharges.

morphology and amplitude in that period. A total of 692, 60-s periods constituting 11.5 h in the seizure group and in 328, 60-s periods constituting 5.5 h in the control group were scored. Seizures were marked throughout the recording for patients in seizure group and the total number of seizures in each 8-h EEG epoch was documented. Medical records of all the individuals in the study population were reviewed to collect the following variables: age, etiology, gender, history of seizure disorder and recent episode of seizure preceding monitoring.

Data Analysis

The primary unit of analysis was an 8-h EEG epoch with the dependent variable being the number of seizures within each epoch. Independent variables included EEG features. A total of 127, 8-h epochs were available in the group of 10 patients who had seizures and LPDs. Of those epochs, 23 contained seizures and 100 contained LPDs. Of 23 epochs with seizures, 20 contained both LPDs and seizures. A total of 55, 8-h epochs were contained in the group of 10 patients with LPDs without seizures. Of those epochs, 39 contained LPDs and 0 contained seizures. Mixed-effects models were constructed only for epochs which contained LPDs. Mixed-effects models were created using R package lme4 (ver 1.1–26) with subject ID as a random variable and the variables of interest as fixed effects (14). For the first analysis, all 20 patients with a total of 139 epochs (all epochs containing LPDs) were used. For the secondary analysis, 100 epochs of only 10 patients with LPDs and seizures were examined. Statistics were performed in R (version 4.0.4; R Foundation for Statistical Computing). The statistical significance was a corrected $p < 0.05$ for primary outcome with false discovery rate correction for comparison of the absolute amplitude for the total group and absolute amplitude for seizure-only group (15). Other variables were considered exploratory and presented with uncorrected *p*-values.

RESULTS

Table 2 summarizes the clinical characteristics of the study population. Overall, subdural hemorrhage (SDH) ($n = 4$) and infection ($n = 4$) were the most common causes of LPDs. Overall, 7 subjects (5 in the seizure group and 2 in the non-seizure group) had undergone craniotomy either immediately before cEEG or had a history of craniotomy in the past. A total of 2 patients with SDH had cEEG done before SDH evacuation and 2 had cEEG after SDH evacuation. Approximately 80% of patients in both the groups ($N = 8$, $N = 8$) had a suspected clinical seizure preceding the monitoring as recorded from the patient chart. None of the patients had any positive clinical signs while showing LPDs on their cEEG monitoring. Approximately 20% had left temporal LPDs, 30% had left frontal LPDs, 20% had right frontal, 5% had left frontotemporal, 5% had left parasagittal, 5% had right parasagittal, 5% had right central, 5% had right frontotemporal, and 5% had left frontotemporal LPDs.

Comparison of LPD Features Between Epochs Containing Seizures ($N = 23$) and Epochs Without Seizures ($N = 116$) for all 20 Patients

A total of 8-h EEG epochs from all 20 patients (10 who had seizures and 10 without seizures) were included in this analysis. Results are shown in **Table 3**. Absolute amplitude ($p = 0.04$ corrected) and relative amplitude ($p = 0.04$ uncorrected) of LPDs was significantly higher in the epochs that had seizures when compared to epochs without seizures, shown in **Figures 1A,B**. Additionally, the number of seizures was significantly higher in epochs with LPDs with the plus feature (mean 10.6) compared to those without plus feature (mean 1.2) shown in **Figure 2A** (uncorrected $p = 0.002$). The number of seizures was also significantly higher in epochs with LPDs of relative amplitude ≥10 (mean 5.0) compared to epochs with LPDs of relative

TABLE 2 | Patient characteristics.

Characteristics	LPD and seizure group, $N = 10$	LPD and no seizure group, $N = 10$
Age in years (range)	61 (30–85)	62 (28–88)
Gender [Female *n* (%)]	3 (30)	6 (60)
Etiologies		
Ischemic stroke	1	2
SDH	3	1
CNS tumor	3	0
CNS infection	1	3
PRES	1	1
AVM	0	1
TBI	0	1
Encephalomalacia	0	1
Shunted hydrocephalus	1	0
Number of patients on IV sedation	7	6
Number of patients on AEDs	10	9

LPD, lateralized periodic discharges; SDH, subdural hemorrhage; CNS, central nervous system; PRES, Posterior reversible encephalopathy syndrome; AVM, Arteriovenous malformations; TBI, Traumatic Brain Injury; IV, Intravenous; AEDs, Antiepileptic drugs.

TABLE 3 | Comparison of LPD features between epochs containing seizures ($N = 23$) and epochs without seizures ($N = 116$) for all 20 patients.

Variable	Epoch with seizure Mean	Epoch without seizure Mean	*P*-value
Absolute amplitude	145.4	110.7	0.04*
Relative amplitude	9.0	6.7	0.04
LPD burden	40.0	38.0	0.88
Frequency	1.1	1.06	0.74
Prevalence			0.57
Sharpness			0.58
Polarity			0.45
Plus feature			0.002
Number of phases			0.45

LPD, lateralized periodic discharges.

amplitude <10 (mean 0.96) (uncorrected $p = 0.005$) shown in **Figure 2B**.

Comparison of LPD Features Between Epochs Containing Seizures ($N = 23$) and Epochs Without Seizures ($N = 77$) for 10 Patients With Seizures

A total of 8-h EEG epochs from only 10 patients who had seizures were included in this analysis. Results are shown in **Table 4**. Absolute amplitude of LPDs showed significant difference at the epoch comparison level within the seizure group ($p = 0.04$ corrected). As in the previous analysis with all patients, the number of seizures was higher in the epochs with LPD relative amplitude ≥10 (mean 5.0) compared to relative amplitude of <10 (mean 1.5) and was again significant with an uncorrected $p = 0.03$. The Number of seizures in epochs with LPDs with the plus feature (mean 12.1) was significantly higher when compared to epochs without the plus feature (mean 1.6) with uncorrected $p = 0.001$. No significant association was found between other features of LPDs like frequency, prevalence, sharpness, burden, polarity, or number of phases with seizure risk.

TABLE 4 | Comparison of LPD features between epochs containing seizures ($N = 23$) and epochs without seizures ($N = 77$) for 10 patients with seizures.

Variable	Epochs with seizure Mean	Epochs without seizures Mean	*P*-value
Absolute amplitude	145.4	119.3	0.04*
Relative amplitude	9.0	7.3	0.13
LPD burden	40.0	41.2	0.97
Frequency	1.10	1.10	0.84
Prevalence			0.47
Sharpness			0.80
Polarity			0.30
Plus feature			0.02
Number of phases			0.30

*LPD, Lateralized periodic discharges; *means corrected for multiple comparisons.*

DISCUSSION

In this study, we primarily evaluated the association of LPD amplitude (both absolute and relative) with seizures in 8-h epochs. On an individual level, EEG epochs that had seizures were found to be associated with LPDs of higher amplitude when compared to epochs without seizures (**Figures 3A,B**, **4A,B**). Secondarily, we evaluated the association between electrographic features of LPDs and number of seizures. We found that LPDs with higher relative amplitude and presence of plus features were associated with increased seizure numbers. Our finding suggests that LPDs with higher absolute and relative amplitude are associated with increased seizure risk. Comparing LPD amplitude between patients is confounded by several factors such as dipole orientation, skull thickness, and the distance between the LPD generating region and the scalp electrodes. As such LPD amplitude in and of itself is unlikely to contribute to improved risk stratification of methods like 2HELPS2B (10). But on an individual patient level if LPD amplitude is increasing or decreasing it suggests that the seizure risk is similarly increasing or decreasing.

The previous large studies analyzing the association of characteristics of periodic patterns with seizures did not specifically evaluate a correlation between LPD amplitude and seizure risk (10, 16). Our study differs from prior studies in methodology, in that we abstracted the LPD characteristics semi-quantitatively instead of relying on clinical reports which often do not have accurate amplitude data. To overcome the

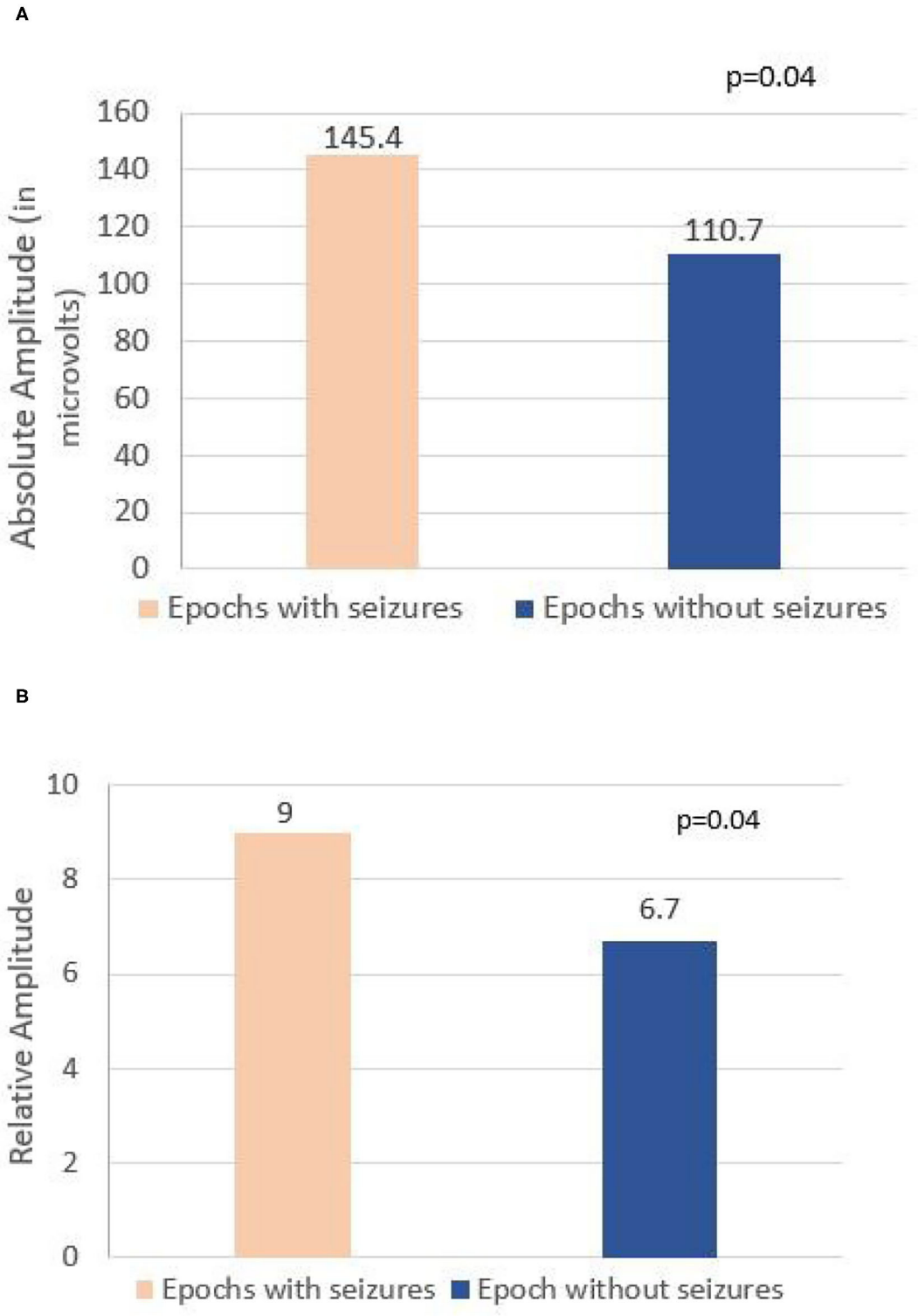

FIGURE 1 | (A) Comparison of absolute amplitude of lateralized periodic discharges (LPDs) between epochs with seizures and epochs without seizures in all 20 patients. **(B)** Comparison of relative amplitude of LPDs between epochs with seizures and epochs without seizures in all 20 patients.

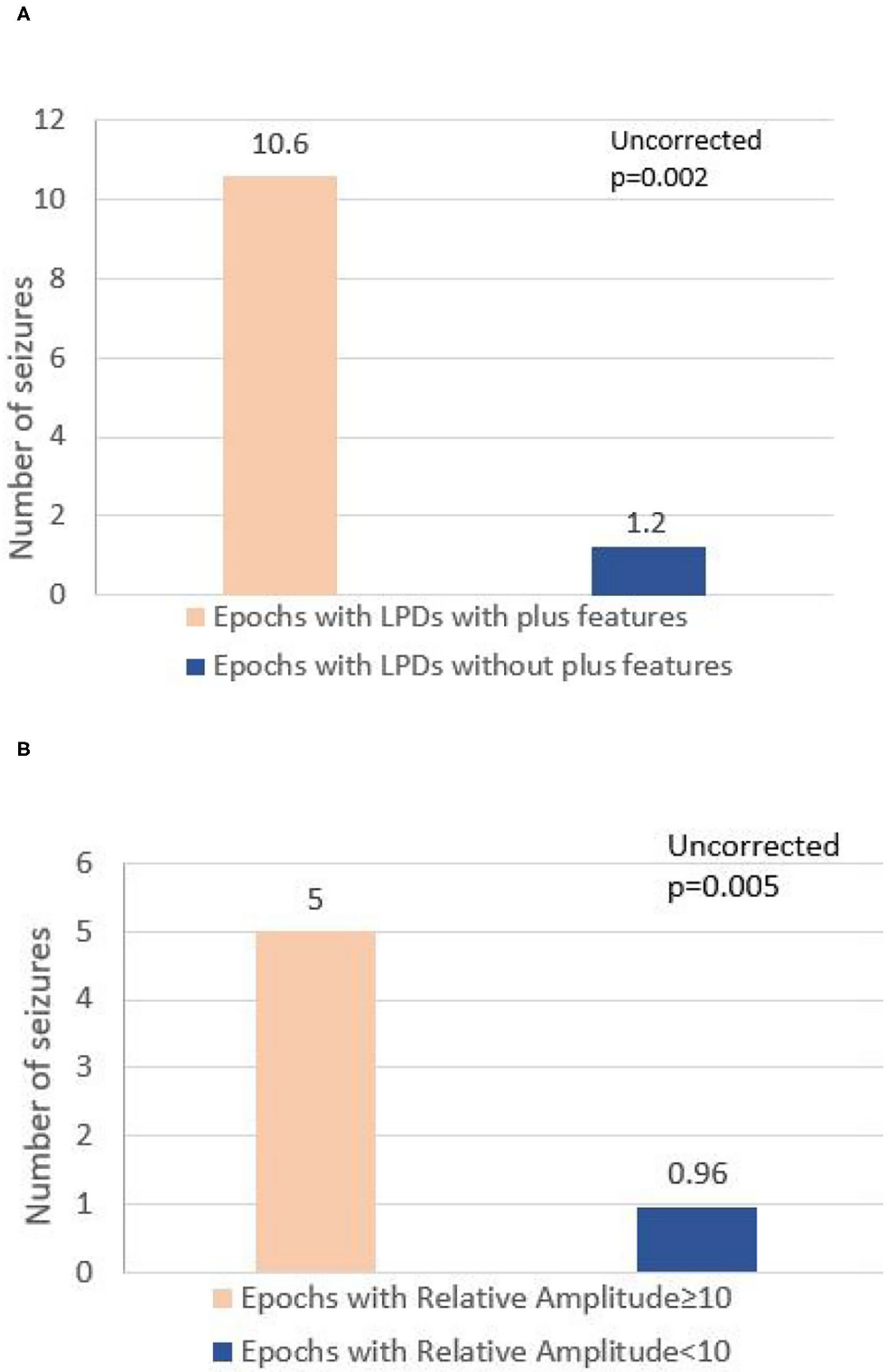

FIGURE 2 | (A) Comparison of number of seizures between epochs with LPDs with plus features and epochs with LPDs without plus features in all 20 patients. **(B)** Comparison of number of seizures between epochs with LPD relative amplitude ≥10 and epochs with LPD of relative amplitude <10 in all 20 patients.

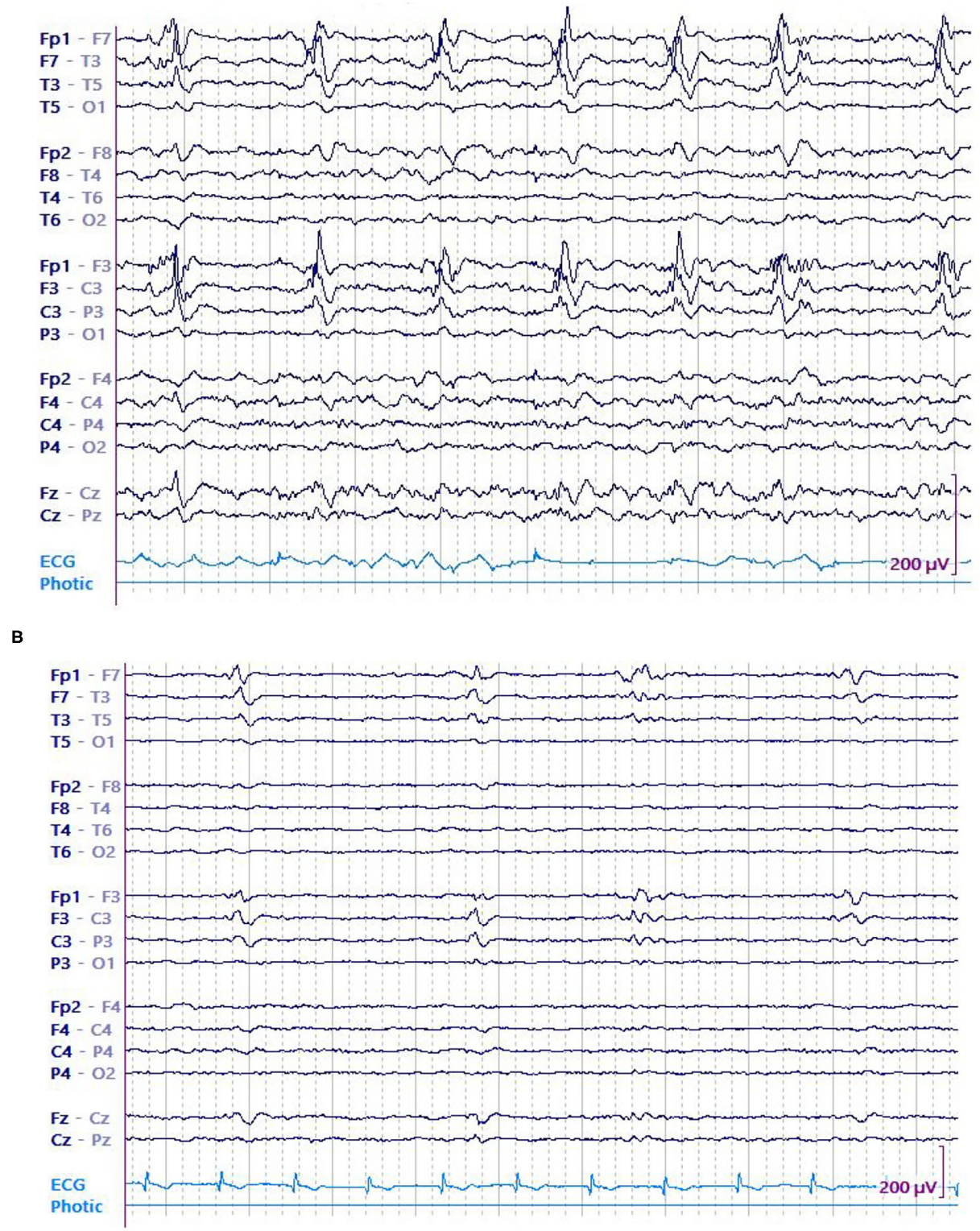

FIGURE 3 | A 74 y/o gentleman with history of left frontoparietal crani for resection of the tuberculum sella meningioma a month earlier presented with dysarthria and underwent continuous EEG (cEEG) monitoring. EEG showed continuous high amplitude left frontal LPDs occurring at 0.5 Hz that evolved into recurrent left sided electrographic seizures. Patient was started on anti-seizure medications including levetiracetam, lacosamide, fosphenytoin, and clobazam. His seizures resolved eventually and LPDs decreased in amplitude concurrent with resolution of seizures. **(A)** LPDs in epoch with seizure. **(B)** LPDs in epoch without seizure.

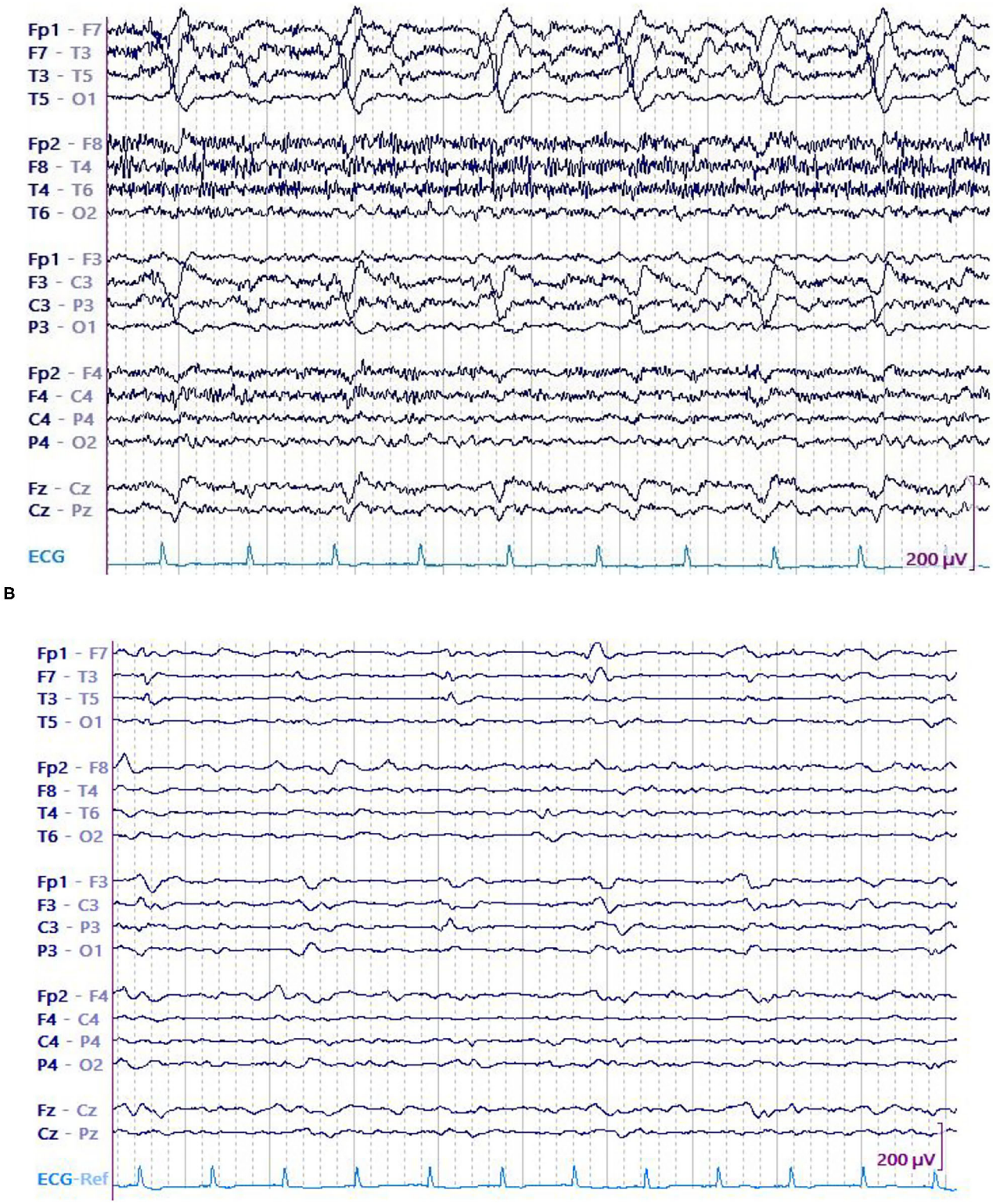

FIGURE 4 | A 75 y/o woman presenting with parieto-temporal mass underwent cEEG. Her EEG showed high amplitude left temporal LPDs occurring at 0.5 Hz and brief electrographic seizures over the left temporal region. Patient was started on anti-seizure medications that include levetiracetam and valproate. After 28 h, no seizures were detected. Amplitude of the LPDs was decreased. **(A)** LPDs in epoch with seizure. **(B)** LPDs in epoch without seizure.

confounding factors associated with amplitude measurement, we used a mixed-effects model in which an intercept is fitted for each subject allowing for isolating the variable of interest, and found that LPD amplitude changes on an individual level are associated with seizure number. This finding suggests that LPD amplitude, which is easily quantifiable, could be tracked epoch-to-epoch on a routine clinical basis to aid the overall impression of seizure risk.

Our study also confirmed the association between LPDs with "plus" features and increased seizure risk which is well-established (10, 16–18). However, we did not find a significant relationship between other LPD features like frequency, prevalence or morphology, and seizure risk as demonstrated by previous studies (10, 16, 18, 19). This discrepancy is most likely due to the sample size and not because these are not risk factors for seizure. It is potentially interesting that these well-established seizure risk factors were not as powerful as LPD amplitude on an individual patient level in this study.

Though not directly tested in our study, it is suggested that electrographic features of LPDs like amplitude and "plus" feature, as well as other markers like frequency are not just proxies for the severity of the underlying "pro-ictal" state but may have a role in assessing the ictal nature of these discharges (8, 13). These electrographic features of LPDs can help to guide treatment. LPD amplitude should be another one of these features to follow, as decreasing amplitude is suggestive of decreased extent and/or degree of paroxysmal depolarizing shifts underlying LPD generation. Further studies to expand upon these findings would include use of multimodal monitoring to evaluate metabolic stress associated with LPD amplitude and other LPD features. Methods other than LPD amplitude like electric source imaging and slope of discharge have been proposed to quantify the scope of the depolarization block underlying the discharges in LPDs. However, electric source imaging is limited in critical care EEG as it requires expertise beyond that of a typical clinical neurophysiologist and source imaging needs patient-specific head models, electrode imaging, and increased electrode density for best accuracy. Slope of the discharge like LPD amplitude is relatively easy to quantify in routine EEG interpretation, but similar to LPD amplitude, slope is affected by dipole orientation, the distance between the LPD generating region and the scalp electrodes. Subsequent studies are needed to explore the association between LPD slope and seizure risk.

There are several limitations of this study. First, the relatively small sample size which is the reason we were unable to match one of the key variables, the gender. Second, its retrospective nature creates a probable selection bias; however, this was minimized by establishing the study size, admission criteria, and review methodology *a priori*. Third, the generalizability of this study is also limited by the fact that we selected only the patients with structural brain abnormalities. Fourth, selection of short epochs and a single discharge of LPD pattern representing the 60 s epoch of the pattern. These limitations could have contributed to our results not showing a significant association between other well-known LPD features and seizure risk (10, 16, 18, 19). Future studies replicating our findings on the large sample size are required to further our current understanding of the association between LPD amplitude and seizures. Studies using larger scale and big data approaches with automated labeling of LPDs, seizures, and LPD characteristics are needed to further explore the complex interplay between LPDs, discrete seizures, and the underlying "pro-ictal state" giving rise to the ictal–interictal continuum. Additional studies using high-density EEG arrays in patients with LPDs would allow improved localization of LPD generators for the examination of the spatial extent of LPDs in source space.

CONCLUSIONS

In summary, this retrospective preliminary study on patients with structural brain abnormality with LPDs demonstrated an association between absolute amplitude and relative amplitude of LPD with seizure. Reduction in the absolute and relative amplitude of these discharges was associated with decreased risk of seizure on an individual level. This is one of the first studies that highlighted the direct relationship between LPD amplitude and seizure risk. In addition, other features like plus feature also show a similar association with seizures. These features can be useful to augment clinical suspicion if an LPD pattern warrants empiric treatment and may also serve as a marker of response to treatment. Future research should explore the effect of anti-seizure treatment on electrographic features of LPDs, including LPD amplitude.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SF: substantially contributed to design, acquisition, analysis, and drafting the manuscript. MS: contributed to study design, data acquisition, and critically revised the manuscript. KG: contributed to conception, interpretation of data, and critically revised the manuscript. AS: contributed to design, data analysis, and critically revised the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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Association Between Partial Pressure of Carbon Dioxide and Immediate Seizures in Patients With Primary Intracerebral Hemorrhage: A Propensity-Matched Analysis

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Purpose: To explore the value of partial pressure of carbon dioxide ($PaCO_2$) levels in arterial blood for predicting immediate seizures (ISs) in patients with primary intracerebral hemorrhage (ICH).

Methods: Demographic information and clinical data from patients with primary ICH were prospectively collected, including arterial blood gas analysis. Immediate seizures (ISs) were determined as seizures in the first 24 h after admission. Univariate and multivariate analyses were performed to assess the association of $PaCO_2$ levels with ISs. Propensity-score matching (PSM) analyses were adopted to reduce the baseline difference between ISs and non-ISs groups.

Results: A total of 596 patients with primary ICH were initially screened in this clinical study, 368 of whom fulfilled all the inclusion criteria [mean age, (60.46 ±12.78) years; 57.9% female patients]. ISs occurred in 30 of the 368 (8.15%) patients with primary ICH of this cohort. Patients with ISs had significantly lower $PaCO_2$ levels [34.35(32.38–37.53) vs. 39.45(35.90–43.43), mmHg, $p < 0.001$] and were younger than those without ISs [(54.57±12.15 vs. 60.99 ±12.72) years, $p = 0.008$]. Multivariate analysis showed that lower initial $PaCO_2$ (≤37.2 mmHg) level was a significant independent predictor of ISs [odds ratios (OR) 0.141, 95% confidence interval (CI) 0.057–0.351, $p < 0.001$], as well as younger age (OR 0.961, 95% CI 0.928–0.995, $p = 0.023$) and hematoma expansion (OR 0.340, 95% CI 0.134–0.863, $p = 0.023$). Receiver operating characteristic curve (ROC) analysis demonstrated that the optimal cutoff value of $PaCO_2$ level for predicting ISs was 37.20 mmHg in patients with primary ICH (the area under the curve (AUC) was 0.760 with a corresponding sensitivity of 76.67% and specificity of 67.46%, 95%CI = 0.713–0.802, $p < 0.001$). After PSM, the matched ISs group had significantly lower $PaCO_2$ levels compared with the matched non-ISs group [34.45(32.43–38.18) vs. 41.75(35.85–43.98) mmHg, $p < 0.05$] in the univariate analysis. The lower initial $PaCO_2$ level was still independent of ISs following primary ICH.

Conclusions: The lower initial $PaCO_2$ level was associated with an increased risk of ISs in patients with primary ICH.

Keywords: intracerebral hemorrhage, carbon dioxide, epilepsy, risk factor, stroke

INTRODUCTION

Intracerebral hemorrhage (ICH) occurs in 15–25% of all strokes and is the most devastating and untreatable type of hemorrhagic stroke with a high risk of disability and mortality (1, 2). Seizures are a frequent and intractable complication of ICH, and they vary widely among epidemiological studies, ranging from 2.5 to 28% (3–9), with the majority occurring at or near onset (10, 11). The reported literature generally classifies seizures by the time of onset as immediate (<24 h after admission), early (1–14 days), or late (>2 weeks) (12). Most animal models have shown that the first seizure occurred in the first 24 h post-ICH (13). Clinically, ∼90% of the seizures occur within the first 3 days post-ICH (11, 14, 15). Following ICH, the risk factors for immediate seizures (ISs) include young age and lobar location of ICH (5, 12).

Carbon dioxide (CO_2) plays a crucial role in neuronal metabolic activity, neurotransmitter function, and regulating cerebral blood flow (CBF) (16, 17). Acute hemorrhagic stroke, including ICH, appears to correlate with a significant decrease in CO_2 levels (10). Published animal studies have demonstrated that CO_2 levels influence tissue pH, which plays a vital role in developing acute epilepsy (18, 19). Previous literature indicated that CO_2 concentrations and respiratory mechanisms might be associated with seizures (20–22). The hippocampus and cerebral cortex, frequently involved in seizures, are susceptible to CO_2 and may mediate a neuroendocrine response to CO_2 (19). Prior studies demonstrated that lower partial pressure of carbon dioxide ($PaCO_2$) was associated with febrile convulsions or the absence of seizures in children (23, 24). One recent study revealed that early decreased $PaCO_2$ levels in the first 24 h were independently associated with an increased incidence of acute seizures in patients receiving extracorporeal membrane oxygenation for respiratory failure (25). To date, the association of $PaCO_2$ with ISs following ICH has not previously been reported in the literature (12, 26). Also, Hextrum et al. have reported that the initial $PaCO_2$ level is a stronger predictor of disease progression than the 72-h nadir (27). We, therefore, sought to test the hypothesis whether the initial $PaCO_2$ level was associated with ISs in patients with primary ICH.

MATERIALS AND METHODS

Study Population

Patients with ICH presenting directly to Dehua County Hospital from January 7 2018 to 21 May 2021, were enrolled in the study. Immediate seizures (ISs) were determined as seizures in the first 24 h after admission (5, 12, 28). Neurosurgeons or nurses witnessed ISs in the hospital. The inclusion criteria were: (1) baseline computed tomography (CT) within 6 h after hemorrhage was performed in all patients, and a follow-up CT scan was performed within 24 h; (2) computerized tomography angiography (CTA) was completed within 72 h of admission to exclude cerebrovascular diseases such as intracranial aneurysms, cerebral arteriovenous malformations, and moyamoya disease; (3) arterial blood gas analysis was performed within 2 h of admission. The exclusion criteria were as follows: (1) patients underwent emergency surgery before follow-up CT;(2) patients with suspicious and pre-admission seizures described by family members; (3) patients with hemorrhage induced by brain infarction, vascular malformations, and a brain tumor; (4) an initial ICH volume <1 ml; (5) primary intraventricular hemorrhage (IVH); (6) acute kidney injury or chronic kidney disease; (7) historical modified Rankin Scale (mRS) scores >1; (8) malignant tumor. Study inclusion/exclusion is summarized in **Figure 1**.

Antiepileptic drugs (AEDs), including sodium valproate, phenobarbital, or levetiracetam, were given if clinical seizures were observed. Multiple AEDs were used in combination when seizures were poorly controlled.

Data Collection

Demographic information and clinical data, including age, sex, medical history, vital admission signs, baseline Glasgow coma score (GCS) score, time from symptom onset to initial CT, baseline ICH volume, primary IVH, ICH location, arterial blood gas analysis, admission laboratory, hematoma expansion (HE), treatment received, mechanical ventilator, and all other data related to their hospitalization were prospectively collected. Arterial blood gas analysis, including $PaCO_2$, was conducted within 2 h after arrival at our department and simultaneously obtained using i-STAT Analyzer (Abbott Park MN: 300-G, Singapore).

CT Scan Analysis

Patients with primary ICH were categorized into two groups for the statistical analysis: patients with deep or lobar ICH. Primary ICH with selective involvement of the thalamus, basal ganglia, internal capsule, deep periventricular white matter, or brain stem was defined as deep ICH, whereas ICH isolated in the cortex (with or without subcortical white matter involvement) was defined as lobar ICH (29). Follow-up CT was carried out within 24 h after hospital admission to identify a HE diagnosis. ICH volumes were calculated using a post-processing workstation (Advantage Workstation 4.6, GE Healthcare, Chicago, Illinois, USA) (30). HE was defined as a 33% increase in the hematoma volume or >6 mL on follow-up imaging (31).

Clinical Prognostic Assessment

Functional outcome was measured at 90 days after ICH onset with the modified Rankin Scale (mRS) score. A favorable outcome was defined as an mRS score of 0–2, and an unfavorable outcome was defined as an mRS score of 4 or greater (32).

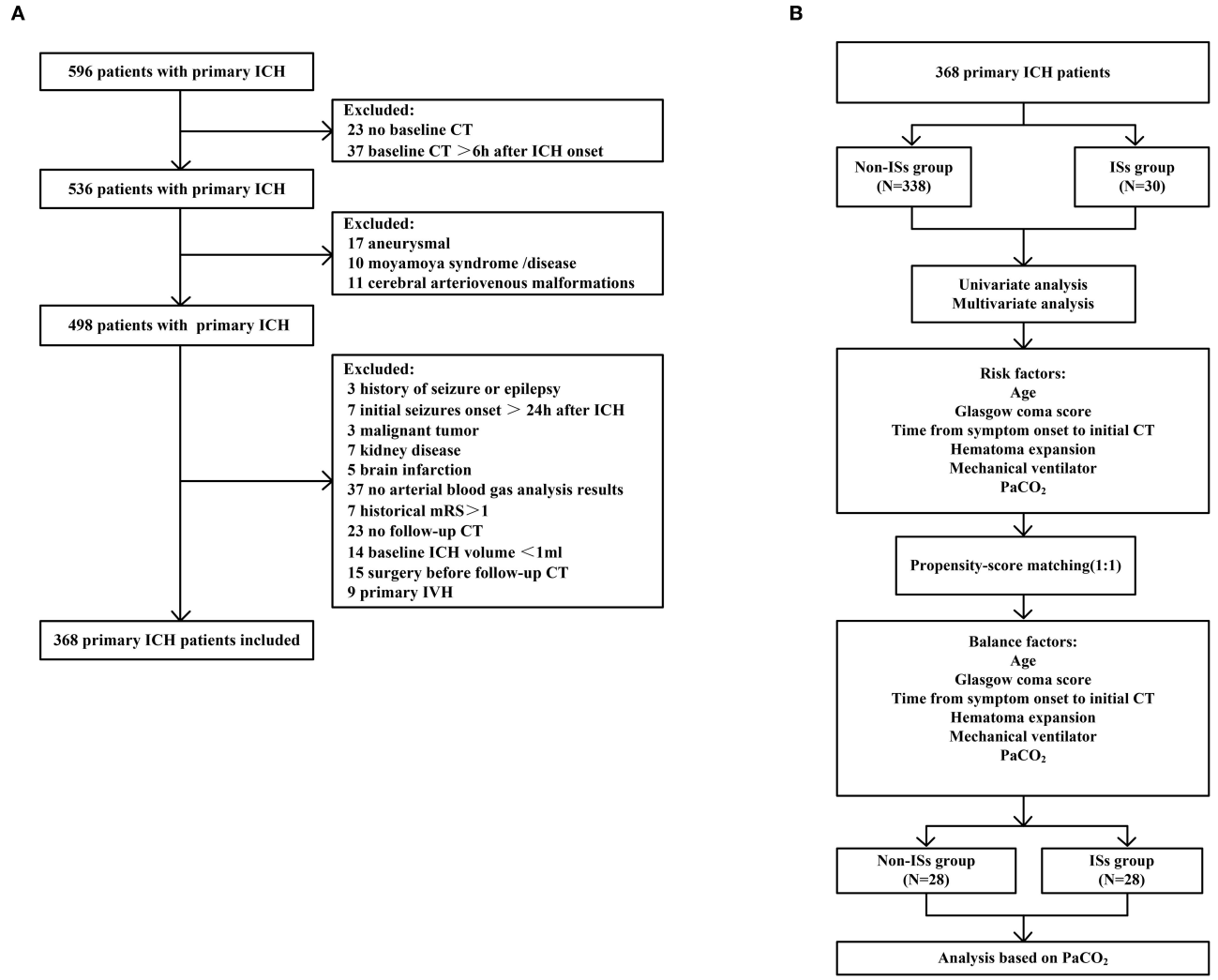

FIGURE 1 | Flow diagram of the patient selection process. **(A)** Flowchart of patient inclusion; **(B)** Flowchart of propensity-score matching. ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage.

Statistical Analysis

Normally distributed continuous variables were presented as mean ± standard deviation (SD), non-normally distributed continuous variables as median (interquartile range, IQR), and categorical variables as frequencies (percentages). Median with IQR was shown for violin plots. Categorical data were analyzed by chi-squared test or Fisher's exact test. Normally and non-normally distributed variables were analyzed for significance by Student's t-test or Mann–Whitney U test, respectively. The correlation was determined using the Spearman rank test. Risk factors with $p < 0.1$ in univariate analyses were included in the multivariate models. Moreover, the receiver operating characteristic (ROC) curve was plotted by MedCalc (MedCalc Software, Ostend, Belgium), and the area under the ROC curve (AUC) was calculated to evaluate the predictive power of $PaCO_2$ for ISs. The best cutoff value of $PaCO_2$ for predicting ISs was selected based on the ROC cutoff value, and patients were divided into "≤optimal cutoff value" and ">optimal cutoff value." Propensity score matching (PSM) analysis was implemented with a 1:1 nearest-neighbor matching algorithm to balance confounders between the two groups. Variables with $p < 0.05$ in the univariate analysis were entered into the PSM. All statistical analyses were performed using SPSS Statistics 25.0 software (SPSS Inc., Chicago, USA) and Prism 8.3.0 (GraphPad Software, San Diego, CA, USA). Differences were considered statistically significant when $p < 0.05$.

RESULTS

As described in **Figure 1** (the detailed flow of the selection process), a total of 596 patients with primary ICH were initially screened in this clinical study, 368 of whom fulfilled all the inclusion criteria [mean age (60.46 ±12.78) years; 57.9% female patients]. Thirty patients (8.15%) experienced

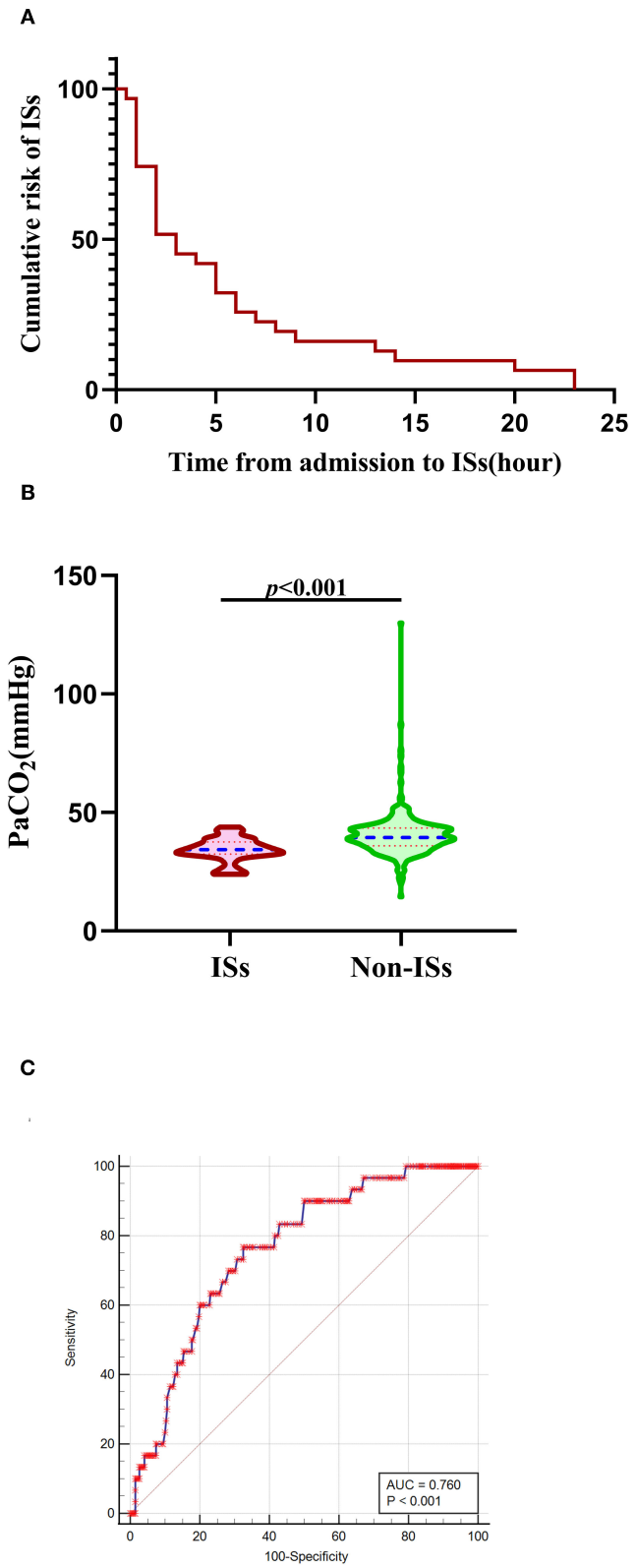

FIGURE 2 | Association of initial $PaCO_2$ levels with ISs. **(A)** The cumulative risk of ISs using Kaplan-Meier analysis within 24 h after admission in the ISs group. *(Continued)*

FIGURE 2 | (B) $PaCO_2$ levels in patients with ISs ($n = 30$) and non-ISs ($n = 338$). **(C)** ROC curve analysis for predicting ISs. The optimal cutoff value of $PaCO_2$ level for predicting ISs was 37.20 mmHg in patients with primary ICH (the AUC was 0.760 with a corresponding sensitivity of 76.67% and specificity of 67.46%, 95%CI = 0.713–0.802, $p < 0.001$). Median with IQR was shown for all violin plots in panel B. Mann–Whitney tests were performed to compare differences between groups. AUC, area under the curve; ICH, intracerebral hemorrhage; ISs, immediate seizures; IQR, interquartile range; $PaCO_2$, partial pressure of carbon dioxide; ROC, Receiver operating curve.

ISs, and 53 patients developed early HE after primary ICH. The median baseline GCS score was 12.0 (7.0–15.0), and the median baseline ICH volume was 12.0 ml (5.0–27.00 ml). The median time from symptom onset to initial CT was 2 h (1–3 h), and the median time from admission to ISs onset was 3 h (1–7 h). Cumulative ISs rate using Kaplan–Meier analysis within 24 h after admission in the ISs group is illustrated in **Figure 2A**.

Baseline demographic and clinical characteristics are summarized in **Table 1**. The 368 patients with primary ICH were stratified into ISs-group ($N = 30$) and non-ISs group ($N = 338$). In the univariate analysis, significant differences were observed in age, mechanical ventilator (MV) within 24 h, GCS score, HE, and $PaCO_2$ between the ISs and non-ISs groups ($p < 0.05$). The $PaCO_2$ level was significantly lower in the ISs group than that in the non-ISs group [34.35 (32.38–37.53) vs. 39.45(35.90–43.43), mmHg, $p < 0.001$; **Table 1** and **Figure 2B**]. Patients were younger in the ISs group than the non-ISs group (54.57±12.15 vs. 60.99 ±12.72, years, $p = 0.008$; **Table 1**). Multicollinearity analyses were carried out among the predictors included in the multivariate analysis model. A variable inflation factor (VIF) > 5 or tolerance < 0.2 indicates the existence of multiple collinearity (33). We observed no significant collinearity between the covariates included in the multivariable models as judged by VIF and tolerance (**Table 2**). Therefore, six covariates were included in stepwise multivariate analysis. In the multivariate logistic regression model, lower initial $PaCO_2$ (≤37.2 mm Hg) level was a significant independent predictor of ISs (OR 0.141, 95% CI 0.057–0.351, $p < 0.001$), as well as younger age [odds ratios (OR) 0.961, 95% confidence interval (CI) 0.928–0.995, $p = 0.023$; **Table 3**)] and HE (OR 0.340, 95% CI 0.134–0.863, $p = 0.023$; **Table 3**). However, baseline GCS score and MV within 24 h were not independent predictors of ISs ($p > 0.05$; **Table 3**). The Hosmer–Lemeshow test, used to access good-of-fit for multivariate models, indicated that the model fitted to a satisfactory extent ($\chi^2 = 5.896$, $p = 0.659$). Interestingly, Spearman correlation analysis detected a positive correlation of $PaCO_2$ with GCS score ($r = 0.1055$, $p = 0.0432$). ROC analysis for assessing the ability of initial $PaCO_2$ to identify ISs is shown in **Figure 2C.** The optimal cutoff value of the initial $PaCO_2$ level for predicting ISs was 37.20 mmHg in patients with primary ICH [the area under the curve (AUC) was 0.760 with a corresponding sensitivity of 76.67% and specificity of 67.46%, 95%CI=0.713-0.802, $p < 0.001$; **Figure 2C**].

TABLE 1 | Univariate analysis of association with ISs before and after propensity-score matching in spontaneous intracerebral hemorrhage patients.

Characteristics	Before propensity-score matching			After propensity-score matching		
	Non-ISs (*N* = 338)	ISs (*N* = 30)	*P*-value	Non-ISs (*N* = 28)	ISs (*N* = 28)	*P*-value
Age, yrs, mean ± SD	60.99 ±12.72	54.57±12.15	0.008	55.61±10.71	54.71±12.56	0.776
Gender (*N*, %)			0.161			0.397
Male	192(74.3)	21(70.0)		17(60.7)	20(71.4)	
Female	146(25.7)	9(30.0)		11(39.3)	8(28.6)	
Admission vital signs						
Temperature, °C, mean ± SD	36.49±0.45	36.63±0.42	0.116	36.59±0.53	36.65±0.42	0.635
SBP, mmHg, mean ± SD	184.74±30.59	184.50±40.76	0.969	190.25±36.89	182.18±40.48	0.439
DBP, mmHg mean ± SD	104.99±18.39	100.70±20.15	0.268	109.0±22.52	100.43±20.83	0.145
Medical history						
Hypertension (*N*, %)	314(92.9)3	26(86.7)	0.217	226(92.9)3	24(85.7)3	0.388388
Chronic obstructive pulmonary disease	100(29.6)	5(16.7)	0.133	6(21.4)	5(17.9)	0.737
Diabetes (*N*, %)	31(9.2)	3(10.0)	0.881	4(14.3)	3(10.7)	0.686
Coronary heart disease (*N*, %)	26(7.7)	3(10.0)	0.653	1(3.6)	3(10.7)	0.299
Baseline Glasgow coma score, median (IQR)	12(7.75–15.0)	9.50(5.75–12.50)	0.008	6.0(5.0–11.75)	9.50(5.25–13.50)	0.199
Time from symptom onset to initial CT, hours, median (IQR)	2.0(1.0–3.0)	1.0(1.0–2.0)	0.079	1.5(1.0–2.0)	1.0(1.0–2.0)	0.930
Baseline volume, ml, median (IQR)	12(5.0–26.27)	11.0(5.75–33.95)	0.495	10.03(6.25–23.95)	10.05(5.25–29.66)	0.954
ICH location (N, %)			0.855			0.783
Lobar	141(41.7)	12(40.0)		11(39.3)	10(35.7)	
Deep	197(58.3)	18(60.0)		17(60.7)	18(64.3)	0.078
Intraventricular hemorrhage (*N*, %)	64(18.9)	5(16.7)	0.760	5(17.9)	4(14.3)	0.716
MV within 24 h (*N*, %)	87(25.7)	16(53.4)	0.001	16(57.1)	14(50.0)	0.592
Hematoma expansion (*N*, %)	43(12.7)	10(33.3)	0.002	5(17.9)	8(28.6)	0.342
Treatment			0.289			0.365
Conservative therapy (*N*, %)	255(75.4)	20(66.7)		22(78.6)	19(67.9)	
Surgery (*N*, %)	83(24.6)	10(33.3)		6(21.4)	9(32.1)	
Admission laboratory						
Hemoglobin, g/L, mean ± SD	136.09±19.89	138.80±21.66	0.479	137.54±20.70	140.54±21.01	0.593
Hematocrit, %, mean ± SD	40.21±5.35	40.72±6.25	0.627	40.70±5.75	41.19±6.14	0.761
Arterial blood gas analysis						
Partial pressure of carbon dioxide, mmHg, median (IQR)	39.45(35.90–43.43)	34.55(32.38–37.53)	<0.001	41.75(35.85–43.98)	34.45(32.43–38.18)	0.001
Partial pressure of oxygen, mmHg, median (IQR)	96(76–125)	114(78.25–135.25)	0.231	91.50(77–112)	114(80–134.75)	0.174
Pondus hydrogenii, median (IQR)	7.40(7.37–7.43)	7.41(7.36–7.46)	0.333	7.39(7.36–7.41)	7.41(7.35–7.46)	0.232
Arterial oxygen saturation, median (IQR)	97(96–99)	97(95–99)	0.883	97(96–98.75)	97.5(95.0–99.0)	0.947
modified Rankin Scale (*N*, %)			0.001			0.515
0–2	163(48.2)	5(16.7)		7(25.0)	5(17.9)	
3–6	175(51.8)	25(83.3)		21(75.0)	23(82.1)	

DBP, diastolic blood pressure; ISs, immediate seizures; IQR, Interquartile range; MV, mechanical ventilator; SBP, Systolic Blood Pressure.

To further account for significant differences in baseline characteristics between the ISs group and non-ISs group, we conducted a PSM. After PSM, two patients in the ISs group could not be matched. The significant differences in age, MV within 24 h, GCS score, and HE between the two groups were balanced. The matched ISs group had significantly lower $PaCO_2$ levels compared with the matched non-ISs group [34.45(32.43–38.18) vs. 41.75(35.85–43.98) mmHg, $p < 0.05$; **Table 1** and **Figure 3A**)] in the univariate analysis. The lower initial $PaCO_2$ level was still an independent predictor of ISs. After PSM, the optimal cutoff value for initial $PaCO_2$ levels as a predictor for ISs following primary ICH was determined as 39.4 mmHg (the AUC was 0.765 with a corresponding sensitivity of 89.29% and specificity of 60.71%, 95%CI = 0.632–0.868, $p < 0.001$; **Figure 3B**).

Patients with ISs had a statistically worse prognosis than patients without ISs (**Table 1**). For the functional outcome of mRS, the distribution of 90-day mRS of both groups is illustrated

in **Figure 4**. Interestingly, no significant difference was witnessed between the two groups after PSM (**Table 1**).

No statistically significant difference was observed in the $PaCO_2$ level between a favorable outcome and an unfavorable outcome [39.55(36.13–43.07) vs. 39.00(34.63–43.08) mmHg $p = 0.341$]. ROC analysis indicated an AUC of 0.529 for $PaCO_2$ levels as a prognostic predictor in patients with ICH.

DISCUSSION

Four principal findings emerge from our study:(1) the lower initial $PaCO_2$ ($\leq$37.2 mmHg) level was a significant independent predictor of ISs in patients with primary ICH; (2) HE and younger age were significantly associated with ISs;(3) the initial $PaCO_2$ level was positively associated with GCS score; and (4) patients with ISs had a statistically worse prognosis than patients without ISs, while no significant difference was witnessed between two groups after PSM. Following ICH, reported risk factors for ISs included age and HE (5, 12), which were balanced in this study. After PSM, there were no significant differences in age and HE between the two groups. The matched ISs group had lower initial $PaCO_2$ levels compared with the matched non-ISs group in the univariate analysis. To the best of our knowledge, lower initial $PaCO_2$ was first reported as a risk factor for ISs following ICH.

Acute hemorrhagic stroke was associated with a significant decrease in CO_2 levels (10). Decreased $PaCO_2$ can elevate the blood pH, which induces cerebral vasoconstriction in the brain and consequently reduces CBF and intracranial pressure (34, 35). Animal models frequently reported CO_2 levels with epilepsy as a trigger for seizures (18, 19). Previous studies demonstrated that lower $PaCO_2$ was associated with febrile convulsions or the absence seizure in children (23, 24). One recent study revealed that early decreased $PaCO_2$ levels in the first 24 h were independently related to an increased incidence of acute seizures in patients receiving extracorporeal membrane oxygenation for respiratory failure (25). This study found that lower initial $PaCO_2$ was a significant independent predictor of ISs following primary ICH, even after adjusting for confounders or PSM.

It has been well documented that CBF is associated with $PaCO_2$ levels, and $PaCO_2$ is one of the most decisive parameters that affect CBF (36). Middle cerebral artery (MCA) flow changes by 4% for every 1 mmHg increase or decrease in $PaCO_2$ between 20 and 80 mmHg (16). Crucially, for every 1 mm Hg incremental lowering of $PaCO_2$, CBF decreases by 3% (27). Prior study has hinted that an association between acute hemorrhagic stroke, lower $PaCO_2$, and brain tissue hypoxia is purported to be driven by the onset of cerebral vasoconstriction (27, 37). Hextrum S and colleagues have reported that lower initial $PaCO_2$ was associated with an increased risk of developing ischemic lesions (27). The vasoconstrictive effects of lower $PaCO_2$ may be compounded by other factors that reduce CBF (acute blood pressure reduction in ICH, lowering intracranial pressure) to increase the risk of secondary ischemic injury (27), which results in the dysfunction of neuronal metabolic activity, thereby producing an acute epileptic seizure. Cerebral ischemia and reperfusion injury exacerbate seizures when CBF gradually returns to normal and subsequent oxygen and arterial $PaCO_2$. In addition, the vasoconstrictive effects of lower $PaCO_2$ reduce hemoglobin oxygen release, increasing neuronal excitability and possibly releasing excitatory toxins such as glutamate (38), which may induce ISs. Decreased $PaCO_2$ can induce seizures by affecting cortical pH, γ-aminobutyric acid (GABA) release, and brain electrical activity (19). Lower cerebrospinal fluid (CSF) $PaCO_2$ levels reduce cerebral blood volume and CBF through cerebral arterial vasoconstriction, which causes

TABLE 2 | Multicollinearity test for the factors of a multivariate model.

	Multicollinearity statistics	
Independent Variable	**Tolerance**	**Variable inflation factor**
Age	0.967	1.034
Baseline Glasgow coma score	0.523	1.913
Time from symptom onset to initial CT, hours, median (IQR)	0.931	1.074
Partial pressure of carbon dioxide ≤37.2 mmHg	0.963	1.039
Hematoma expansion	0.972	1.028
Mechanical ventilator within 24 h	0.533	1.877

TABLE 3 | Predictors for ISs of spontaneous intracerebral hemorrhage in multivariate model.

	Unadjusted OR (95%CI)				Adjusted AOR (95%CI)			
Independent variable	**OR**	**Lower**	**Upper**	***P*-value**	**OR**	**Lower**	**Upper**	***P*-value**
Age	0.957	0.926	0.990	0.010	0.961	0.928	0.995	0.023
Baseline Glasgow coma score	0.891	0.813	0.977	0.014	0.976	0.850	1.120	0.726
Time from symptom onset to initial CT, hours, median (IQR)	0.944	0.842	1.059	0.326	0.962	0.863	1.072	0.480
Partial pressure of carbon dioxide ≤37.2mmHg	0.872	0.819	0.929	<0.001	0.141	0.057	0.351	<0.001
Hematoma expansion	0.292	0.128	0.664	0.003	0.340	0.134	0.863	0.023
Mechanical ventilator within 24 h	0.303	0.142	0.647	0.002	0.409	0.138	1.210	0.106

CI, Confidence interval; OR, Odds ratios.

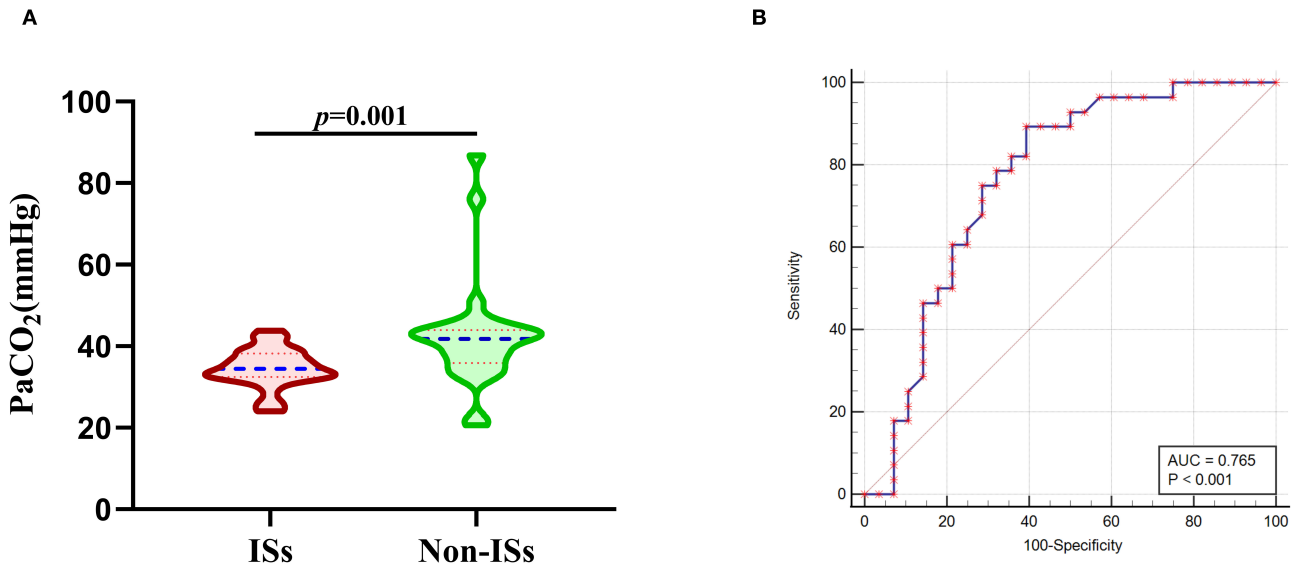

FIGURE 3 | Association of initial $PaCO_2$ levels with ISs after PSM. **(A)** $PaCO_2$ levels in patients with ISs ($n = 28$) and non-ISs ($n = 28$) after propensity-score matching. **(B)** ROC curve analysis for predicting ISs after PSM. The optimal cutoff value for $PaCO_2$ levels as a predictor for ISs following primary ICH was determined as 39.4mmHg (the AUC was 0.765 with a corresponding sensitivity of 89.29% and specificity of 60.71%, 95%CI = 0.632–0.868). Median with IQR was shown for all violin plots in **(A)**. Mann-Whitney tests were performed to compare differences between groups. AUC, area under the curve; ICH, intracerebral hemorrhage; ISs, immediate seizures; IQR, interquartile range; ISs, immediate seizures; $PaCO_2$, partial pressure of carbon dioxide; ROC, Receiver operating curve.

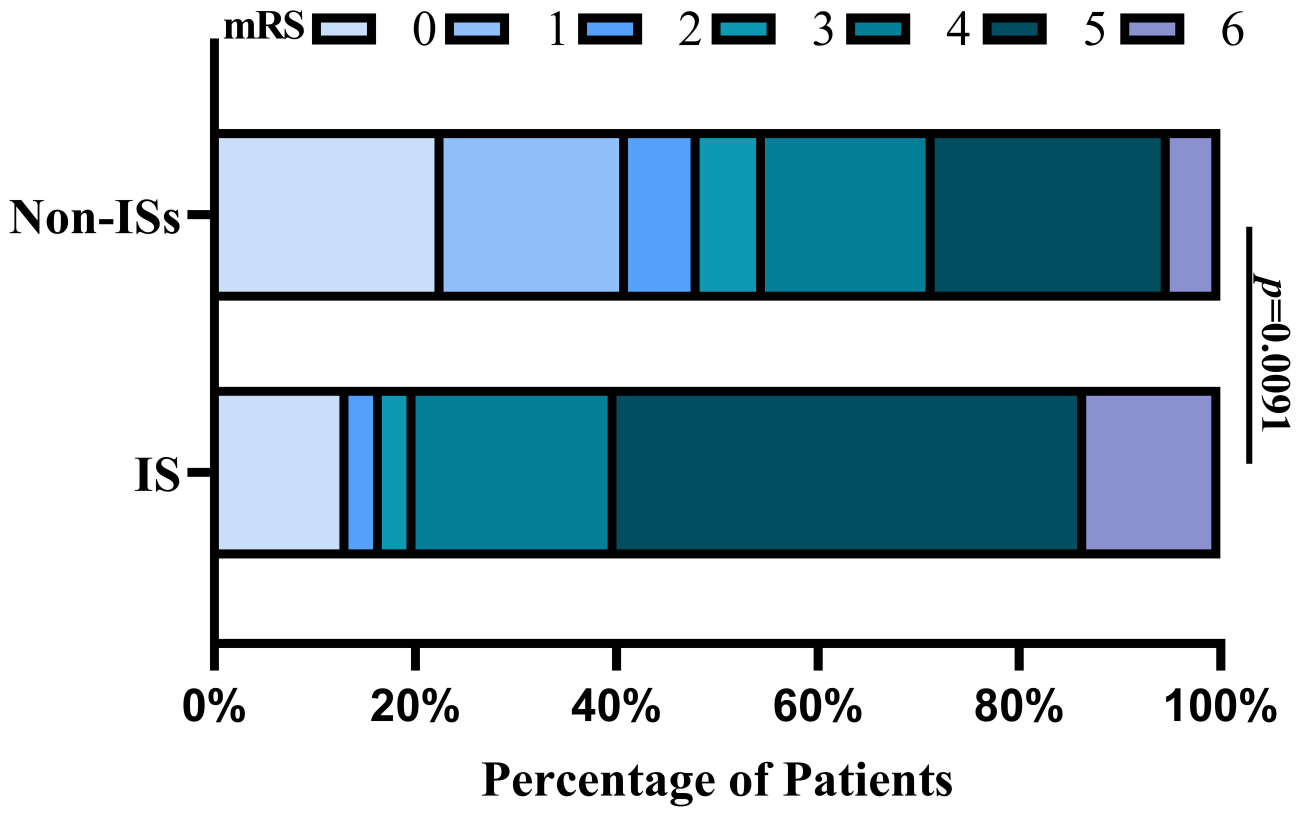

FIGURE 4 | Distributions of mRS scores at 90 days between the ISs and non-ISS groups. Proportions of patients within each score category on the 7-point scale (where o indicates no symptoms and 6 indicates death) at 90 days. ISs, immediate seizures; mRS, modified Rankin Scale.

ischemia and hypoxia in brain tissue, contributing to ISs following ICH (39).

Clinical observations and experimental animal models have demonstrated that changes in CO_2 have significant effects on neuronal excitability and seizure propensity in susceptible individuals (40–42). Reduced CO_2 increases neuronal excitability in the hippocampus, contributing to acute seizures (40). The hippocampus, frequently involved in seizures, is susceptible to CO_2 and mediates a neuroendocrine response to CO_2 (40, 41). In the hippocampal slice preparation, decreasing CO_2 levels reduced extracellular adenosine concentration and increased neuronal excitability via adenosine A_1 receptors, adenosine triphosphate (ATP) receptors, and ecto ATPase, causing ISs (40).

As is well-known, inflammation response to ICH is a significant factor in acute seizures (26, 43). Shreds of evidence from clinical and experimental studies indicated that brain inflammation plays an essential role in seizures (26, 43). The elevation of inflammatory cytokines, such as tumor necrosis factor and interleukin, were also detected in patients with epilepsy and in epilepsy models (38, 43). Interestingly, lower $PaCO_2$ can increase tumor necrosis factor and interleukin (38, 44). In the present study, decreased $PaCO_2$ level was observed in the ISs group after ICH, supporting a possible link between $PaCO_2$, inflammation, and seizures.

Interestingly, one unexpected finding is that the risk of ISs was no different between those with lobar and deep ICH, unlike the results of previous literature (12). The result is noteworthy for the following reasons. On the one hand, the classification of hematoma location in this study is different from previous literature (12). In a study by Cheng Qian et al. (12), which classified ICH locations into subcortical, thalamic, ganglionic, infratentorial (cerebellum and/or pons), and other hematomas, subcortical hematomas were associated with ISs. On the other hand, prior studies have focused on the relationship between early seizures (1–7 days or 1–14 days) and ICH location, rather than ISs (<24 h after admission) (15, 28). Early seizures and ISs have different temporal boundaries, and so the results are not universally identical.

The prognostic significance of $PaCO_2$ levels in critically ill patients, including ICH, remains controversial. Hextrumet al. have previously demonstrated that lower initial $PaCO_2$ was independently associated with a greater risk of in-hospital death in patients with ICH (27). A recent study has shown that decreased $PaCO_2$ improves cerebral autoregulation and possible outcome in patients following ICH (45). Contrary to previous studies (25, 27, 45), we found that $PaCO_2$ level was not associated with unfavorable outcomes. ROC analysis indicated an AUC of 0.529 for $PaCO_2$ levels as a prognostic predictor in patients with ICH, indicating that the predictive value of $PaCO_2$ level in predicting poor prognosis was weak. Lower initial $PaCO_2$ level may be a marker of illness severity rather than a cause of worse clinical outcomes. This hypothesis supported the current study results of a positive correlation between the initial $PaCO_2$ level and the commonly used disease severity scores-GCS score. The inconsistency of the data obtained in this study with previous studies may be due to the limited sample size and different inclusion and exclusion criteria.

The ISs incidence in our study is in line with the study of Szaflarski et al., demonstrating that 8.4% of patients with ICH had a seizure within the first 24 h of stroke onset in a population-based study (28). According to our definition of ISs, the incidence of ISs in the previous study is 8.4%. Whether there is an independent causal relationship between ISs and neurologic outcomes in patients with ICH remains controversial. Cheng Qian et al. have reported that ICH patients with ISs had the highest mortality rate (12). Conversely, Szaflarski JP et al. have demonstrated that ISs are not independent predictors of in-hospital mortality, which is consistent with the fact that ISs are predominantly lobar ICH without intraventricular spread and are smaller, implying a better prognosis (5). In the present study, patients with ISs had a statistically worse prognosis than patients without ISs at the 90-day follow-up after ICH onset.

This was a single-center clinical study and a hospital-based analysis with inherent limitations when interpreting the findings. Firstly, there were relatively few patients with ISs in the current research. Furthermore, $PaCO_2$ levels of CSF had not been collected, and $PaCO_2$ levels in arterial blood cannot directly reflect the actual level in the brain tissue. A single measurement may not fully reflect accurate $PaCO_2$ levels over time. Continuous dynamic $PaCO_2$ monitoring was the evident approach for improving accuracy. Thirdly, the sample sizes decreased, which may influence IS prediction accuracy for ISs due to the stringent inclusion/exclusion criteria. Fourthly, $PaCO_2$ levels are within the normal range in some patients with ICH with ISs, so the result is not straightforward to interpret. More insight into detailed mechanisms awaits further study. Finally, the diagnosis of seizures was made clinically, and information on electroencephalography was not obtained.

CONCLUSIONS

The lower initial $PaCO_2$ levels may be a crucial biomarker in predicting ISs in patients following ICH. The $PaCO_2$ level is readily available as an indicator of blood gas analysis at admission and may help identify high-risk patients with ISs. However, further large-scale or randomized studies are needed to verify these findings and determine whether changes in $PaCO_2$ levels over time are associated with the onset of ISs.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research Ethics Committee of Dehua County

Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZP and YZ designed the study. ZP, QZ, and YZ drafted the manuscript. ZP, CW, XC, and XL collected and analyzed data. YZ helped in the statistical analysis and result interpretation. XZ and YZ were identified as the guarantor of the article, taking responsibility for the integrity of the work as a whole, and prepared the figures and interpreted the results. JW, XZ, and YZ supervised the study and revised manuscript. All authors read and approved the final manuscript.

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Predictive Factors of Acute Symptomatic Seizures in Patients With Ischemic Stroke Due to Large Vessel Occlusion

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Introduction: Acute symptomatic seizures (ASz) after ischemic stroke are associated with increased mortality; therefore, identifying predictors of ASz is important. The purpose of this study was to analyze predictors of ASz in a population of patients with ischemic stroke due to large arterial vessel occlusion (LVO).

Materials and Methods: This retrospective study examined patients with acute ischemic stroke caused by LVO between 2016 and 2020. Identification of predictive factors was performed using univariate and subsequent multiple logistic regression analysis. In addition, subgroup analysis regarding seizure semiology and time of seizure occurrence ($\leq$ 24 h and $>$ 24 h after stroke) was performed.

Results: The frequency of ASz among 979 patients was 3.9 % ($n = 38$). Univariate logistic regression analysis revealed an increased risk of ASz in patients with higher National Institutes of Health Stroke Scale (NIHSS) score at admission or 24 h after admission, hypernatremia at admission $\geq$ 145 mmol/L, and pneumonia. Further multiple logistic regression analysis revealed that NIHSS 24 h after admission was the strongest predictor of ASz, particularly relating to ASz occurring later than 24 h after stroke. Patients who experienced a seizure within the first 24 h after stroke were more likely to have a generalized tonic-clonic (GTCS) and focal motor seizure; beyond 24 h, seizures with impaired awareness and non-convulsive status epilepticus were more frequent.

Conclusion: NIHSS score 24 h after admission is a strong predictive factor for the occurrence of ASz in patients with ischemic stroke caused by LVO. The semiology of ASz varied over time, with GTCS occurring more frequently in the first 24 h after stroke.

Keywords: epilepsy, seizure, intravenous thrombolysis, mechanical recanalization, stroke unit

INTRODUCTION

Cerebrovascular disease is the most common cause of epilepsy in the elderly, accounting for up to 39–49% of all newly diagnosed epilepsies in patients aged > 60 years (1, 2). Due to demographic changes, the incidence of stroke-related epilepsy is expected to rise and pose an increasing challenge for the healthcare system (3). Depending on the time course, seizures after stroke are defined according to the International League Against Epilepsy (ILAE) either as an acute symptomatic seizure (ASz) if they occur within 7 days, or as an unprovoked late seizure if they occur later than 7 days (4). Acute symptomatic seizures are thought to result from local cellular biochemical dysfunction of electrically excitable tissues, whereas late seizures are caused by post-ischemic remodeling of the damaged brain tissue and neuronal network, leading to an acquired predisposition to seizures and the diagnosis of post-stroke epilepsy (5–8). A large systemic review and meta-analysis examined the frequency of seizures after ischemic stroke; the frequency of ASz was found to be 3.3% and the late post-stroke seizure frequency was 1.8% (9). Because ASz are associated with an increased risk of mortality, knowledge of predictive factors is essential (10, 11). Various risk factors with different levels of evidence are described in the literature. The severity of stroke, estimated by the National Institutes of Health Stroke Scale (NIHSS), and cortical involvement were identified as independent risk factors for the occurrence of ASz (11–16). Data are inconclusive regarding other possible risk factors, such as cardioembolic infarct etiology, anterior circulation cerebral infarction, hemorrhagic transformation, previous transient ischemic attack (TIA), acute non-neurological infection, and history of diabetes mellitus (10, 11, 13, 17). Based on these results, different prediction models have been developed to assess the individual risk for post-stroke seizures (18, 19). Furthermore, therapy with statins in the acute phase of stroke was reported to reduce the rate of seizures (20). Systemic thrombolysis and mechanical thrombectomy as established reperfusion procedures have also been the subject of research, with recent studies showing no association with ASz frequency (21, 22).

The variability among identified predictive factors may be explained by the heterogeneous designs of the available studies, with varying levels of evidence (registry studies, retrospective and prospective designs, mono- or multi-centric studies, systematic reviews), inclusion criteria (hemorrhagic and ischemic stroke), and definitions of ASz occurring later than 7 days (17, 23, 24). Furthermore, the studies were conducted over an extended period, including several studies in which neurological treatment in stroke units differed and new therapeutic milestones, such as mechanical recanalization, had not yet been established.

The purpose of this study is to analyze predictive factors for ASz in a well-defined patient population who experienced an ischemic stroke due to large vessel occlusion (LVO) and who were treated after mechanical recanalization had become the standard therapy for LVO in 2016.

MATERIALS AND METHODS

This study analyzed data from patients with acute ischemic stroke who were treated at the University Hospital Frankfurt between 2016 and 2020. The Local Ethics Committee of Goethe University Frankfurt approved the study (IRB: 19-285). Due to the retrospective design of this study, the requirement for written informed consent of the patients was waived. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were closely followed (25).

We included patients with a final International Statistical Classification of Diseases and Related Health Problems, 10th revision (IDC-10) diagnosis of "acute ischemic stroke caused by an occlusion of a large cerebral vessel." The occlusion of a large cerebral vessel was confirmed either by imaging with CT or MR angiography, or by infarct demarcation that could only be explained by a proximal vessel occlusion. LVO was defined according to the literature as an occlusion of the internal carotid artery, middle cerebral artery (including M1 and M2 segments), anterior cerebral artery (including A1 and A2 segments), posterior cerebral artery (including P1 and P2 segments), vertebral artery, or basilar artery. LVOs were further divided into either anterior (internal carotid artery, middle cerebral artery, and anterior cerebral artery) or posterior (posterior cerebral artery, vertebral artery, and basilar artery) circulation.

The collected data contained the following variables: age; sex; NIHSS score at admission, 24 h after admission, and at discharge; modified Rankin Scale (mRS) score prior to stroke and at discharge; type of LVO; stroke etiology according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria (26); history of arterial hypertension, diabetes mellitus, atrial fibrillation, chronic alcohol consumption, previous stroke, and brain tumor; known neurodegenerative disease; previous treatment with oral anticoagulants, antiplatelet agents, or statins; serum level of sodium (mmol/L), glucose (mg/dl), and total cholesterol (mg/dl) at admission; and hemorrhagic transformation. In addition, preexisting treatment with anti-seizure medication (ATC code N03A irrespective of indication, e.g., mood stabilizer or management of neuropathic pain) was ascertained. Furthermore, treatment with mechanical thrombectomy or systemic thrombolysis was assessed. In patients who underwent mechanical thrombectomy, the outcome of mechanical recanalization was reported according to the TICI (thrombolysis in cerebral infarction) grading system, with a score of at least 2b considered successful reperfusion (27). Mechanical thrombectomy is routinely performed under general anesthesia with subsequent weaning on the intensive care unit. The occurrence of pneumonia during hospital stay was assessed, which was defined by radiological evidence of pneumonia-compatible findings (e.g., infiltrates, consolidation) with associated clinical (e.g., purulent sputum, hypoxia, dyspnea, tachypnea, pathologic auscultation of the lungs, fever > 38.3°C) and laboratory signs (e.g., leukopenia < 4,000 leukocytes/mm^3, leukocytosis > 12,000/mm^3).

An ASz was defined as either clinically observed ictal stigmas or subclinical seizure patterns or non-convulsive status epilepticus (NCSE) recorded on electroencephalography (EEG) within the first 7 days after stroke (seizure latency) (4). EEG was performed according to the indication of the attending physician; standard continuous EEG diagnostics was not performed. There was no prophylactic antiseizure medication administered after ischemic stroke. Further subgroup analysis was performed for seizures occurring $\leq$ 24 h and later than 24 h until 7 days of stroke onset. Based on the reported semiology and EEG patterns, seizures were subdivided into: (I) seizures with impaired awareness or NCSE, (II) focal motor seizures, and (III) generalized tonic-clonic seizures (GTCS) (28).

For the regression analysis, we further divided the numerical and ordinally scaled variables into categories. NIHSS score was divided into three groups: 0-5 points, corresponding to none or mild neurological deficit; 6-15 points, corresponding to moderate neurological deficit; and more than 15 points, corresponding to severe neurological deficit. We also divided the mRS score into two groups: 0-2 points for patients with no significant or only slight disability in their daily lives, and 3-5 points for patients with moderate-to-severe disability. Furthermore, sodium level at admission was classified as hyponatremia ($\leq$ 135 mmol/L), normal (136–144 mmol/L), or hypernatremia ($\geq$ 145 mmol/L). The glucose level was classified as hypo- ($\leq$ 50 mg/dl) or hyperglycemia ($\geq$ 200 mg/dl).

Statistical analyses were performed using SPSS (version 27.0.1.0, IBM Corp., Armonk, NY, USA). For statistical evaluation, univariate binary logistic regression analysis was initially performed for independent variables, with ASz as the dependent variable. Based on this analysis, significant (p-value < 0.1) independent variables were selected for further multiple binary logistic regression analysis. Due to a total of 38 ASz, the number of covariates to be included was limited to 4 variates (the number of positive cases in the dependent variable divided by 10). Intergroup differences in seizure semiology regarding time of occurrence were calculated using the chi-squared test. P-values were corrected for multiple testing by using the Benjamini–Hochberg false discovery rate method. For multiple logistic regression and the chi-squared test, a p-value < 0.05 was determined to be significant.

RESULTS

A total of 979 patients were included in this study, with an ASz frequency of 3.9 % ($n = 38$). For an overview of patient characteristics and the results of the univariate binary logistic regression analysis, (see **Table 1**). Among the evaluated independent variables, univariate binary logistic regression analysis revealed an increased risk of ASz in patients with a NIHSS score > 15 points at admission (47.4 vs. 33.7%, $p = 0.09$), 24 h after admission (47.8 vs. 23.5%, $p = 0.025$) and at discharge (33.3 vs. 9.5%, $p = 0.021$), which was also found for the numeric NIHSS score at admission, after 24 h and at discharge. Furthermore, patients with ASz were more likely than patients without ASz to have hypernatremia at admission (18.4 vs. 6.5%, $p = 0.048$) or pneumonia (47.4 vs. 29.4%, $p = 0.07$). A mRS score at discharge of 3-5 points was significantly more common in patients who suffered an ASz than in those who did not (87.0 vs. 49.3%, $p = 0.017$), which corresponds to greater disability in these patients after stroke.

Based on the univariate logistic regression, NIHSS score at admission (numeric), NIHSS after 24 h (numeric), hypernatremia at admission, and pneumonia were included in the final multiple logistic regression analysis. Because mRS at discharge and NIHSS score at discharge are typically ascertained beyond 7 days after stroke, they were not suitable for the prediction of ASz and therefore were not included. Following multiple logistic regression analysis, NIHSS score after 24 h was the strongest predictor for the occurrence of ASz (OR: 1.096, 95% CI: 1.036–1.159, $p < 0.001$), whereas NIHSS score at admission, pneumonia, and hypernatremia at admission did not reach the level of significance (**Table 2** and **Figure 1**).

Seizures occurred at a median (minimum–maximum) of 2 (0–7) days after stroke onset. More than half ($n = 22$, 57.9 %) of the seizures occurred within the first 2 days, and over three-quarters ($n = 29$, 76.3 %) of the seizures occurred within the first 3 days. For subgroup analysis of seizures, we divided them into two groups: seizure onset within the first 24 h after stroke ($n = 11$, 28.9%), and seizure onset later than 24 h after stroke ($n = 27$, 71.1%). We performed a multiple logistic regression analysis for each subgroup and included the following variables: NIHSS score at admission (numeric), NIHSS score after 24 h (numeric), hypernatremia at admission, and pneumonia. A high NIHSS score 24 h after admission was a risk factor only for the occurrence of seizures with onset later than 24 h after stroke (OR: 1.103, 95 % CI: 1.035–1.174, $p = 0.002$). The other variables had no significant influence on stroke occurrence in the subgroup analysis (**Table 3**). Regarding seizure semiology, significantly more GTCSs (54.5 vs. 14.8%, $p = 0.028$) and more focal motor seizures (36.4 vs. 7.4%, $p = 0.047$) occurred in the subgroup of patients who had their seizure within the first 24 h after stroke. In contrast, there were significantly more seizures with impaired awareness in the subgroup of patients who suffered from ASz later than 24 h after stroke (77.8 vs. 9.1%, $p = 0.003$). For details, refer to **Table 4**.

DISCUSSION

The aim of this study was to investigate predictors of ASz in a well-defined study population of patients with LVO treated after the paradigm shift in stroke therapy to the widespread use and availability of mechanical thrombectomy (29). In our analysis, NIHSS score after 24 h was shown to be the strongest predictor for the occurrence of ASz in patients with ischemic stroke due to LVO. A higher NIHSS score correlates with a larger volume of damaged brain tissue and concomitant cortical involvement, which can explain the increased seizure risk (30). Our study showed a stronger predictive value of the NIHSS score after 24 h compared with the NIHSS score at admission. Furthermore, in the subgroup analysis, we demonstrated that a high NIHSS score was particularly associated with the occurrence of seizures later than 24 h after stroke.

TABLE 1 | Univariate logistic regression analysis of clinical parameters and their association with acute symptomatic seizures in patients after ischemic stroke.

Predictor		Number of available data; %	Acute symptomatic seizure, $n = 38$	No acute symptomatic seizure, $n = 941$	Corrected p-value
Age	Mean ± SD	979; 100%	72.3 ± 11.6	71.0 ± 14.0	0.87
Female gender		979; 100%	17; 44.7%	453; 48.1%	0.89
NIHSS at admission	≤5*	978; 99.9%	4; 10.5%	261; 27.8%	0.18
	6–15		16; 42.1%	362; 38.5%	0.17
	>15		18; 47.4%	317; 33.7%	**0.09**
	Median (Q1–Q3)		15 (9–21)	12 (5–17)	**0.029**
NIHSS after 24 h	≤5*	754; 77.0%	4; 17.5%	340; 46.5%	**0.09**
	6–15		8; 34.8%	219; 30.0%	0.19
	>15		11; 47.8%	172; 23.5%	**0.025**
	Median (Q1–Q3)		15 (6–24)	6 (2–15)	**0.043**
NIHSS at discharge	≤5*	607; 62.0%	5; 27.8%	399; 67.7%	**0.02**
	6–15		7; 38.9%	134; 22.8%	**0.08**
	>15		6; 33.3%	56; 9.5%	**0.021**
	Median (Q1–Q3)		11.5 (3.75–20.25)	2 (0–8)	**0.014**
mRS at admission	0-2*	944; 96.4%	30; 81.1%	764; 84.2%	0.87
	3-5		7; 18.9%	143; 15.8%	
mRS at discharge	0-2*	629; 64.2%	3; 13.0%	307; 50.7%	**0.017**
	3-5		20; 87.0%	299; 49.3%	
Vascular territory	Anterior circulation*	979; 100%	34; 89.5%	770; 81.8%	0.32
	Posterior circulation	979; 100%	3; 7.9%	158; 16.8%	0.17
	Both circulations	979; 100%	1; 2.6%	13; 1.4%	0.6
Etiology	Unknown or ESUS*	978; 99.9%	12; 31.6%	206; 21.9%	0.91
	Atherothrombotic		10; 26.3%	323; 34.4%	0.3
	Cardioembolic		16; 42.1%	367; 39.0%	0.9
	Other		0; 0.0%	44; 4.7%	1.0
Acute stroke therapy	ST	979; 100%	17; 44.7%	413; 43.9%	1.0
	MT	979; 100%	19; 50.0%	453; 48.1%	0.93
	ST and MT	979; 100%	12; 31.6%	252; 26.8%	0.88
	MT with TICI ≥ 2b	472; 100%	17; 89.5%	386; 85.2%	0.85
Preexisting therapies	Oral anticoagulant	979; 100%	5; 13.2%	144; 15.3%	0.88
	Antiplatelet	979; 100%	11; 28.9%	302; 32.1%	0.86
	Statin	979; 100%	14; 36.8%	250; 26.6%	0.34
	Anti-seizure medication	979; 100%	1; 2.6%	61; 6.5%	0.7
Blood glucose level at admission	≤50 mg/dl	954; 97.4%	1; 2.6%	2; 0.2%	0.15
	≥200 mg/dl		2; 5.3%	82; 9.0%	0.82
Sodium level at admission	≤135 mmol/l	966; 98.7%	2; 5.3%	80; 8.6%	0.89
	≥145 mmol/L		7; 18.4%	60; 6.5%	**0.048**
Total cholesterol level > 200 mg/dl		763; 78%	4; 18.2%	152; 20.5%	0.93
Arterial hypertension		979; 100%	28; 73.7%	695; 73.9%	1.0
Atrial fibrillation		979; 100%	16; 42.1%	359; 38.2%	0.85
Chronic alcohol consumption		979; 100%	2; 5.3%	51; 5.4%	1.0
Neurodegenerative disease		979; 100%	3; 7.9%	53; 5.6%	0.89
Previous brain tumor		979; 100%	0; 0.0%	7; 0.7%	1.0
Previous ischemic stroke		979; 100%	11; 28.9%	177; 18.8%	0.29
Hemorrhagic transformation		979; 100%	2; 5.3%	27; 2.0%	0.75
Pneumonia		979; 100%	18; 47.4%	277; 29.4%	**0.07**

**Indicates the reference category in regression analysis. P-values were corrected using the Benjamini–Hochberg false discovery rate method with a p-value < 0.1 considered statistically significant; significant values are marked bold. NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; ESUS, embolic stroke of undetermined source; ST, systemic thrombolysis; MT, mechanical thrombectomy; SD, standard deviation; Q1, first quartile; Q3, third quartile.*

In contrast, no significant association was found between the NIHSS score and the occurrence of seizures within the first 24 h after stroke. In the literature, it was described that most seizures occurred within the first 24 h after stroke (31). This finding could not be reproduced in our study, but there were significant differences regarding seizure semiology. Significantly more focal motor seizures or GTCSs occurred within 24 h after stroke; beyond that period, seizures with reduced consciousness or NCSEs were more common. This observation could be explained by studies that did not include EEGs in their analysis, which may have led to an underestimation of the frequency of non-motor seizures or NCSEs and a predominance of motor seizures, which were more likely to occur in the first 24 h. However, besides differences in seizure semiology, ASz in our study showed a predominance within the first 48 h, which may be explained by different pathophysiological processes of ASz. Within the first hours, acute neuronal excitability due to ischemic disturbance of cellular integrity and pericellular milieu (i.e., electrolytes and neurotransmitters) may represent the prominent factor in seizure development, whereas subsequent tissue destruction and necrotic remodeling processes with surrounding inflammation could be responsible for the development of ASz beyond the first 24 h (32). This supports the hypothesis that in ASz occurring within 24 h after vascular occlusion, the extent of infarction is less important than the acute disturbances of cerebral integrity, for which a possible predisposition of the patient might be relevant. However, an increased risk in patients with a previous stroke, chronic alcohol consumption, previous brain tumor or a neurodegenerative disease was not observed. In this context, it would be of interest to investigate to what extent the risk of post-stroke epilepsy differs regarding the time of occurrence after stroke. Hemorrhagic transformation has been reported to be associated with an increased risk of ASz due to the deposition of blood degradation products such as hemosiderin, leading to local irritation of the brain (16). While hemorrhagic transformations have been consistently reported as an independent predictor of ASz (16, 33), this was not demonstrated in our study, although there was a tendency toward higher incidences of ASz in those patients. A possible reason for the missing of statistical significance might be the overall low incidence of hemorrhagic transformations in the included cohort in comparison to other trials (34).

It has been established that electrolyte imbalances are associated with ASz, with low sodium levels being particularly significant (35). Although hyponatremia seems to be more frequently associated with ASz, our study found an increased risk of ASz in patients with hypernatremia at admission (35). In particular, hypernatremia with a rapid onset, in contrast to chronic hypernatremia, is reported to show a significantly increased risk of ASz (35). Since hypernatremia was recorded

TABLE 2 | Multiple logistic regression analysis showing the influence of different variables on seizure risk.

Predictor	*P*-value	Exp(B)	95% CI lower bound	95% CI upper bound
NIHSS after 24 h	**<0.001**	1.096	1.036	1.159
NIHSS at admission	0.28	0.96	0.893	1.033
Hypernatremia ≥145 mmol/L at admission	0.69	1.360	0.301	6.154
Pneumonia	0.39	1.498	0.602	3.728

95% CI [95% confidence interval for Exp(B)].
NIHSS, National Institutes of Health Stroke Scale. A p-value of < 0.05 was determined significant; significant values are marked in bold.

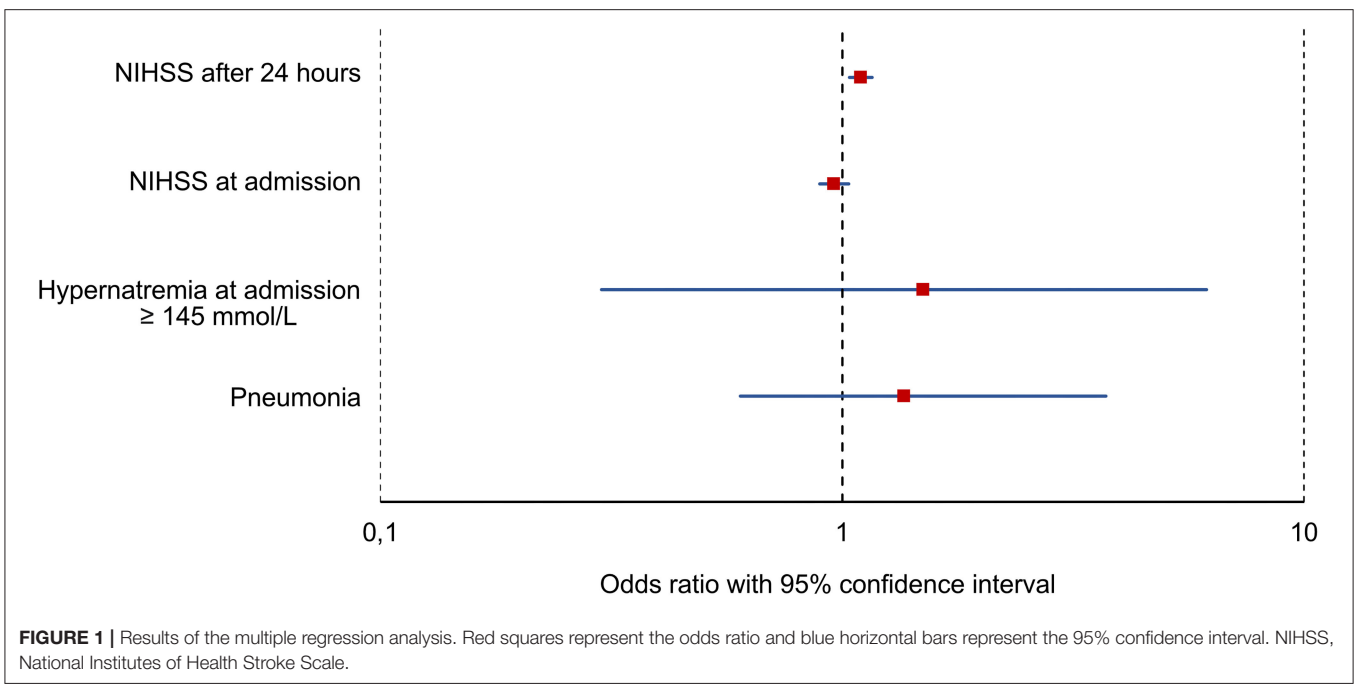

FIGURE 1 | Results of the multiple regression analysis. Red squares represent the odds ratio and blue horizontal bars represent the 95% confidence interval. NIHSS, National Institutes of Health Stroke Scale.

TABLE 3 | Multiple logistic regression analysis with subgroups of seizure patients.

Predictor	Acute symptomatic seizure with stroke latency ≤ 24 h				Acute symptomatic seizure with stroke latency > 24 h			
	P-value	Exp(B)	95% CI lower bound	95% CI upper bound	*P*-value	Exp(B)	95% CI lower bound	95% CI upper bound
NIHSS after 24 h	0.224	1.066	0.962	1.182	**0.002**	1.103	1.035	1.174
NIHSS at admission	0.571	1.040	0.909	1.189	0.150	0.940	0.865	1.022
Hypernatremia ≥ 145 mmol/L at admission	0.366	2.755	0.306	24.820	0.952	0.939	0.119	7.402
Pneumonia	0.309	0.319	0.035	2.884	0.157	2.101	0.752	5.870

95% CI [95% confidence interval for Exp(B)].
NIHSS, National Institutes of Health Stroke Scale. A p-value of < 0.05 was determined significant; significant values are marked in bold.

at admission, a further differentiation between acute or chronic hypernatremia was not possible. Besides initial electrolyte imbalances, critically ill patients on an intensive care unit or stroke unit bear an increased risk for the occurrence of subsequent hypernatremia (e.g., iatrogenic), which was not evaluated in our study (36). Furthermore, there was a trend toward an increased risk of seizures in patients with pneumonia in univariate regression analysis; however, this did not reach the significance level in multiple logistic regression analysis. This lack of effect might be attributed to the small sample size of those who suffered an ASz and the wide 95% confidence interval. In subgroup analysis, this tendency was particularly evident between pneumonia and the occurrence of seizures later than 24 h after stroke (OR: 2.101, 95 % CI: 0.752–5.870, $p = 0.157$). Considering the predominance of ASz within the first 48 h and the increased risk of early pneumonia in patients with LVO due to general anesthesia during mechanical thrombectomy as well as stroke-related dysphagia, all pneumonias during hospital stay without formal classification into community- or hospital-acquired (>48 h after admission) were included (37). However, a more detailed analysis of the temporal association between the occurrence of pneumonia and ASz would be of interest and might be addressed in further studies. Acute non-neurological infections have been demonstrated as a predictive factor in other studies, but these studies usually did not include exclusively pneumonia (11, 13). Apart from concomitant fever, the epileptogenic effect of infections is attributed to the fact that the resulting inflammatory response, particularly by cytokines, lowers the seizure threshold and predisposes the brain to seizures (38).

Previous studies have shown associations with pre-existing diabetes mellitus and with the presence of hyperglycemia in experimental data (13, 39). In our study, hyperglycemia was not associated with an increased risk of ASz; however, hypoglycemia ≤ 50 mg/dl showed a trend toward more ASz. Since hypoglycemia ≤ 50 mg/dl was only observed in a very small number of patients ($n = 3$), this effect needs to be evaluated in future studies. As these factors are reversible causes, knowledge of their potential risk for ASz is important. Therefore, in patients with a recent stroke after LVO, regular monitoring of blood glucose and sodium levels should be performed with the aim of achieving normoglycemia and normonatremia. In addition, pneumonia prophylaxis should be practiced in addition to early treatment initiation after pneumonia has been diagnosed.

TABLE 4 | Seizure semiology in patients with acute symptomatic seizures (ASz) in relation to time of stroke.

Seizure semiology	Corrected *P*-value	ASz with latency to stroke ≤ 24 h ($n = 11$)	ASz with latency to stroke > 24 h ($n = 27$)
Impaired awareness ($n = 22$)	**0.003**	$n = 1$ (9.1 %)	$n = 21$ (77.8 %)
Focal motor seizure ($n = 7$)	**0.047**	$n = 4$ (36.4 %)	$n = 2$ (7.4 %)
GTCS ($n = 10$)	**0.028**	$n = 6$ (54.5 %)	$n = 4$ (14.8 %)

Impaired awareness includes non-convulsive status epilepticus (NCSE). P-values were corrected using the Benjamini–Hochberg false discovery rate method and $p < 0.05$ was considered statistically significant; significant values are marked in bold. GTCS, generalized tonic-clonic seizure.

Regarding reperfusion therapies, in addition to the established systemic thrombolysis, mechanical thrombectomy has been widely available since 2015/2016 as a therapeutic option for emergency reopening of LVO (29, 40). Among the included patients, 50% with ASz and 48.1% without ASz received mechanical thrombectomy. Initial reports suggested that these methods may lead to an increased risk of ASz due to either neurotoxicity or reperfusion damage (41, 42). However, recent studies have not confirmed this and have instead supported the protective effect of reperfusion therapies in reducing the extent of infarction (21, 22). In concordance, this study, which examined only patients with ischemic stroke due to LVO, showed no association between treatment with systemic thrombolysis or mechanical thrombectomy and the occurrence of ASz. Previous studies described an increased risk of post-stroke epilepsy in severe strokes of the anterior circulation, which was attributed to a larger tissue damage (43). In our study, vascular territory (anterior or posterior circulation) was not found to be a predictive factor of ASz, although the overall smaller number of patients with posterior circulation infarcts should be noted. Further studies with a larger number of ASz and a volumetric evaluation of infarct size and location are required to determine their influence on the occurrence of ASz.

Despite a careful evaluation of all patients, this study had several limitations. Due to the limited number of ASz cases, the

possible influence of predictive factors might have been missed. This may explain why some previously described predictors did not reach statistical significance in our analysis. Nevertheless, while this study bears the risk of missing rare variables as predictors, the well-defined population of this single center study allowed us to collect data on seizure semiology and time of seizure onset; this information was often lacking in larger registry studies. The total number of ASz cases may still be underestimated without routine or continuous use of EEG, especially in intensive care units (44). Further studies with prospective designs to detect seizures by routine and continuous EEG in addition to systematic clinical examinations as well as studies with a larger sample size and long-term follow-up are necessary.

CONCLUSION

A high NIHSS score 24 hours after admission is one of the most important predictive factors for the occurrence of ASz in patients following ischemic stroke, especially for ASz occurring later than 24 h after stroke. Semiology of ASz differed significantly, with focal motor seizures or GTCSs occurring more frequently within the first 24 h after stroke, whereas seizures with impaired awareness or NCSE were more frequent beyond 24 h.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following restrictions: Anonymised data will be made available after reasonable request due to german regulations on data protection.

ETHICS STATEMENT

This retrospective study was reviewed and approved by the Ethics Committee of the Medical Faculty of the Goethe University Frankfurt. Written informed consent for was not required for this study.

AUTHOR CONTRIBUTIONS

LT and KK conducted the study, collected the data, and wrote the original draft of the manuscript. LT, RG, and KK carried out the statistical analysis of the data. AS, WP, and KK were responsible for the methodological conceptualization of the study. AS was responsible for the supervision of the study. HS, FR, JS, and JZ contributed to the finalization of the manuscript and the formal analysis of the data. LT, AS, FR, WP, HS, RG, JS, JZ, and KK reviewed and revised the manuscript. All authors contributed to the manuscript and accepted the final version of the manuscript.

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Predicting Global Functional Outcomes Among Post-traumatic Epilepsy Patients After Moderate-to-Severe Traumatic Brain Injury: Development of a Prognostic Model

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Objective: The development of post-traumatic epilepsy (PTE) following traumatic brain injury (TBI) is associated with unfavorable functional outcomes, and the global function of PTE patients might change dynamically overtime. Predicting the long-term functional outcomes of patients with PTE may help to develop accurate rehabilitation programs and improve their quality of life. Based on this, the objective of this study is to use clinical data to derive and validate a model for predicting the functional outcomes of patients with PTE after moderate-to-severe TBI.

Methods: This study retrospectively analyzed 721 patients with PTE after moderate-to-severe TBI in the Epilepsy Centre, Beijing Tiantan Hospital, from January 2013 to December 2018. All patients had favorable global function as indicated by the Glasgow Outcome Scale-Extended (GOSE) at the time of their first late post-traumatic seizure (PTS) onset, and the 5-year global function after the first late PTS onset was chosen as the principal outcome of interest. To identify possible predictors for the global functional outcomes, univariate and multivariate logistic regression techniques were used. A prognostic model was established using these identified predictors, the internal validation with the bootstrapping method was performed, and the model was then visualized as a graphical score chart.

Results: The 5-year global functional outcome of 98 (13.59%) patients was unfavorable, and the temporal lobe lesion was found as the strongest predictor of unfavorable outcomes. The final prognostic model also included the following other predictors: gender, age at TBI, multiple injuries, the severity of TBI, and latency of PTE. Discrimination was satisfactory with C-statistic of 0.754 (0.707 – 0.800), the goodness-of-fit test indicated good calibration ($P = 0.137$), and the C-statistic was 0.726 for internal validation. A graphical score chart was also constructed to provide the probability of an unfavorable 5-year global functional outcomes more readily.

Conclusions: Clearer treatment strategies are essential to help ameliorate the global functional outcomes of patients with PTE. Our proposed prognostic model has significant potential to be used in the clinic for predicting global functional outcomes among patients with PTE after moderate-to-severe TBI.

Keywords: post-traumatic epilepsy, traumatic brain injury, global functional outcome, risk factor, prognostic model

INTRODUCTION

Traumatic brain injury (TBI) is one of the leading causes of death and disability worldwide (1, 2), and there are approximately one million new cases of TBI annually in China alone (3). Previous large-scale studies have concluded that only about 40–50% of individuals achieve a favorable outcome 6 months after moderate-to-severe TBI (4, 5), and within 10 years after TBI, the long-term outcome may tend either to deteriorate or improve (6, 7). Pre-injury employment, white-collar work, and shorter post-trauma amnesia duration have been reported as prognostic factors for better long-term outcomes (7), while male gender, younger age, less severe TBI have shown good prognostic effects on long-term outcomes in several studies (7, 8), but no such prognostic effects were observed in other studies (6, 9). Crucially, however, the importance of rehabilitation programs for certain TBI patients has been highlighted for favorable outcomes (6).

Post-traumatic seizure (PTS) is one of the most common sequelae of TBI and is classified as immediate PTS (within 24 h postinjury), early PTS (between 1 and 7 days postinjury), or late PTS (more than 7 days postinjury) according to the time of occurrence, and recurrent unprovoked late PTS is referred to as PTE (10). The presence of PTE in particular has been found to develop in 4.2–53% of patients who suffer moderate-to-severe TBI (10–13). Since TBI most commonly occurs in young adults (3), who may survive for decades after their injury (14), TBI might in fact become a chronic health condition rather than an acute event (15), especially for those who develop PTE after TBI. Some authors have reported that the development of PTE following TBI is independently associated with unfavorable functional outcomes (16–19). Hence, predicting the long-term outcomes of patients with PTE may help clinicians to provide more personalized medical care and rehabilitation programs that can better improve these patients' quality of life.

During clinical admission of PTE patients, clinicians may pay more attention to the seizure outcome rather than the global functional outcome. Although many studies have focused on the global functional outcome of patients with TBI (5, 7, 20), few studies have systematically investigated the global functional outcome of patients with PTE as well. This lack of study prevents clinicians from effectively identifying patients whose global function prognoses were likely to deteriorate and from further developing clearer treatment strategies for them. Briefly, clinical management of PTE requires recognition of the heterogeneous endophenotypes associated with functional outcomes. Identifying the risk factors for functional decline in patients with PTE and establishing a simplified prognostic model for predicting the long-term functional outcome may therefore become quite useful in improving the therapy of PTE.

This study sought to describe global function changes up to 5 years after the first late PTS onset, identify predictors that significantly relate to 5-year global functional outcomes, and to develop a prognostic model that can be used at the clinic for predicting unfavorable functional outcomes among patients with PTE after moderate-to-severe TBI.

Abbreviations: PTE, post-traumatic epilepsy; TBI, traumatic brain injury; PTS, post-traumatic seizure; GOSE, Glasgow Outcome Scale-Extended; SE, status epilepticus; EEG, electroencephalogram; ASMs, antiseizure medications; ILAE, International League Against Epilepsy; DRE, drug-resistant epilepsy; SD, standard deviation; IQR, inter-quartile range; ROC, reiver operating characteristic curves; AIC, Akaike information criterion; AUC, areas under receiver operating characteristic curves; OR, odds ratio; CI, confidence intervals; GCS, Glasgow Coma Scale.

METHODS

Study Participants

Clinical data of 2,862 patients who were diagnosed with PTE in the Epilepsy Center of Beijing Tiantan Hospital from January 2013 to December 2018 were retrospectively reviewed. All PTE patients meeting inclusion criteria were followed up continuously for at least 3 years in the clinic or by telephone, and all last-time follow-ups were completed between September 2019 and August 2021 at which time the score on the Glasgow Outcome Scale-Extended (GOSE) (21) was recorded to assess global functional outcomes. For each patient enrolled in this study, the total duration of case review plus continuous follow-up was a minimum of 5 years.

Inclusion criteria consisted of: (1) age 16–55 years at the time of TBI; (2) "moderate-to-severe" severity of TBI; (3) meeting the diagnostic criteria of PTE; and (4) having a favorable global function (GOSE 5 to 8) at the onset of the first late PTS. Excluded criteria were: (1) perinatal injury, febrile convulsion, or seizure prior to TBI; (2) pre-existing neurological disease, systemic metabolic disease, or major organ disease; (3) GOSE score not being able to be accurately recorded due to a lack of sufficient information; and (4) age >80 years at the time when the 5-year GOSE score is recorded.

The study was approved by the Ethics Committee of the Beijing Tiantan Hospital affiliated with the Capital Medical University of the People's Republic of China. The study was conducted in accordance with the Declaration of Helsinki, and all participants provided informed consent for the use of their medical records.

Data Collection

Clinical data including demographic information, TBI details, the clinical condition of PTE (such as the presence of acute seizure, the latency of PTE, the type of seizure, seizure frequency, and the presence of status epilepticus [SE]), the electroencephalogram (EEG), the usage of antiseizure medications (ASMs), and patients' drug responses were collected, as mentioned in our previously published study (22).

The severity of TBI was judged based on neurological and imaging evaluations: moderate TBI was characterized by loss of consciousness or post-trauma amnesia lasting 30 min to 24 h, with or without skull fracture; and severe TBI was characterized by brain contusion, intracranial hematoma, loss of consciousness lasting $\geq$24 h, or post-trauma amnesia lasting $\geq$24 h (10). In addition, this study recorded severe TBI cases as "severe TBI with conservative treatment" or "severe TBI with surgical operation" (puncture drainage or decompressive craniectomy during the acute phase of TBI, with or without following cranioplasty operation) according to their courses of treatment. Lesions caused by TBI were also divided into temporal lobe (left/right) lesions or lesions outside the temporal lobe, and classified craniocerebral injuries as either a single injury or multiple injuries (22).

Acute seizure refers to a seizure that occurs within 7 days after TBI, including immediate PTS and early PTS. This study recorded the time interval between TBI and the onset of the first late PTS as the latency of PTE. Additionally, in accordance with the 2017 classification of the International League Against Epilepsy (ILAE) (23), the seizure type of PTE within the first 2 years of the course of PTE was recorded as generalized onset seizure, focal onset seizure, or mixed onset seizure, and the presence of SE of each individual within the first 2 years of the course of PTE was also recorded in accordance with the 2015 definition of SE by the ILAE as well (24). To enable the final model to play a predictive role in the early stages of the development of PTE, this study only included data from the first 2 years of PTE in the initial analysis.

For each patient, two neurologists (TTY and XL) reviewed the original EEG data or the EEG report and assessed the EEG as "normal EEG", "abnormal background without epileptiform discharges", or "epileptiform discharges". The EEG was a randomly selected routine interictal EEG (20–40 min monitoring) during the outpatient visits. The usage of ASMs and the drug response for each individual were also recorded, and the development of drug-resistant epilepsy (DRE) was assessed by two neurologists (TTY and QW) according to the definition of DRE by the ILAE (25).

Global Function

Scores on the GOSE were used for global functional outcome assessment (21) and were obtained through structured interviews (26). The GOSE is a global scale for functional outcomes that rates patient status into eight categories: 1, death; 2, vegetative state; 3, lower severe disability; 4, upper severe disability; 5, lower moderate disability; 6, upper moderate disability; 7, lower good recovery; and 8, upper good recovery (26). In this study, a GOSE score of 5–8 was defined as indicative of favorable global function and a GOSE score of 4 or less was defined as indicative of unfavorable global function. The GOSE at the onset of the first late PTS was recorded based on information recalled by the patients or their caregivers when the patient first visited our epilepsy center. At the last follow-up from September 2019 to August 2021, the 5-year GOSE of each patient was also recorded in the clinic or by telephone. All patients enrolled in this study were divided into two groups: patients with a 5-year GOSE score of 5–8, the favorable outcome group and patients with 5-year GOSE score of 4 or less, the unfavorable outcome group.

Predictors

Eleven variables were analyzed as potential predictors of functional outcomes, including demographic characteristics (gender, age at TBI), TBI details (severity of TBI, lesion location, single, or multiple injuries), and PTE characteristics (the presence of acute seizure, latency of PTE, type of seizure, the presence of SE, EEG findings, and the development of DRE).

Statistical Analysis

To carry out our statistical data analysis, SPSS 23.0 software (IBM Crop., Armonk, NY) and *R* version 4.1.1 software were used. Continuous data were transformed into mean $\pm$ SD or median and interquartile range (IQR), and numerical data were transformed into percentages. The Mann-Whitney *U*-test was used to compare continuous data and the χ^2 or Fisher exact test was used to compare numerical data as appropriate. After this, univariate and multivariate logistic regression were performed to identify predictors significantly related to global functional outcomes. Predictors with $p < 0.3$ in the univariate logistic regression analysis were included in the initial multivariable logistic regression for further analysis, and the data were converted to adjusted odds ratios (ORs) with 95% CIs. A two-sided test with a $p < 0.05$ was deemed to be statistically significant.

Development, Validation, and Presentation of the Prognostic Model

In the univariate and multivariate logistic regression analysis, two continuous variables, age at TBI and the latency of PTE, were converted into dichotomous variables. Age at TBI was recorded as $<$ 30 years old (youth), or $\geq$ 30 years old (young and middle-aged, middle-aged). Previous studies have reported that the latency of PTE in most PTE patients is $<$ 1 year, accounting for 60%−80% of all cases (11, 14, 27). Accordingly, the latency of PTE was classified as either $<$ 12 months or $\geq$ 12 months.

After including all candidate predictors with $p < 0.3$ from the univariate logistic regression into the initial multivariable logistic regression, the nonsignificant predictors were then eliminated in a backward stepwise fashion and the final model we selected was the model with the minimum Akaike Information Criterion (AIC).

Next, the performance of this prognostic model was evaluated in terms of discrimination and calibration. Discrimination indicates whether the model can correctly distinguish favorable

TABLE 1 | The favorable outcome group vs. the unfavorable outcome group comparison summary table.

	Total ($n = 721$)	Favorable ($n = 623$)	Unfavorable ($n = 98$)	*P*-Value[†]
Demographics				
Gender (males, %)	638 (88.5%)	544 (87.3%)	94 (95.9%)	0.013*
Course of PTE (years, IQR)[a]	7.9 (6.6–8.9)	7.9 (6.5–9.0)	7.8 (6.8–8.9)	0.594
Age at TBI (years, IQR)	26.0 (21.0–35.0)	25.0 (21.0–34.0)	30.0 (23.0–42.3)	0.000**
Age at last follow-up (years, IQR)	38.0 (32.0–48.0)	37.0 (32.0–47.0)	38.0 (33.0–51.0)	0.094
Multiple injuries	383 (53.1%)	311 (49.9%)	72 (73.5)	0.000**
Lesion location				0.000**
Outside temporal lobe	291 (40.4%)	273 (43.8%)	18 (18.4%)	
Left temporal lobe	180 (25.0%)	141 (22.6%)	39 (39.8%)	
Right temporal lobe	250 (34.7%)	209 (33.5%)	41 (41.8%)	
Severity of TBI				0.000**
Moderate TBI	245 (34.0%)	227 (36.4%)	18 (18.4%)	
Severe TBI + C	120 (16.6%)	106 (17.0%)	14 (14.3%)	
Severe TBI + S	356 (49.4%)	290 (46.5%)	66 (67.3%)	
The presence of acute seizure	34 (4.7%)	27 (4.3%)	7 (7.1%)	0.223
Latency of PTE (months, IQR)[b]	12.0 (4.0–58.0)	12.0 (5.0–60.0)	7.0 (2.0–18.0)	0.000**
Seizure type				0.034*
Generalized onset	102 (14.1%)	85 (13.6%)	17 (17.3%)	
Focal onset	547 (75.9%)	482 (77.4%)	65 (66.3%)	
Mixed onset	72 (10.0%)	56 (9.0%)	16 (16.3%)	
The presence of SE	48 (6.7%)	38 (6.1%)	10 (10.2%)	0.130
EEG fundings				0.147
Normal	130 (18.0%)	106 (17.0%)	24 (24.5%)	
Abnormal background	100 (13.9%)	85 (13.6%)	15 (15.3%)	
Epileptiform discharges	491 (68.1%)	432 (69.3%)	59 (60.2%)	
The presence of DRE	122 (16.9%)	108 (17.3%)	14 (14.3%)	0.454

*[†] Comparison between favorable outcome group and unfavorable outcome group; [a] the time interval between the onset of first late PTS and the last-time follow-up; [b] the time interval between TBI and the onset of first late PTS; *$p < 0.05$; **$p < 0.01$; continuous data were transformed into the median and interquartile range, numerical data were transformed into percentages.*

TBI, traumatic brain injury; SE, status epilepticus; EEG, electroencephalogram; DRE, drug-resistant epilepsy; severe TBI + C, severe TBI with conservative treatment; severe TBI + C, severe TBI with surgery; PTS, post-traumatic seizure; IQR, interquartile range.

and unfavorable 5-year global functional outcomes and was measured by calculating the areas under the receiver operating characteristic curves (AUC) to form the C-statistic. An AUC of > 0.7 indicates acceptable discrimination. After calculating the discrimination, this study applied 1,000 bootstrap resamples to establish a calibration curve used to indicate whether actual outcomes agree with predicted risks, and this study evaluated calibration by using a goodness-of-fit test, where a p-value > 0.05 indicates good calibration. Finally, internal validation was also performed with the bootstrapping method.

For ease of use at the clinic, this study presented the prognostic model as a graphical score chart in a simplified, color-coded version (28). In this graphical score chart, predictors were cross-tabulated, and the probabilities of unfavorable 5-year global functional outcomes for each individual with values of each predictor were estimated in each cell. The cells of the chart were then colored into four groups, according to the ranges of the probabilities.

RESULTS

Patients Characteristics

After retrospectively screening the clinical records of 2,862 patients diagnosed with PTE, 1,208 patients met the inclusion criteria mentioned above. Of all the 1,208 patients, 18 patients had the perinatal injury, febrile convulsion, or seizure prior the TBI, 87 patients had pre-existing neurological disease, 377 patients lacked sufficient information for GOSE records, 5 patients were more than 80 years old when the 5-year GOSE was recorded, and all of these patients were excluded, leaving us with a total of 721 patients with PTE after moderate-to-severe TBI for analysis. The percentage of patients who were male was 88.5%, with a median age of all patients at TBI of 26.0 years (IQR, 21.0–35.0), the median age at last follow-up of 38.0 years (IQR, 32.0–48.0), and median PTE course of 7.9 years (IQR, 6.6–8.9). The total rate of unfavorable outcomes (GOSE scores of 4 or less) 5 years later was 13.59% (98/721). The characteristics of all patients and the differences between the two groups are shown in **Table 1**.

TABLE 2 | Univariate logistic regression of unfavorable 5-year global functional outcomes.

Variable	OR	OR 95%*CI*	*P*-Value
Gender (Female)	0.293	0.088–0.726	0.019*
Age at TBI (≥30.0 years)	1.988	1.294–3.059	0.002**
Lesion location			
Outside temporal lobe	Ref		
Left temporal lobe	4.195	2.348–7.759	0.000**
Right temporal lobe	2.975	1.686–5.445	0.000**
Multiple injuries	2.778	1.749–4.540	0.000**
Severity of TBI			
Moderate TBI	Ref		
Severe TBI + C	1.666	0.786–3.466	0.174*
Severe TBI + S	2.870	1.691–5.105	0.000**
The presence of acute seizure	1.698	0.665–3.812	0.228*
Latency of PTE (≥12.0 months)	0.397	0.254–0.614	0.000**
Seizure type			
Generalized onset	Ref		
Focal onset	0.674	0.384–1.238	0.184*
Mixed onset	1.429	0.663–3.071	0.359
The presence of SE	1.749	0.800–3.510	0.134*
EEG findings			
Normal	Ref		
Abnormal background	0.779	0.378–1.564	0.489
Epileptiform discharges	0.603	0.362–1.029	0.057*
The presence of DRE	0.795	0.419–1.410	0.455

*$p < 0.30$; **$p < 0.01$.
TBI, traumatic brain injury; severe TBI + C, severe TBI with conservative treatment; severe TBI + C, severe TBI with surgery operation; PTS, post-traumatic seizure; SE, status epilepticus; EEG, electroencephalogram; DRE, drug-resistant epilepsy; OR, odds ratio; CI, confidence intervals; Ref, reference.

TABLE 3 | Multivariate logistic regression of unfavorable 5-year global functional outcomes.

Variable	β-Coefficient	OR (95%*CI*)	*P*-Value
Intercept	−3.278	*NA*	*NA*
Gender (Female)	−1.130	0.323 (0.095–0.826)	0.035*
Age at TBI (≥ 30.0 years)	0.608	1.836 (1.162–2.905)	0.009*
Lesion location			
Outside temporal lobe	Ref		
Left temporal lobe	1.109	3.031 (1.626–5.817)	0.001**
Right temporal lobe	0.981	2.668 (1.482–4.970)	0.001**
Multiple injuries	0.606	1.834 (1.100–3.120)	0.022*
Severity of TBI			
Moderate TBI	Ref		
Severe TBI + C	0.415	1.514 (0.694–3.248)	0.289
Severe TBI + S	0.710	2.034 (1.156–3.724)	0.017*
Latency of PTE (≥ 12 months)	−0.667	0.513 (0.320–0.815)	0.005**

*$p < 0.05$; **$p < 0.01$.
TBI, traumatic brain injury; severe TBI + C, severe TBI with conservative treatment; severe TBI + C, severe TBI with surgery; OR, odds ratio; CI, confidence intervals; NA, not applicable.

Risk Factors for Functional Disability

All of the 11 tested variables had no correlation (absolute value of correlation coefficient < 0.3) with each other (**Supplementary Figure S1**). The univariate logistic regression showed that 10 of the 11 variables had a $P < 0.3$; the exception was the development of DRE (**Table 2**). All of 10 variables with $P < 0.3$ were entered into the initial multivariable logistic regression. After backward stepwise elimination, 6 variables remained in the final logistic regression model, with a minimum AIC of 520.24. These variables were gender, age at TBI, lesion location, single or multiple injuries, the severity of TBI, and latency of PTE (**Table 3**), and the multicollinearity was low (variance inflation factors < 5) for the final model (**Supplementary Table S1**).

All 6 terms in the final model were statistically significant ($P < 0.05$). Female patients were less like to have unfavorable functional outcome than male patients (OR, 0.32; 95% CI, 0.10–0.83; $P = 0.035$). Patients who had TBI at the age of 30.0 years or older were more likely to have unfavorable functional outcomes than those who had TBI younger than 30.0 years (OR, 1.84; 95% CI, 1.16–2.91; $p = 0.009$). Patients who had temporal lobe lesion were more likely to have unfavorable functional outcomes than those who had lesions outside temporal lobe (left temporal lobe: OR, 3.03, 95% CI, 1.63–5.82, $P < 0.001$; right temporal lobe: OR, 2.67, 95% CI, 1.48–4.97, $p = 0.001$). Patients who had multiple injuries were more likely to have unfavorable functional comes than those who had a single injury (OR, 1.83; 95% CI, 1.10–3.12; $P = 0.022$). Patients who suffered severe TBI with surgery operation were more likely to have unfavorable functional outcomes than those who suffered moderate TBI (OR, 2.03; 95% CI, 1.16–3.72; $p = 0.017$). Patients with a latency of 12.0 months or longer were less likely to have unfavorable functional outcomes than those with shorter PTE latency (OR, 0.51; 95% CI, 0.32–0.82; $P = 0.005$). **Figure 1** is a forest plot that visualizes the results.

Prognostic Model Development and Validation

The above model demonstrated good internal validity, with a C-statistic of 0.754 (95% CI, 0.707–0.800) (**Figure 2A**), and the calibration curve was roughly arranged along the 45° diagonal lines, indicating good calibration as well (**Figure 2B**). The χ^2 statistic of the Hosmer–Lemeshow goodness-of-fit test was 12.33 ($p = 0.137$). By using Youden's index, it was found the optimal cutoff value of the prognostic model is −1.814, corresponding to the estimated probability of an unfavorable global functional outcome of 14.0%. The sensitivity and specificity of this prognostic model were 73.47 and 67.26%, respectively. In addition, this study applied bootstrap testing to validate the model and found a C-statistic of 0.726 for internal validation.

Presentation of the Prognostic Model

Taking the convenience of clinical practical application into consideration, this study presented the prognostic model as a graphical score chart in **Figure 3**. Here, we can directly see a patient's probability of an unfavorable 5-year global functional outcome simply by finding the corresponding cell of a given individual according to the value of each predictor. According to the cut-off value of the prognostic model, patients were divided

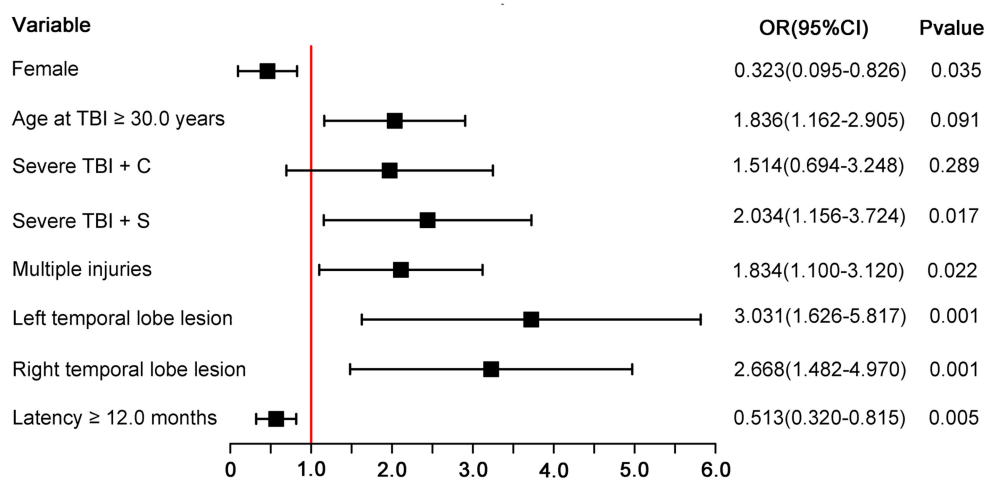

FIGURE 1 | Forest plot for each predictor. The odds ratio for each predictor is presented by a square, and the confidence interval is presented by a horizontal line. Severe TBI + C, severe TBI with conservative treatment; severe TBI + C, severe TBI with surgery operation; CI, confidence intervals; OR, odds ratio.

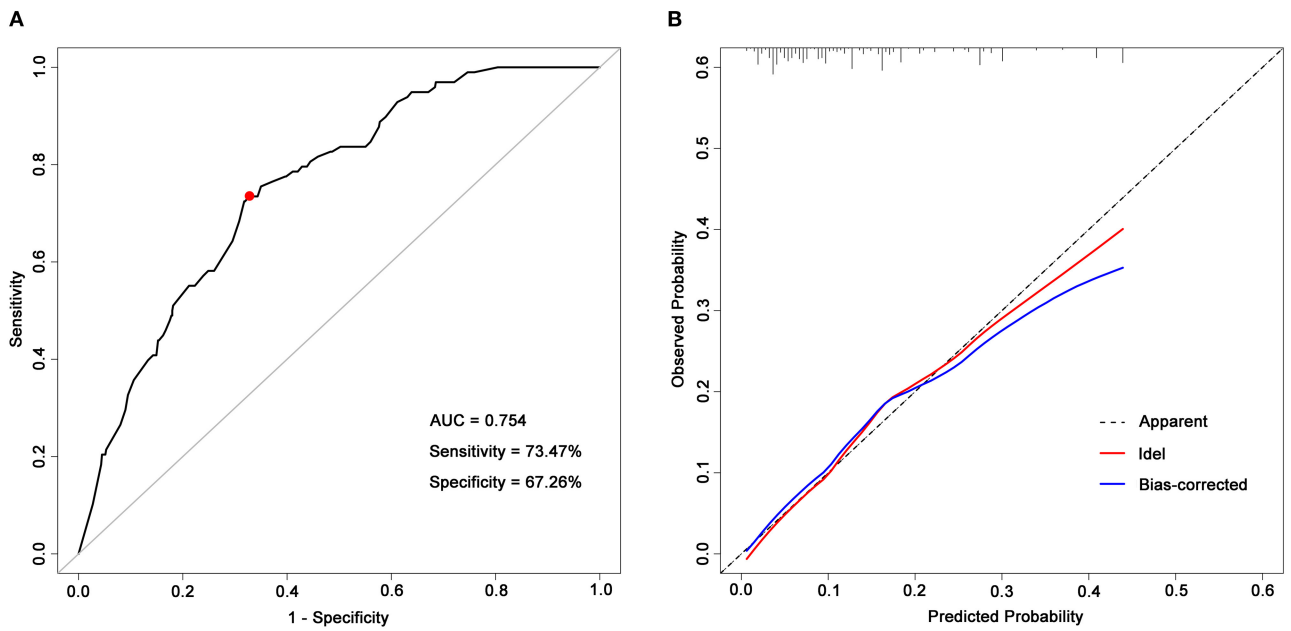

FIGURE 2 | ROC curve and a calibration curve of the prognostic model. **(A)** ROC curve of the prognostic model. The prognostic model had acceptable discriminative power with an AUC of 0.754 (95% CI, 0.707–0.800). The red dot represents the optimal cutoff value, corresponding to the sensitivity and specificity of 73.47 and 67.26%, respectively; **(B)** Calibration curves of predicted probability of a 5-year unfavorable global functional outcome (*x*-axis) vs. observed probability (*y*-axis). The Hosmer–Lemeshow goodness-of-fit test was used to compare predicted probability and observed probability, p-value > 0.05 indicates good calibration. AUC, areas under receiver operating characteristic curves.

into four categories, and **Table 4** shows that observed unfavorable outcome rates of different categories matched closely with the estimated rates according to the prognostic model.

DISCUSSION

This is one of the first studies to focus on the long-term global functional outcomes over 5 years and to investigate the predictors of global functional outcomes in a sample of patients with PTE after moderate-to-severe TBI, and this study now presents the following findings. First, the global function of PTE patients assessed based on GOSE score showed dynamic changes overtime: with a favorable global function at the onset of first late PTS, 13.59% of patients experienced deterioration in their conditions and had an unfavorable global functional outcome 5 years later. Second, it was found that gender, age at TBI, lesion

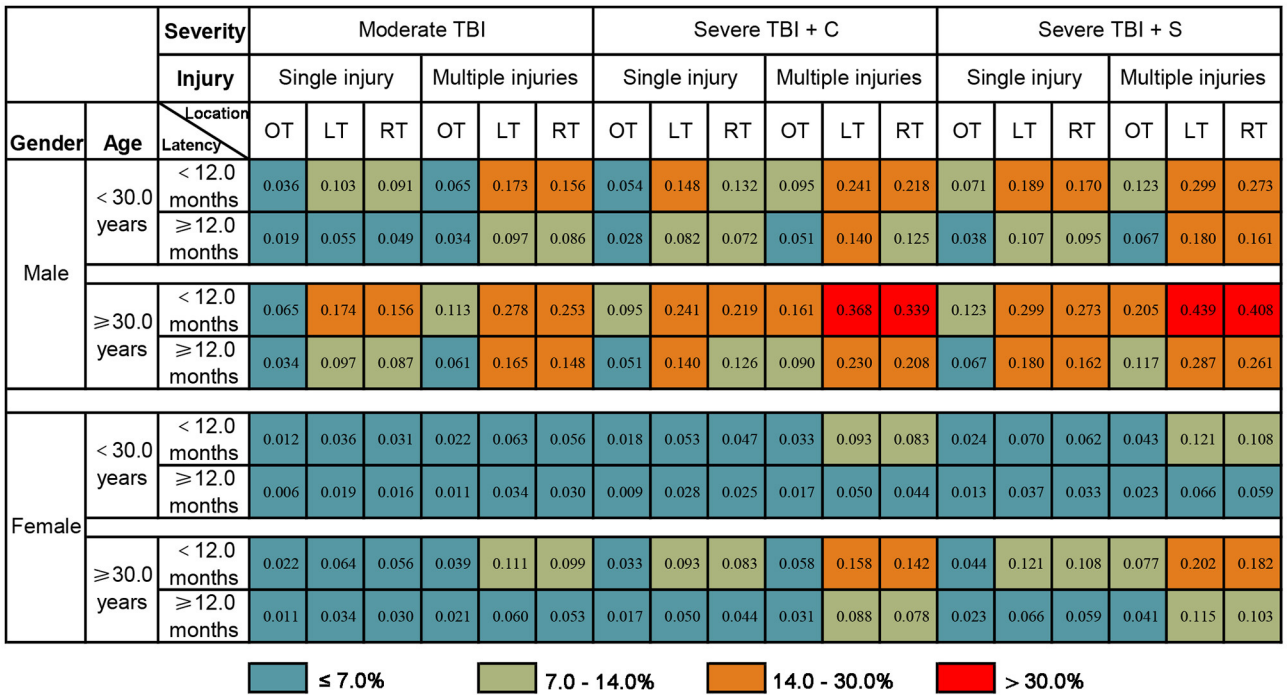

FIGURE 3 | The probability of an unfavorable 5-year global functional outcome of PTE patients. The number in each box represents the probability of an unfavorable 5-year global functional outcome. Determine individual risk in two steps: Step 1, Find the corresponding cell of a given individual according to the value of each predictor; Step 2, Determine the associated risk of unfavorable 5-year global functional outcome. For example, a male patient who suffered severe TBI (single injury on the left temporal lobe) at 30.0 years old, underwent conservative treatment, with a PTE latency of 6 months. The probability of an unfavorable 5-year global functional outcome for this given patient is 24.1%. TBI, traumatic brain injury; severe TBI + C, severe TBI with conservative treatment; severe TBI + C, severe TBI with surgery operation; OT, outside temporal lobe lesion; LT, left temporal lobe lesion; RT, right temporal lobe lesion.

TABLE 4 | The number of patients at each risk level and the observed proportion of unfavorable 5-year global functional outcomes.

Predicted probability	Total (No.)	Unfavorable outcome (No.)	Observed proportion
(0.00–0.07]	276	12	4.35%
(0.07–0.14]	175	15	8.57%
(0.14–0.30]	218	51	23.39%
(0.30–1.00]	52	20	38.46%

location, multiple injuries, the severity of TBI, and latency of PTE were predictors for 5-year global functional outcomes. Finally, a prognostic model for global function prediction by using the above variables was developed and it was presented as a graphical score chart. This model achieved significant potential to be used in clinics based on our above analysis and may help to screen patients at high risk of unfavorable global functional outcomes and to develop more effective strategies for rehabilitation.

As previously mentioned, GOSE is the recommended measurement for measuring the global function following TBI, and it outlines the overall impact of TBI on function, independence, and participation (29). To date, several studies have used GOSE for functional outcome assessment in TBI patients (5, 7, 20, 30, 31) and have suggested that there is a dynamic process of change in global functional outcomes over time, which we also found in this study.

Although the method by which gender affects the global functional outcomes remains poorly understood (32), this study found that female PTE patients were less likely to experience deterioration in a global function, and it was consistent with several previous long-term studies (20, 31) yet contrary to others (7, 33). Due to a different profession and hobbies characteristics, the TBI mechanism is different between males and females (34). Previous animal studies have shown female rodents have better outcomes after TBI than males because of the neuroprotective effect of sexual hormones (estrogen and progesterone) (35, 36); while several clinical studies also have found differences in TBI outcomes between genders, but suggesting that sexual hormones do not provide a neuroprotective effect on clinical outcomes (37, 38). Therefore, the difference in global functional outcomes between genders is still controversial, that may need to be explored in further large-sample, age-stratified, prospective studies. In addition, we realized that the influence of gender on epileptic seizure may also play a role in global functional outcomes since a larger proportion of patients were males in this present study than in previous studies (88.5% vs. 72.0–78.4%) (7, 20, 31). One other demographic characteristic, age, however, has been shown in the literature to have a clear effect

on long-term functional outcomes (older patients were more likely to experience deterioration) (8, 20, 31, 39), and the findings of this present study are consistent with these earlier works. We hypothesize that the better functional outcomes of younger patients might be related not only to their physical status but also to social factors such as better medical care and better return-to-work characteristics (39).

Some authors have reported that the severity of TBI was associated with functional outcomes: the more severe the TBI, the worse the functional outcomes (39). Considering that we lacked the Glasgow Coma Scale (GCS) scores of some patients in this retrospective study, this study instead assessed the severity of TBI according to neurological and imaging evaluation (10) and found that patients who suffered severe TBI were more likely to have deterioration of global function. In addition, this study found that among patients with severe TBI, the risk of unfavorable 5-year global functional outcomes was higher in those who received surgery (OR, 2.03) than in those who received conservative treatment (OR, 1.51) compared to patients with moderate TBI. The difference may be related to the TBI condition of those patients who underwent surgery (for example, those who had marked cerebral edema, increased intracranial pressure, etc.) or to the surgical procedure itself, which may have resulted in secondary brain damage.

Multiple injuries and injuries located in the temporal lobe (especially the left temporal lobe) were also associated with unfavorable 5-year global functional outcomes. The specific role of the temporal lobe in the overall brain network may explain our findings. For most people (who are right-handed), left temporal injury is more likely to interfere with dominant-hand-motor pathways, compromise language regions, and affect language function. As language function is extremely important in independence, employment, social and leisure activities, family and friendship, and returning to normal life after TBI, we may expect patients with left temporal lobe injuries to have low long-term functional outcomes. Moreover, previous literature has also reported that epilepsy with temporal lobe damage was more likely to develop into DRE (40, 41).

We were surprised to find that, in addition to the latency of PTE, other characteristics of PTE (such as seizure type, presence of SE, drug responsiveness to ASMs, and EEG findings) were not associated with 5-year global functional outcomes. This suggests that more attention should be paid to the etiology of epilepsy, TBI, rather than to the seizure itself when assessing the functional outcome of patients with PTE. The latency of PTE ranges from 7 days to decades, with 60–80% of patients having a latency of <1 year (11, 14, 27). In this study, patients with a latency of shorter than 12 months were more likely to have deterioration of global function 5 years later, while those with longer latencies tended to have a stable global function. We realize that this result may be related to the design of the present study as it only included patients who had GOSE scores of 5–8 at their first late PTS onset. These patients who had long latencies may have already experienced a dynamic process of change in global function and already reached a stable state of global function at the onset of their first late PTS. Future prospective studies with long-term follow-up of new TBI cases and evaluation of the seizures and global function of TBI patients at different time points may help us better clarify the relationship between latency of PTE and functional prognosis.

Though it is not free from limitations (discussed below), this study has the following strengths. First, this study recorded the 5-year GOSE after the onset of the first late PTS, and the follow-up period was long enough to detect changes since the functional prognosis tends to become stable 5–10 years after TBI (6, 7). Second, this is the first study to identify the factors that affect the long-term functional outcomes among patients with PTE after moderate-to-severe TBI, establish a prognostic model, and construct a graphical score chart for clinical use, and the prognostic model can provide a more individualized prediction of the long-term functional outcomes for a patient with PTE. Specifically, based on gender, age, easily ascertainable TBI details, and latency of PTE, this prognostic model exhibited acceptable predictive capability (with a C-statistic of >0.75), and the prognostic model can be easily integrated into daily clinical practice simply by checking the graphical score chart. Once externally validated, our research may provide a basis for more effective courses of treatment.

LIMITATIONS

There are several limitations to this study that constrain the generalizability of our findings. First, only patients with PTE were included; patients without PTE after TBI were not included as controls. The unfavorable outcomes might be mediated by the presence of PTS, rather than directly and independently correlated with factors analyzed in this study, which means that there might be selection bias that this study did not take into account. Furthermore, as this was a retrospective study, the model was developed based on factors that were recorded in the medical records or supplemented by recollections of patients or their caregivers. However, there could be other risk factors that affect global functional outcomes that need to be considered but were missed due to a lack of reliable data (such as pre-injury employment, education, etc.). This made it difficult to correct for potential confounding of variables. Finally, information bias may also exist. Further external validation is therefore needed to evaluate the prognostic model, and further large-scale prospective studies are needed to clarify fully the factors that affect the long-term functional outcomes of PTE.

CONCLUSION

The global function of PTE patients assessed based on the GOSE score showed dynamic changes over time. Effective screening of high-risk patients and clearer treatment strategies are therefore essential to help ameliorate unfavorable outcomes. In this study, it was found that suffering TBI at the age of 30.0 years or older, having severe TBI (especially severe TBI with surgery), having multiple injuries, and having temporal lobe lesions were risk factors for an unfavorable 5-year global functional outcome, while being female and long (12.0 months or longer) PTE latency were protective factors. This study developed a

prognostic model using these identified predictors to predict 5-year outcomes among patients with PTE after moderate-to-severe TBI, and the model achieved significant potential for clinical use. However, additional prospective studies are still needed to validate and further explore predictors of the functional outcomes of PTE patients.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available from the corresponding author, upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Beijing Tiantan Hospital affiliated with the Capital Medical University of the People's Republic of China. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

TY, XL, RL, and QW were major contributors to the acquisition of data. TY, LS, JW, and QW analyzed the data. TY drafted and revised the manuscript and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. All authors contributed to the study's conception and design.

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REVIEW
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Adult Critical Care Electroencephalography Monitoring for Seizures: A Narrative Review

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Electroencephalography (EEG) is an important and relatively inexpensive tool that allows intensivists to monitor cerebral activity of critically ill patients in real time. Seizure detection in patients with and without acute brain injury is the primary reason to obtain an EEG in the Intensive Care Unit (ICU). In response to the increased demand of EEG, advances in quantitative EEG (qEEG) created an approach to review large amounts of data instantly. Finally, rapid response EEG is now available to reduce the time to detect electrographic seizures in limited-resource settings. This review article provides a concise overview of the technical aspects of EEG monitoring for seizures, clinical indications for EEG, the various available modalities of EEG, common and challenging EEG patterns, and barriers to EEG monitoring in the ICU.

Keywords: EEG, critical care, seizures, monitoring, quantitative EEG

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INTRODUCTION

Electroencephalography (EEG) provides a continuous, non-invasive, and relatively inexpensive monitoring of cerebral function in real time that allows for an immediate detection of cerebral activity (1). Although seizure detection is the primary cause to obtain an EEG, several other important clinical indications have emerged over the years. Several guidelines from the Neurocritical Care Society (NCS), American Clinical Neurophysiology Society (ACNS), and European Society of Intensive Care Medicine (ESICM) are available to clinicians on the appropriate clinical scenarios that require EEG monitoring (2–4). The ACNS has recently updated a standardized set of critical care EEG terminology to assist with the identification and classification of clinically significant abnormal electrocerebral patterns (5).

Although the ideal application of continuous EEG (cEEG) is the standard 21-electrode montage from the International 10–20 system applied by a trained technician, the demanding critical care setting may not permit this in resource-limited areas (6, 7). Rapid application of limited EEG montages is now available to reduce not only the technician's time to apply EEG leads, but also to reduce the time to detect electrographic seizures (8–11). Furthermore, quantitative EEGs (qEEG) provides a computational analysis of the EEG signal that allows for the rapid review of large amounts of data accumulated over several hours in the intensive care unit (ICU) (12–22).

This review article provides a concise overview of seizure monitoring in the ICU, the technical aspects of EEG monitoring, clinical indications of EEG, the various modalities of EEG, common and challenging EEG patterns, and barriers to EEG monitoring.

METHODS

A PubMed/Medline literature search was performed for relevant articles published from January 2000 to May 2022, using the following search terms: "adult critical care EEG," "adult neurocritical care EEG," "continuous EEG," and "quantitative EEG." The search was limited to articles describing human subjects that were published in the English language. Clinical trials, meta-analysis, review articles, and practice guidelines were all eligible for inclusion. Abstracts were subsequently reviewed and included for relevance. Pertinent topics identified after full text review were also included when possible.

TECHNICAL ASPECTS OF EEG MONITORING IN THE ICU

The EEG is a differential amplifier - an apparatus that measures the voltage difference in electrical potential between two inputs while amplifying the difference (6). The electrical signal recorded by the EEG is generated by local field potentials from ionic currents flowing in the extracellular space by the pyramidal neurons in the cortical layers (6, 23). Synchronous activation of at least 10 cm^2 of cortex is required to produce an electrical signal (24).

Scalp disk electrodes are the most common type of electrode used in EEG. However, subdermal needles and wire electrodes are also available (25). Disk electrodes are created by inert silver-silver chloride or gold metal held to the scalp by collodion to avoid interference with the electrical recording (25). The contact impendence should be between 1–10 kΩ and 5–10 kΩ typically accepted by most EEG laboratories (26). However, magnetic resonance imaging (MRI) and computed tomography (CT) compatible plastic electrodes are also available, and considered standard of care in the ICU (27–29).

Scalp electrodes should be arranged using the International 10–20 system with a 21-electrode montage. The abbreviations used on the EEG include: Fp (frontal-polar), F (frontal), C (central sulcus), P (parietal), O (occipital), T (temporal), and Z (sagittal) (6). Even numbered electrodes are located on the right hemisphere, while odd numbered electrodes are located on the left hemisphere (6). The lower integer electrodes are closer to the midline, while the larger integer electrodes are furthest away from midline (6). Additional channels may be added while in the ICU including a one-channel electrocardiogram, electromyography, respiratory sensors, and horizontal/vertical axis electrodes around the eyes (6).

The more commonly used montages are the bipolar montages (which include the longitudinal bipolar and transverse bipolar montage), referential montages, and common average montages (6). If the net polarity of the electrical signal is negative, there is an upward deflection on the EEG while the opposite is true of a net positive polarity (6). The EEG signal is composed of different frequency bands, the typical adult frequency bands include delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–30 Hz), and gamma (30–100 Hz) (30). A standard routine EEG (rEEG) recording should include at least 20 min, a short-term EEG includes 1–8 h, and a cEEG is 12–24 h or more (6, 25).

Intracortical depth electrodes are available to monitor limited cortical area but not commonly used in clinical practice (31, 32). These electrodes are placed in stuporous or comatose patients through cranial bolts at the bedside and have a similar safety profile to other intracranial monitoring probes (31). A retrospective study of 61 patients admitted for multimodal intracranial monitoring showed that of the 19 patients (31%) undergoing intracranial EEG, only one developed a complication related to invasive monitoring (malfunction or dislodgement of the device) (33). Depth EEG may be more sensitive than the scalp cEEG monitoring for detecting non-convulsive seizures, but the clinical and outcome relevance is not well-established (31). In a retrospective study of 14 patients undergoing concurrent scalp and intracranial EEG, 10 patients demonstrated electrographic seizures with the intracranial EEG. This contrasted with the detection on the scalp EEG where two patients showed intermittently correlated ictal activity, another two patients showed non-ictal appearing rhythmic delta activity, and six patients showed no concurrent ictal activity (34).

When issues of availability arise for the full 21-electrode EEG montage, limited montages may be used in the ICU setting. These include the sub-hairline (4 bipolar derivation—bilateral temporal and frontal) EEG montage and the FDA approved 8-channel rapid response headband EEG system (8–11). **Figure 1** illustrates the utility of rapidly applying a point-of-care EEG in a critically ill patient.

A prospective study of 170 critically ill patients was conducted comparing the full-montage 10–20 placement of electrodes to the sub-hairline electrode montage. Out of the 8% of patients with seizures, the specificity to detect seizures with the sub-hairline montage was 100%, however, the sensitivity was only 54% (8). In another prospective study of 70 patients in a medical-surgical ICU who were simultaneously connected with a full 10–20 system and the four-channel sub-hairline montage demonstrated a sensitivity of 68% and specificity of 98% for seizure detection for both focal and generalized seizures (9).

Several important studies regarding the FDA approved eight-channel rapid response headband EEG system garnered confidence in its use in the ICU. In a small prospective study comparing 10 patients using the rapid response EEG device to the 20 patients using the 18-electrode EEG montage, the time to diagnosis of status epilepticus and on-call work force demand decreased. Mean time to interpretation was 23.8 min using rapid response EEG vs. 126.5 min when using the 18-channel (10). In a recent larger prospective multicenter non-randomized observational study (DECIDE trial) of five academic hospitals in the US, 164 critically ill patients were evaluated for possible non-convulsive status epilepticus (NCSE) by using the rapid response electroencephalography system. With the use of the device compared to clinical diagnosis alone, the sensitivity

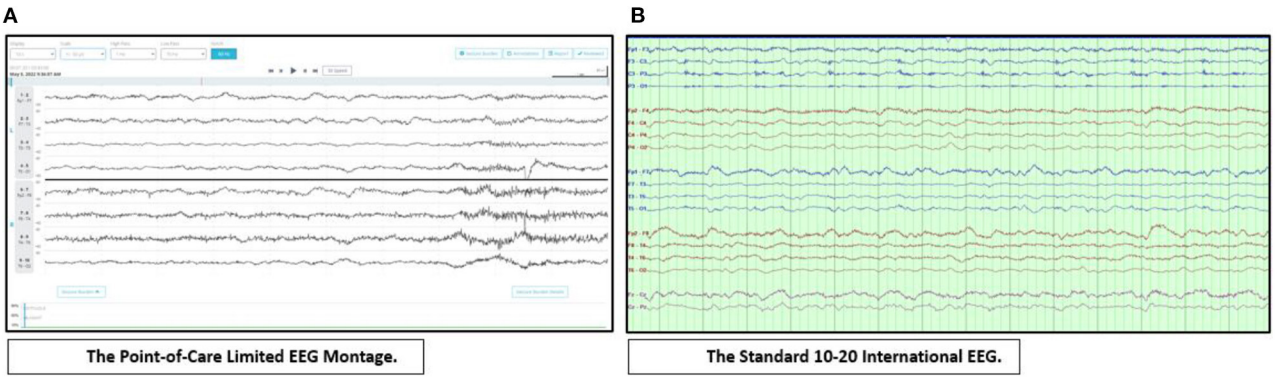

FIGURE 1 | Point-of-care EEG. Suspected seizures in a 62-year-old man with decreased level of consciousness ruled out within 10 min with the use of a point-of-care limited EEG montage. The findings were later confirmed with the standard cEEG. **(A)** displays diffuse, irregular, attenuated mixed frequency delta-theta activity in the point-of-care limited EEG montage. Display: 10 s, Scale: ±50 μV, High Pass: 1 Hz, Low Pass: 70 Hz, Notch: 60 Hz. **(B)** displays diffuse, irregular, attenuated mixed frequency delta-theta activity in the standard International 10–20 EEG. Bipolar montage, LFF: 1 Hz, HFF: 70 Hz, Notch: 60 Hz, Sensitivity: 7 μV/mm, Timebase: 30 mm/s.

of the physician's electrographic seizure diagnosis improved from 77.8 to 100%, and the specificity improved from 63.9 to 89%. Time to EEG placement was a median of 5 min with the rapid response system vs. 239 min with conventional EEG (11). Furthermore, this rapid response modality may be economically feasible for both resource limited and rich regions but requires further investigation (35).

INDICATIONS FOR EEG MONITORING IN THE ICU

The clinical use for EEG increased with the growing indications in critically ill patients. In a retrospective cross-sectional study with the National Inpatient Sample Data from 2004 to 2013—with more than 7,000,000 critically ill patients identified, of whom 22,728 received EEG—it was found that there was a >10-fold increase in EEG use from 0.06 to 0.8% by the end of the study (36). Despite this increase in EEG use, the EEG remains an underutilized tool. In a prospective multicenter observational study, only 37% of patients had EEG monitoring in those who met at least one of the indications for EEG monitoring (as per the ESICM) (37).

Several different critical care and neurophysiology societies provide guidelines for the indications of EEG in the ICU (2–4). The main recommendations include seizure detection for: (1) patients with convulsive status epilepticus (CSE) without return to baseline; (2) comatose patients with or without brain injury and without clear explanation of their mental status; and (3) unresponsive hypoxic-ischemic brain injury (HIBI) patients, during hypothermia, and within 24 h of rewarming (2–4). Other indications include the use of EEG to detect delayed cerebral ischemia in subarachnoid hemorrhage patients, prognostication after coma especially in patients with HIBI, and for monitoring of continuous sedation. It is important to note that the current 2020 American Heart Association adult post-cardiac arrest care algorithm recommends EEG in HIBI patients who are not following commands (38).

Continuous EEG (cEEG) vs. Intermittent Routine EEG (rEEG)

Most seizures are non-convulsive in the ICU, making EEG a critical tool for the detection and management of ictal events (39, 40). In a systematic review and meta-analysis study of over 20,000 critically ill adult patients with concern for seizures, cEEG was superior to rEEG in detecting non-convulsive seizures (NCS) and non-convulsive status epilepticus (NCSE). The prevalence of detection for NCS, NCSE, and either NCS or NCSE by using cEEG was 17.9, 9.1, and 15.6%, respectively. The corresponding prevalence was high in post-CSE (33.5, 20.2, and 32.9%), central nervous system (CNS) infection (23.9, 18.1, and 23.9%), and post-cardiac arrest patients (20.0, 17.3, and 22.6%). This was in comparison to patients suffering from subarachnoid hemorrhage, intracerebral hemorrhage, subdural hemorrhage, acute ischemic stroke, sepsis, and traumatic brain injury (39).

A recent multicenter randomized clinical trial in Switzerland (CERTA study) studied 364 patients using either the cEEG (30–48 h total) or two rEEGs (20 min each). Continuous EEG was associated with increased detection of ictal and interictal features, however, the primary outcome of mortality at 6 months was similar between cEEG and rEEG (40). The study should reassure providers with limited-resource settings, but it does not support that cEEG should be abandoned when available (41).

To improve upon seizure risk stratification and the cost-effectiveness of cEEG, the 2HELPS2B score may be used. The 2HELPS2B score identifies the risk of seizures based on five EEG features (42, 43). The algorithm provides a total score of seven divided into points of 1 for EEG patterns with frequencies >2 Hz, one for independent sporadic epileptiform discharges, one for lateralized periodic discharges (LPD)/bilateral independent periodic discharges (BIPD)/lateralized rhythmic delta activity (LRDA), one for plus features (superimposed rhythmic, fast,

sharp), one for a prior seizure, and finally two for brief potentially ictal rhythmic discharges (BIRD) (42, 43). In a multicenter retrospective analysis of 2,111 patients with a median cEEG duration of 48 h (total of 5,427 studies), the 2HELPS2B score was validated as a clinical tool to aid in seizure detection. The conclusion of this study was that a 1-h rEEG displaying no epileptiform discharges was an adequate screen to rule out electrographic seizures in critically ill patients who did not have a history of epilepsy. However, in patients with highly epileptiform EEG patterns during the first hour (2HELPS2B score of $\geq$2) a cEEG of at least 24 h was recommended (42, 43).

Quantitative EEG (qEEG) in the ICU

The real-time visual analysis and interpretation of the raw EEG possesses multiple challenges. First, there may not be a 24-h availability of an experienced electroencephalographer for real-time interpretation of the data. Second, the sheer volume required to interpret the data takes significant time and effort. Third, subtle changes to trends on raw EEG may be missed by even the most experienced electroencephalographer (12). Quantitative EEG (qEEG) mitigates this burden by allowing the rapid review of a large volume of EEG data in a simplified display (12, 13).

The mathematical algorithms utilized in qEEG is beyond the scope of this review. In brief, the EEG signal is a collection of sinusoidal waves with key properties utilized by the mathematical algorithms to produce different qEEG panels or trends (14). The color spectrogram power scale is measured in decibels (dB) with cooler colors representing lower power and warmer colors representing higher power. Seizures are most easily recognized on a spectrogram by a "flame" appearing pattern due to the abrupt increase in power across a range of frequencies that stands out from the background (14).

The commonly used qEEG panels or trends include compressed spectral array (CSA), density spectral array (DSA), asymmetry relative spectrogram, the fast Fourier transform (FFT) spectrogram, the rhythmicity spectrogram, the amplitude EEG (aEEG), and the seizure detector panel. The compressed spectral array (CSA) generates a three-dimensional display by plotting successive epochs as a function of time (12). The density spectral array (DSA) depicts EEG spectral power amplitude as a gray-scale or color intensity function rather than vertical deflections as seen in the CSA (12). The asymmetry relative spectrogram displays power differences between homologous electrodes at discrete frequencies and illustrates power asymmetry across the two hemispheres (15). It is a line graph that displays an average of the absolute values over a specified frequency range or relative asymmetry data as a function of time (15). The fast Fourier transform (FFT) spectrogram displays color coded power of EEG at different frequencies using a fast Fourier transform analysis of the amplitude of waveforms as a function of time (15). The rhythmicity spectrogram displays a three-dimensional representation of the power characteristics for the EEG and a density spectral array of frequencies as a function of time. It is a graphical depiction of the amplitude of primary rhythmic EEG components present in four frequency bands: 1–4, 4–9, 9–16, and 16–25 Hz (15). Amplitude EEG (aEEG) spectrogram displays amplitude characteristics of the EEG as a function of time (15). The seizure detector trend displays the combination of multiple inputs as a seizure probability, dichotomized into a value of zero or one (15).

In an ICU qEEG Survey conducted in 2016, 75 neurophysiologists from the ACNS responded that they utilized qEEG for seizure detection (92%), burst suppression monitoring (58.7%), and prognosis for cardiac arrest (21.3%). The most frequently used qEEG trends or panels for seizure detection were rhythmicity spectrogram (61%), automated seizure detector (55%), color density spectral array (CDSA)/compressed spectral array (CSA)/density spectral array (DSA)/fast Fourier transformation (FFT) spectrogram (47%), asymmetry index/asymmetry spectrogram (43%), and amplitude-integrated EEG (aEEG) (41%) (13). **Figure 2** illustrates a case on the utility of qEEG in a critically ill patient suffering from focal electro-clinical status epilepticus.

Several studies assessed the diagnostic accuracy of qEEG for seizure detection in critically ill patients. One of the earliest key studies was conducted by Stewart et al., which demonstrated acceptable sensitivity and false-positive rates of CDSA and aEEG for seizure detection in critically ill patients (44). In a cohort of 562 seizures from 58 pediatric and adult patients, the overall sensitivity of the qEEG spectrograms for detecting seizures ranged from 43 to 72%. The highest sensitivity (402/562, 72%) was detected by the seizure detection trend. The asymmetry spectrogram had the highest sensitivity for detecting focal seizures (117/125, 94%). The FFT spectrogram was most sensitive for detecting secondarily generalized seizures (158/187, 84%). Finally, the seizure detection trend was the most sensitive for generalized onset seizures (197/250, 79%) (15). In one retrospective study of 118 adult patients, the CSA-guided review vs. the gold standard visual analysis of the raw EEG was sensitive for seizure detection at 87.3%, periodic epileptiform discharges at 100%, rhythmic delta activity at 97.1%, focal slowing at 98.7%, generalized slowing at 100%, and epileptiform discharges at 88.5%. The average time to review 24 h of cEEG data was 8 ($\pm$4) min for CSA-guided review and 38 ($\pm$17) min for visual analysis of the raw cEEG (16). In a second retrospective study of 118 critically ill adult patients, the overall detection rate of CSA-guided review of cEEG for seizures was 89.0% of 1,190 total seizures, 94% for epileptiform discharges, 100% for periodic epileptiform discharges, rhythmic delta activity, and both focal and generalized slowing (17). In a study of 6-h EEG epochs from 15 critically ill adult patients undergoing qEEG compared with the gold standard of the neurophysiologist analyzing raw EEG, the mean sensitivity for seizure identification ranged from 51 to 67% for qEEG-only read and 63 to 68% for qEEG and raw EEG analysis together. The false-positive rates for qEEG-only read was 1/h and 0.5/h for both qEEG and raw EEG analysis. The median time for review was shorter for qEEG (6 min) and qEEG plus raw EEG review (14.5 min) compared to only raw EEG review (19 min) (19).

Finally, qEEG may also be a useful tool for the non-electroencephalographers. In a prospective, single-institution study of neurocritical care nurses' ability to detect seizures

FIGURE 2 | Quantitative EEG (qEEG) use in the ICU. The quantitative EEG (qEEG) in a 71-year-old man with presumed autoimmune/paraneoplastic encephalitis with focal right temporal electro-clinical status epilepticus. **(A)** displays the qEEG panels in a 6-h window, while **(B)** displays the qEEG panels in 12 h. (1) The artifact intensity panel displays the likelihood that an abrupt change seen on other qEEG trends is likely due to an artifact. Note the abrupt abnormality due to EEG lead disruption in **(B)** on the right hemisphere rhythmicity spectrogram, the right hemisphere FFT spectrogram, and the relative asymmetry spectrogram that was detected by the artifact intensity panel (Black arrow and black box). (2) The seizure probability (0–1) panel provides a value between 0 and 1 to indicate the seizure probability as estimated by the software. (3) The left and right rhythmicity spectrogram panel displays the power characteristics for each frequency band (1–4, 4–9, 9–16, and 16–25 Hz) as a function of time. Note the increased power peaks over the right rhythmicity spectrogram panel. (4) The left and right FFT (fast Fourier transform) spectrogram panel displays the color-coded power of different EEG frequency bands as a function of time. Note the distinct "flame" appearing peaks in the right FFT spectrogram panel indicating discrete right temporal seizures (Red box). (5) The relative asymmetry spectrogram panel (left in blue and right in red) displays power differences between homologous electrodes at discrete frequencies and illustrates power asymmetry across the two hemispheres. Note the several peaks in red. (6) The left (in blue) and right (in red) hemisphere amplitude EEG (aEEG) panel displays amplitude characteristics of the EEG as a function of time. Note the higher amplitudes over the right hemisphere.

on qEEG, the false positive rate was 0.1/h (20). In another prospective single-institution study of 109 critically ill adult patients, the neurocritical care nurses' sensitivity and specificity of detecting seizures from qEEG panels (rhythmicity spectrogram and aEEG) at bedside was 74 and 92%, respectively (21). A retrospective study analyzed the sensitivity and specificity of neurophysiologists and non-neurophysiologists' ability to detect seizures on qEEG in 45 ICU patients with 1-h qEEG

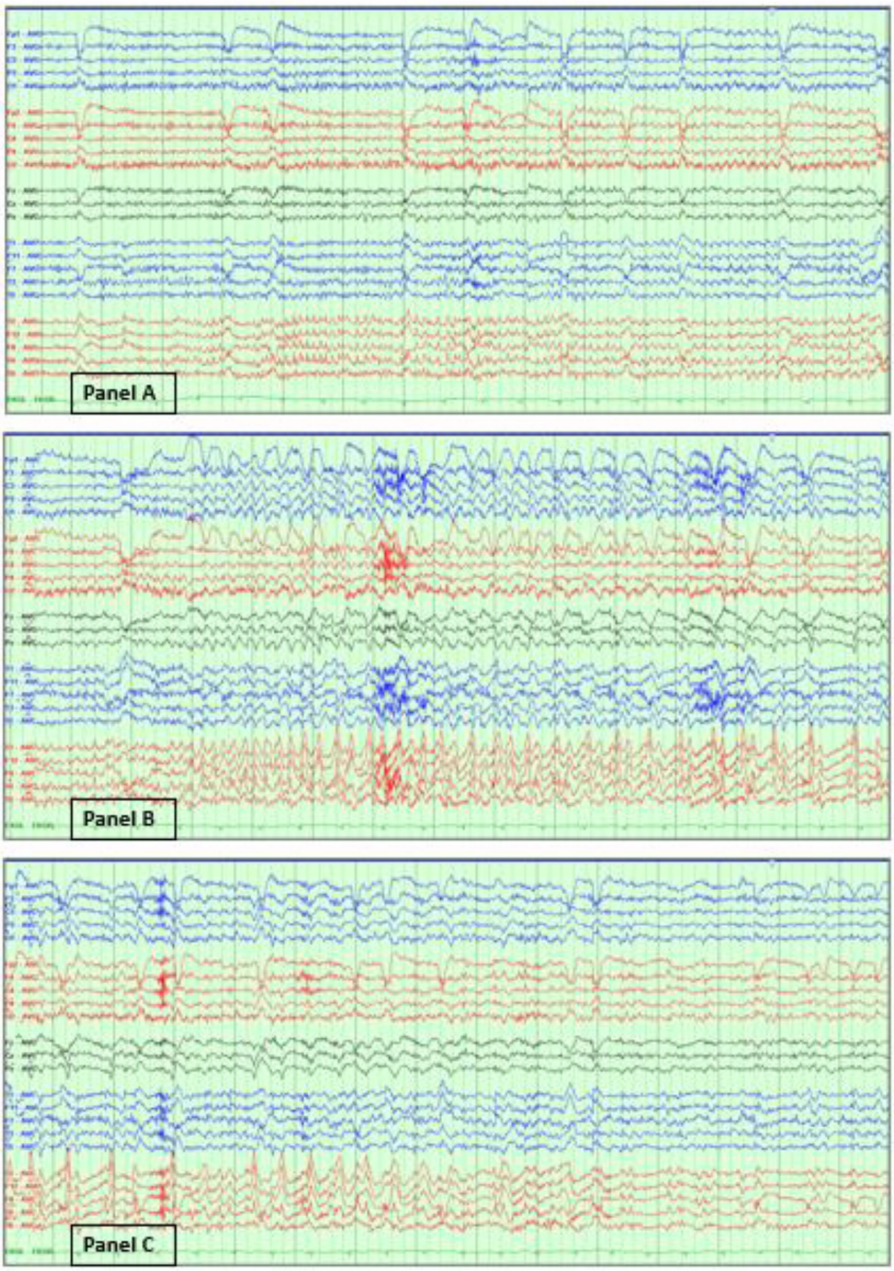

FIGURE 3 | Unequivocal electrographic seizure on EEG in the ICU. Right temporal electrographic seizure **(A–C)** in a 21-year-old woman with herpes simplex (HSV) encephalitis. Average referential montage with double density electrodes added in the bilateral basal temporal regions (T1, F11, T2, F12), LFF: 1 Hz, HFF: 70 Hz, Notch: 60 Hz, Sensitivity: 10 μV/mm, Timebase: 30 mm/s.

panels (180 studies). The data showed the sensitivity and specificity was 87 and 61% for neurophysiologists, 80 and 80% for EEG technologists, and 87 and 61% for neurocritical care nurses, respectively (18). Another retrospective study evaluated the accuracy of seizure burden in 69 critically ill adult patients with super-refractory status epilepticus by using qEEG reviewed by three sets of reviewers: (1) Two board-certified neurophysiologists using raw EEG (gold standard), (2) Two neurocritical care providers with substantial qEEG analysis expertise (qEEG experts), and (3) Two inexperienced qEEG readers (qEEG novice). The raw EEG experts identified 2,950 total seizures in 25 patients, the qEEG experts had 93% sensitivity, 61% specificity, a false positive rate of 6.5 per day, and good agreement ($k = 0.64$) between both qEEG experts, and the qEEG novices had 98.5% sensitivity, 13% specificity, a false positive rate of 15 per

TABLE 1 | The Salzburg criteria for the diagnosis of NCSE (48).

One of the following criteria must be met and be continuously present for 10 s or more for NCS and 30 min for NCSE:
i. Epileptiform patterns occurring >2.5 Hz
ii. Concurrent subtle clinical accompaniments
iii. Spatiotemporal evolution

day, and fair agreement ($k = 0.4$) between both qEEG novices (45).

COMMON ICU EEG PATTERNS

Electrographic Seizure, Electroclinical Seizure, and Status Epilepticus

Electroclinical seizures are defined as paroxysmal events during which a clinical change is accompanied by a characteristic abnormal EEG pattern. The typical changes seen on EEG are, as defined by the ACNS and other societies (5).

1) Repetitive spikes, sharp waves, spike/sharp waves, and slow-wave complexes with a frequency >3 Hz.
2) Repetitive rhythmic waves with either an incrementing onset, decrementing offset, and/or post-discharge slowing or attenuation.
3) Repetitive spikes, sharp waves, spike/sharp waves, and slow-wave complexes with a frequency of 3 Hz or less, and significant improvement in clinical state or EEG background after administration of ASMs (5, 46).

In contrast, electrographic seizures in the absence of a clear clinical change are more challenging to determine. The 2021 ACNS terminology, which is briefly explained below, excludes the unequivocal electrographic seizure definition, which is defined as generalized spike-waves at 3 Hz or more, and/or evolving discharges that reach >4 Hz (5, 46). **Figure 3** illustrates an example of an unequivocal electrographic seizure.

The diagnosis of NCSE relies exclusively on EEG interpretation. NCSE is a condition with high morbidity and mortality and its prompt diagnosis by the clinician is paramount to the care of the critically ill patients (47). Although several criteria have been proposed, the Salzburg criteria has been widely accepted (48). **Table 1** describes the criteria in further details.

The most updated 2021 ACNS terminology was designed to standardize the terminology of periodic and rhythmic EEG patterns in critically ill patients. Its basic premise consists of a main term #1 followed by a main term #2, with modifiers added if appropriate. Main terms #1 refer to localization and include: generalized, lateralized, bilateral independent, and multifocal. Main terms #2 is the description of the activity seen and include: periodic discharges (PDs), rhythmic delta activity (RDA), and spike-and-wave or sharp-and-wave (SW). Modifiers include prevalence, duration, frequency, number of phases, sharpness, amplitude, polarity, stimulus induced, evolving or fluctuating, and plus (+) features, -with the latter describing features of a more ictal appearing pattern (5).

Periodic Discharges (PDs)

Periodic discharges (PDs) are classified as discharges with uniform morphology and duration with a clear inter-discharge interval between consecutive waveforms, and recurrence of the waveform at nearly regular intervals (5). Periodic discharges are subclassified according to their location described as either generalized, lateralized, regional, or bilateral with a variety of prognoses.

Generalized Periodic Discharges (GPDs)

Generalized periodic discharges (GPDs) are bilaterally synchronous and symmetric, however, they can be frontally, occipitally, or midline predominant (5). GPDs are associated with NCS and NCSE. However, this association is less common when compared to lateralized (LPDs) and bilateral independent periodic discharges (BIPD) (49). Furthermore, the most common etiologies associated with GPDs are often seen in acute brain injury, ischemic/hemorrhagic stroke, and hypoxic-ischemic brain injury (HIBI) patients (50).

The morphology of the GPDs may also portend to a specific clinical diagnosis and/or outcome. For example, GPDs with a triphasic morphology, also known as triphasic waves, have long been associated with toxic-metabolic etiologies (51–53). There is evidence, however, that this association may not be accurate, and that GPDs with triphasic morphology maybe associated with developing seizures (54, 55). Features associated with poor outcomes have been described with static GPDs, superimposed faster frequencies, lack of triphasic morphology, and anterior to posterior phase lag (55). **Figure 4** illustrates a case of GPDs in a critically ill HIBI patient associated with poor outcome.

Lateralized Periodic Discharges (LPDs)

Lateralized periodic discharges (LPDs) are asymmetric discharges that are either unilateral or bilateral (5). This pattern was previously called periodic lateralized *epileptiform* discharges (PLEDS) but given the controversy of whether a specific LPD pattern is or is not epileptic, the epileptiform portion was removed from the ACNS guidelines in 2012 (56). LPDs are the most common periodic pattern in the ICU seen in up to 6–9% of hospitalized patients (57). LPDs may occur in the setting of ischemic or hemorrhagic stroke, traumatic brain injury, encephalitis, epilepsy, systemic infections, and other toxic/metabolic related etiologies. LPDs are highly associated with seizures (40–60%) (51, 57, 58). A study conducted in 2017 found that LPDs at frequencies higher than 2 Hz cause cerebral metabolic decompensation with an increase in regional cerebral blood flow and decrease in brain oxygenation indicating tissue hypoxia, which resembles the physiological changes seen in seizures (59). It can manifest as an electrographic pattern only or clinically as focal seizures, generalized seizures, or epilepsia partialis continua (59). **Figure 5** illustrates a case of right temporal LPDs.

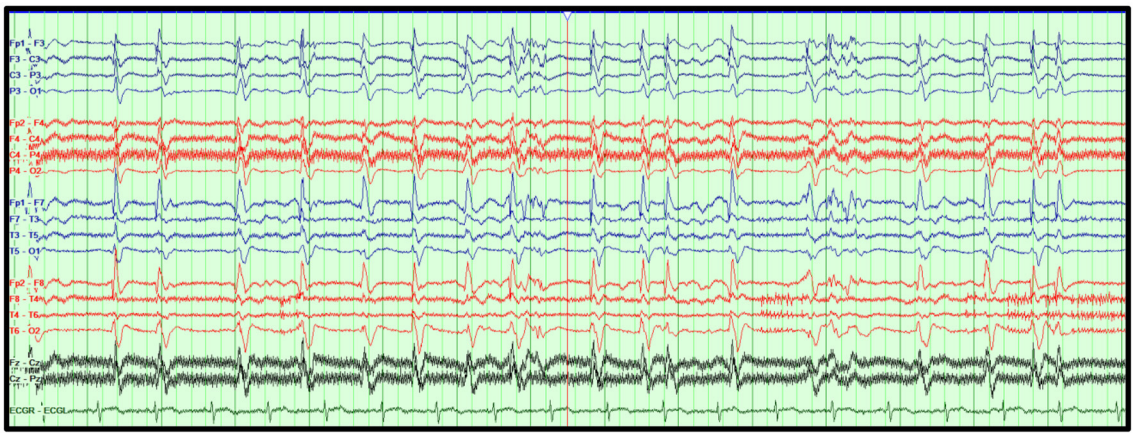

FIGURE 4 | Generalized periodic discharges (GPDs). GPDs at 1–2 Hz superimposed on a diffusely attenuated delta background in an 82-year-old woman who suffered HIBI. Bipolar montage, LFF: 1 Hz, HFF: 70 Hz, Notch: 60 Hz, Sensitivity: 7 μV/mm, Timebase: 30 mm/s.

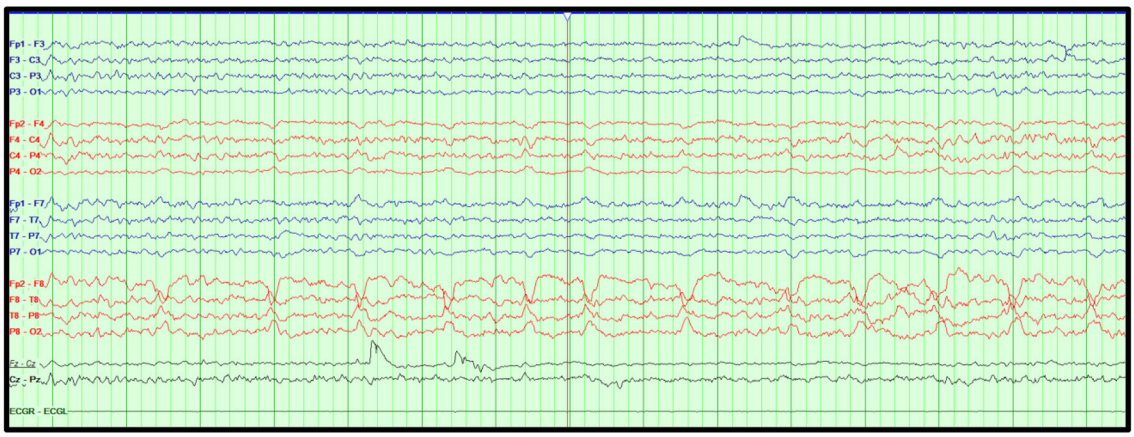

FIGURE 5 | Lateralized periodic discharges. Right temporal periodic discharges in an 18-year-old man with temporal lobe epilepsy with medication non-adherence. Bipolar montage, LFF: 1 Hz, HFF: 70 Hz, Notch: 60 Hz, Sensitivity: 7 μV/mm, Timebase: 30 mm/s.

Lateralized/Generalized Rhythmic Delta Activity (LRDA/GRDA)

Rhythmic delta activity refers to a repetition of a waveform with relative uniform morphology and no interval between consecutive waves (5). The terms lateralized and generalized follow the same rules as periodic discharges.

Lateralized rhythmic delta activity (LRDA) is highly associated with seizures, at an incidence similar to LPDs, with the risk increasing in the presence of any Plus modifiers (49, 60). On the contrary, generalized rhythmic delta activity (GRDA), previously referred to as FIRDA (frontal intermittent rhythmic delta) and OIRDA (occipital intermittent rhythmic delta), is not associated with an increased risk of seizures, regardless if Plus modifiers are present (60).

Burst Suppression/Attenuation Pattern

A burst-suppression pattern is an EEG pattern characterized by a quasi-periodic high amplitude "burst" alternating with periods of suppression (<10 μV) or attenuation (≥10 μV but <50% of the highest voltage background) (5). This EEG pattern can be physiologic (early development in the pre-mature brain), or pathological as seen in HIBI and severe epileptic encephalopathies of infancy (61–63). It can also be induced by anesthetics or hypothermia, which are commonly used to treat status epilepticus and uncontrolled elevated intracranial pressure in patients suffering from brain injury (64, 65).

A burst suppression/attenuation pattern identified in HIBI is typically associated with a poor prognosis (63, 66). For example, the presence of burst suppression with identical bursts had 100% specificity for a poor prognosis (66). This pattern is also highly associated with seizure recurrence (67).

CHALLENGING ICU EEG PATTERNS

Ictal-Interictal Continuum (IIC)

The concept of IIC was first introduced by Pohlmann-Eden et al. (58) The authors initially described LPDs as an active state

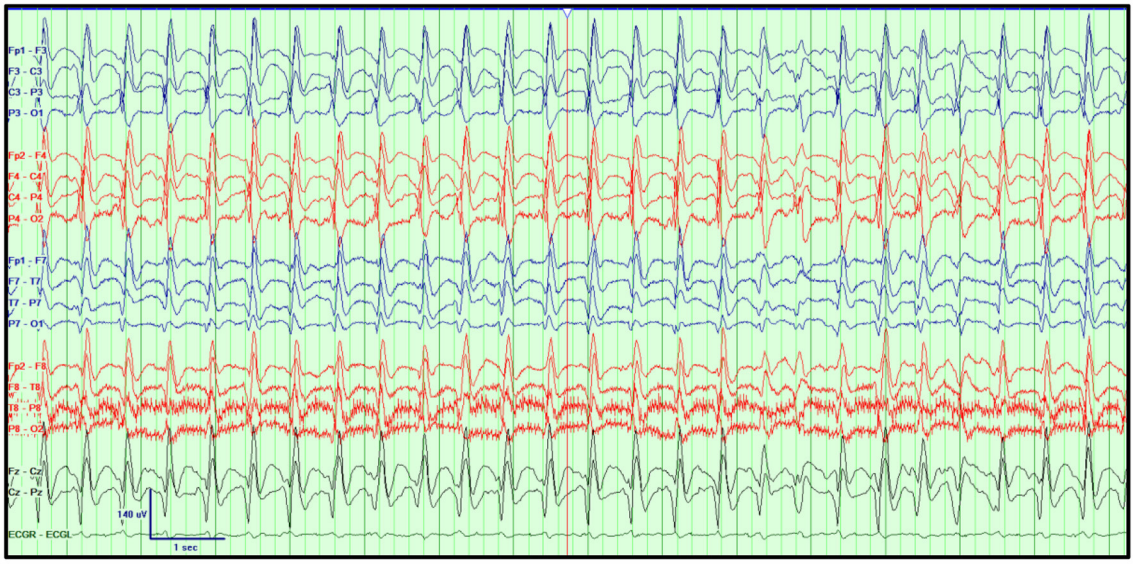

FIGURE 6 | Generalized periodic pattern with triphasic morphology. GPDs with a triphasic morphology at 1–2 Hz with a posterior to anterior gradient superimposed over a diffuse, irregular, delta-theta background in a 52-year-old woman with altered mental status, chronic kidney disease and sepsis treated with cefepime. Bipolar montage, LFF: 1 Hz, HFF: 70 Hz, Notch: 60 Hz, Sensitivity: 7 μV/mm, Timebase: 30 mm/s.

in which "unstable neurobiological processes create an ictal-interictal continuum, with the nature of the underlying neuronal injury, the patient's pre-existing propensity to have seizures, and the co-existence of any acute metabolic derangements all contributing to whether seizures occur or not" (58). At the time of this review, the ACNS recognizes that this is still a term under development without broad consensus, yet, potentially ictal and often warrants a diagnostic treatment trial. Currently, IIC includes rhythmic and periodic patterns occurring at 1–2.5 Hz without spatial evolution or clinical correlate (5). The increased risk for seizures associated with IIC patterns has been well-established, particularly with frequencies >1.5 Hz (49). However, it is still unclear whether IIC causes a similar degree of neuronal injury, worsening outcomes, or require the same degree of aggressive anti-seizure medication (ASM) treatment as do the definitive electrographic seizures.

Generalized Periodic Patterns With Triphasic Morphology

The GPDs with triphasic wave morphology, commonly known as triphasic waves (TWs), was first described by Brickford and Butt (68). Triphasic waves consist of (1) three phases with an initial fast and low-amplitude negative phase, followed by a second positive phase, and finally a third high-amplitude negative phase; (2) occur usually at a frequency of 1.5–2 Hz; (3) has an anterior to posterior, or posterior to anterior lag; and (4) a bi-frontal predominance (69). It was initially associated with hepatic encephalopathy; however, it has since been associated with a variety of metabolic, structural, and toxic encephalopathies. These include, but are not limited to, uremia, hypoglycemia, hyperthyroidism, sepsis, toxicities from various drugs (cefepime, baclofen, and valproic acid), vascular disease, and dementia (51, 70, 71). Triphasic waves may assume an ictal pattern and be associated with seizures. This is particularly true in high-risk patients with a focality on EEG, inter-burst suppression, a history of epilepsy, and abnormal neuroimaging findings (72). Various authors have suggested an algorithm to distinguish ictal appearing TW pattern to facilitate correct therapeutic intervention and avoid unnecessary use of ASMs (69). **Figure 6** illustrates a patient with toxic-metabolic encephalopathy that was confirmed with cEEG.

Stimulus Induced/Terminating Patterns

Stimulus induced rhythmic, periodic, or ictal discharges (SIRPIDs) was described initially in 2004 by Hirsch et al. (73). It is encountered in roughly 10–22% of patients undergoing EEG in the ICU and consist of any rhythmic, periodic, or ictal discharge induced by an alerting stimulus, such as noise, sternal rub, physical examination, suctioning, turning, and other activities related to patient care (73, 74). SIRPIDs include stimulus induced (SI)-periodic discharges, rhythmic delta activity, seizures, and IIC.

A multicenter, international, retrospective study found that SIRPIDs are not associated with worsening mortality after the data was adjusted for other prognostic factors such as age, anoxic brain injury, and absent reactivity on EEG (74). Similar findings were published in the literature (75, 76). SIRPIDs are also suggested to be associated with good prognosis in comatose survivors after cardiac arrest (77). Anti-seizure medications are commonly used to treat SIRPIDs, however, its clinical utility remains uncertain.

EEG Artifacts/Seizure Mimics

Unfortunately, particularly in the ICU setting, several artifacts may obscure the EEG signal. It is imperative for the electroencephalographer to properly identify and attempt to mitigate these artifacts to avoid the misdiagnosis of "noise" as cerebral electrographic abnormalities. This "noise" is detected by EEG electrodes from varying sources contaminating the EEG signal. It is not infrequent for artifact to disrupt the EEG background, obscuring underlying electrographic abnormalities, potentially obscuring electrographic seizures, and/or mimicking ictal patterns. The most common sources of EEG artifact in the ICU are related to (1) physiologic features such as sweat, eye flutter, movements, nystagmus, cardiac cycle, pulse, chest compression, and ventilator-related artifacts; (2) instrument and electrode artifact such as the 50 or 60 Hz electrical artifact; and (3) artifacts from multiple electronic devices (i.e., feeding machines) (78).

COMMON SEIZURE ETIOLOGIES IN THE ICU

Seizures in Patients With Impaired Level of Consciousness

Non-convulsive status epilepticus is an underrecognized cause of impaired level of consciousness in the ICU, particularly in septic patients. In a prospective study of 236 critically ill comatose patients with no clinical signs of seizure, 8% were found to have NCSE with EEG evaluation (79).

In a retrospective study of 154 adult surgical ICU patients who underwent cEEG for altered mental status over a 6-year period, 16% of patients all suffering from sepsis developed NCS with 5% ($n = 8$) developing NCSE. Clinical seizures prior to cEEG were more common among comatose patients who developed NCS or NCSE compared to patients without clinical seizures (70 vs. 27%) (80).

In a retrospective study of 201 patients admitted to a medical ICU without a known acute neurological injury who underwent cEEG, 10% of patients developed electrographic seizures with the majority of septic patients developing electrographic seizures when compared to non-septic patients (32 vs. 9%) (81).

Seizures in Post-convulsive Status Epilepticus (CSE)

As mentioned earlier, patients with convulsive seizures are at greater risk for non-convulsive status epilepticus. In a prospective study of 164 critically ill patients with CSE with clinical control of the seizures within 24 h, 48% of those patients continued to have persistent electrographic seizures with more than 14% meeting criteria for NCSE (82).

Seizures in Traumatic Brain Injury

Traumatic brain injury also poses a risk for seizures in our critically ill patients. In a prospective study of 70 traumatic brain injury patients requiring intensive care, 33% developed seizures 74 h after the initial trauma (83). In another prospective study of 94 critically ill patients undergoing cEEG who suffered from moderate-to-severe traumatic brain injury, 21 (22%) of patients developed convulsive/non-convulsive seizures with six patients developing status epilepticus. In 52% of those patients, the seizures were NCS (84).

Seizures in Subarachnoid Hemorrhage

Seizures developing in the aftermath of a subarachnoid hemorrhage are common in the ICU. In a prospective study of 101 patients with subarachnoid hemorrhage who survived the first 48 h of hospitalization, 26 of those patients were monitored with cEEG. Eight of those patients (8%) were diagnosed with NCSE with an average of 18 days after the subarachnoid bleed day. Risk factors for NCSE included a Hunt and Hess grade IV or V, older age, ventricular drainage, and cerebral edema on CT scans (85).

In another retrospective study of 11 out of 389 critically ill patients suffering from NCSE in the setting of spontaneous subarachnoid hemorrhage, the most common risk factors among the patients included advanced age, female sex, need for ventriculostomy, poor neurological grade (Hunt and Hess Grade III-V), thick cisternal blood clots, and structural lesions (intracerebral hemorrhage and stroke) (86).

Seizures in Intracerebral Hemorrhage

Stroke, particularly hemorrhagic stroke, is a risk for seizures in the ICU. In a retrospective study of 102 patients with intracerebral hemorrhage who underwent cEEG, seizures occurred in 31% ($n = 32$) of patients with 18% ($n = 18$) of those patients developing electrographic seizures only. The first seizure was detected within the first 1 h of cEEG in 56% of patients and within 48 h in 94% of patients. Risk factors associated with seizures included an ICH volume of 30% or more between admission and the 24-h follow-up CT scan (87).

In a prospective study of 109 patients with 63 patients suffering from intraparenchymal hemorrhage ($n = 63$) undergoing cEEG, electrographic seizures occurred in 18 of 63 patients (28%) during the initial 72 h of EEG monitoring with most seizures occurring in lobar hemorrhages and 21% in subcortical hemorrhages (88).

Not only are acute seizures common in intracerebral hemorrhages, but late seizures—that is seizures occurring 7 days after hemorrhagic insult—may also occur. The CAVE score is designed to assist the intensivist with identifying patients most susceptible for late seizures after an intracerebral hemorrhage. The CAVE score (0–4 points) assigns points for the cortical involvement of intracerebral hemorrhage (1 point), patient age <65 years (1 point), hemorrhagic volume >10 ml (1 point), and early seizures within 7 days of the hemorrhagic insult (1 point). In a large retrospective study of 1,318 patients suffering from intracerebral hemorrhage, it was found that the risk for late seizures was 0.6, 2.6, 9.8, 34.8, and 46.2% for CAVE scores of 0–4, respectively (89).

Seizures in Ischemic Stroke

Although seizures are more commonly seen in hemorrhagic strokes, it can also manifest in the setting of acute ischemic strokes. In a prospective study of 109 patients with 46 patients

suffering from ischemic stroke undergoing cEEG, electrographic seizures occurred in 3 of the 46 patients (6%) during the initial 72 h of EEG monitoring (88).

In another prospective study of 100 adult patients undergoing cEEG with an acute ischemic (91 patients) and hemorrhagic stroke (9 patients), two patients with ischemic strokes developed focal electrographic seizures (90).

Seizures in CNS Infection

Central nervous system infections—whether viral, bacterial, or fungal—are also common causes of seizures in the ICU. In a retrospective cohort study of 42 patients with a primary central nervous system infection—viral in 27 patients (64%), bacterial in eight patients (18%), and fungal/parasitic in seven patients (17%)—electrographic seizures were captured in 14 patients (33%) with only five of those patients developing a clinical correlate (91). In a prospective study of 62 critically ill adult patients with acute community acquired bacterial meningitis, 8 (12.5%) of the patients developed seizures (92).

An observational cross-sectional study of 696 episodes of community acquired bacterial meningitis in patients older than 16 years of age with confirmed CSF culture, seizures occurred in 121 patients (17%). The median time was 24 h between the first seizure and admission. Seizures were most common in patients with Streptococcus pneumonia, focal cerebral abnormalities, and a low Glasgow Coma Scale (93).

Seizures in Hypoxic-Ischemic Brain Injury (HIBI)

As described earlier in this article, HIBI is a common cause for seizures in the ICU. In a retrospective observational study of 166 post-anoxic comatose patients admitted to an ICU (all but four patients with out-of-hospital arrest), 107 patients underwent cEEG. Out of the 107, 35 (33%) patients had post-anoxic status epilepticus (94). In a prospective study of 101 critically ill adult comatose post-cardiac-arrest patients who underwent cEEG, 12 (12%) of the patients suffered from NCSE with four patients experiencing NCSE within 8 h of cEEG recording and within 12 h after resuscitation from cardiac arrest (95).

In another prospective study of 103 out of 192 adult patients with cardiac arrest, predominantly out-of-hospital ($n = 148$ or 77%, compared to in-hospital $n = 44$ or 23%), undergoing hypothermia protocol, six patients developed status epilepticus when EEG was obtained on day 2 and 3 of initial injury (96). Finally, in a prospective observational study of 95 patients after cardiac arrest treated with hypothermia, 26 patients (27%) developed electrographic status epilepticus (97).

Since the prevalence of seizures is high in HIBI patients, a recent multicenter clinical trial known as the treatment of electroencephalographic status epilepticus after cardiopulmonary resuscitation trail (TELSTAR) was conducted to determine the degree of treatment required by this unique cohort (50, 98). This was a multicenter clinical trial that randomized open-label treatment assignments and blinded end-point evaluation of 172 adult post-cardiac arrest patients in 11 ICUs in Europe. The goal was to suppress rhythmic and periodic EEG patterns (including GPDs, electrographic seizures, evolving patterns) for at least 48 h along with standard ASM and targeted temperature management or to only treat with standard ASMs and targeted temperature management. The primary outcome was the neurological outcomes according to the Cerebral Performance Category at 3 months—a good outcome (absent to mild-moderate disability) to poor outcomes (severe disability, coma, or death). It was found that at 3 months, 79 of 88 (90%) in the treatment group and 77 of 84 (92%) in the control group had poor outcomes ($P = 0.68$). Mortality at 3 months was 80% in the treatment group and 82% in the control group. The authors highlight limitations to their study that included the trial physicians' ability to withdraw life-sustaining treatment after the 48-h treatment period, the study treating several different patterns that are not clearly ictal in nature, and finally the difficulty in evaluating a sick population who had poor outcomes at the onset (50, 98).

CHALLENGES AND FUTURE DIRECTIONS

The benefits of utilizing cEEG in the ICU comes with its challenges (99). The surge of cEEG may add a burden among EEG technologist and electroencephalographers to cover the clinical need—a relevant issue in the American healthcare system (100, 101). Additionally, the access to cEEG monitoring is also challenging in resource-limited regions. Typically, serial rEEGs in lieu of cEEG are used in these regions. However, with the advent of remotely analyzed point-of-care EEGs, the financial burden may be alleviated in these settings (11, 40).

Further research is required to determine how aggressively challenging EEG patterns (such as IIC) should be treated, the appropriate seizure control or suppression ratio in status epilepticus, and patterns with triphasic morphologies.

The future of critical care EEG appears promising with the improving storage capacity, and the processing power allowing for machine learning utilization. This utilization is a useful tool for predicting seizures, and for an automated interpretation of large data sets (102, 103). However, these applications are not widely used in clinical practice and may not improve the workload of the electroencephalographers (104, 105).

CONCLUSION

In conclusion, the EEG is an essential apparatus in critical care that provides a relatively inexpensive tool for clinicians to monitor cerebral activity in real time. Although the awareness of subtle electro-clinical and electrographic non-convulsive seizures has increased in critical care, cEEG continues to be underutilized. With the rise in cEEG monitoring, the burden falls to the electroencephalographer and the institution to provide this necessary instrument to our critically ill patients. However, with the introduction of qEEG and other future machine learning applications, we may find more

efficient and less taxing means of acquiring this necessary electrocerebral data.

AUTHOR CONTRIBUTIONS

SS and MN wrote the manuscript. AA reviewed and finalized the manuscript, and made critical revisions. All authors contributed to the article and approved the submitted version.

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Phenytoin as seizure prophylaxis in hematopoietic stem cell transplantation with busulfan conditioning

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Background: Phenytoin is widely used as primary seizure prophylaxis in hematopoietic stem cell transplantation in patients undergoing myeloablative conditioning with busulfan. Because of the negative side effects of phenytoin, we abandoned phenytoin use in these patients. To assess the effect of this change, we performed a retrospective cohort study on all patients receiving busulfan.

Methods: We included 139 patients who underwent conditioning with busulfan for hematopoietic stem cell therapy. We registered the use of phenytoin, as well as the occurrence of seizures, until 7 days after busulfan administration. We compared seizure incidence between patients who received phenytoin and those who did not.

Results: Of the 43 patients who received phenytoin prophylaxis, four patients (9.3%) had a seizure during the conditioning regimen, of which two patients had cerebral non-Hodgkin lymphoma. Furthermore, all these 4 patients had very high levels of phenytoin (intoxication). Of the 96 patients that did not receive phenytoin prophylaxis, three patients (3.1%) had a seizure, and one of these patients had an undefined cerebral lesion. Phenytoin did not relate to seizure prevention in a logistic regression analysis.

Conclusion: We conclude that phenytoin prophylaxis in patients treated with busulfan is obsolete and possibly harmful, as phenytoin intoxication can occur. We recommend discontinuing the use of phenytoin as primary seizure prophylaxis in these patients.

KEYWORDS

busulfan, phenytoin (PHT), seizure, acute symptomatic seizure, seizure prophylaxis

Introduction

Busulfan is an alkylating agent, introduced in 1980 by Santos et al. as a myeloablative regimen in combination with cyclophosphamide in hematopoietic stem cell transplantation (1). Busulfan is a small lipophilic molecule, which easily crosses the blood-brain barrier (2). Treatment with busulfan may lead to organ toxicity in about 10% of the patients (3). Moreover, neurotoxicity can occur with the use of busulfan, and it is likely caused by high levels of busulfan in the central nervous system due to its ability to cross the blood-brain barrier (4). Seizures are considered a common (in ∼10% of patients), and possibly preventable, side-effect of busulfan treatment (5, 6).

Phenytoin has been widely used for many years as a drug to prevent seizures induced by busulfan, although a double-blind randomized clinical trial to prove effectivity is missing (4, 7). Despite its effectiveness as an antiepileptic drug, phenytoin has its drawbacks, among others the non-linear pharmacokinetic metabolism, making the elimination very unpredictable with possible consequent toxicity, as well as bothersome side effects (nystagmus, tremors, and myoclonus) (8, 9). Furthermore, phenytoin can cause serious drug-drug interactions, a.o. with busulfan and cyclophosphamide; however, the clinical significance of this interaction is probably negligible (10, 11). Given these factual and possible drawbacks, the benefit-risk ratio of adding phenytoin to busulfan is not clear, and, as we considered that the risks outweighed the benefit (preventing seizures), we decided to stop giving phenytoin to our patients treated with busulfan.

In the current study, we aim to investigate the effect of the discontinuation of phenytoin as primary seizure prophylaxis in busulfan treatment. We performed a retrospective cohort study at our center on a population of patients who underwent hematopoietic stem cell transplantation with a busulfan-based myeloablative stem conditioning regimen.

Methods

We included 139 adult patients who underwent a myeloablative stem cell transplantation with busulfan-based conditioning between March 2008 and January 2019 at Maastricht University Medical Center (MUMC+). All patients received the busulfan conditioning regime for three consecutive days. Depending on the hematological diagnosis, other chemotherapeutic drugs were also used in the regimen (e.g., fludrarabine and anti-thymocyte globulin for myelofibrosis; fludrarabine for chronic myelocytic leukemia, cyclophosphamide in acute lymphocytic, and myelocytic leukemia). In the period that patients received busulfan, patients either received phenytoin to prevent epileptic seizures or (after we decide to stop using phenytoin in January 2013) no prophylaxis with anti-epileptic drugs at all.

Using the electronic patient files, we assessed the occurrence of seizures. This was done by RG, and all descriptions of episodes with possible epileptic origin were double-checked by RR for classification as an actual seizure. We also examined possible causative factors of seizures, like known brain tumors or other cerebral lesions, and electrolyte and/or metabolic disturbances. This assessment was done in consensus by two clinical experts, one in epilepsy (RR) and one in hematology and hematopoietic stem cell transplantation (AD).

The medical ethical committee approved this retrospective study, which has no obligations to the Dutch law for medical research on patients.

Statistical analysis

We compared parameters (mainly proportions) in patients who received phenytoin prophylaxis to those without using Chi-Square and Fisher's exact test (whichever was appropriate). Additionally, we performed a logistic regression analysis to evaluate the influence of several factors, such as phenytoin prophylaxis, busulfan dosage, sex, and age on the occurrence of seizure events. We considered p-values of < 0.05 to be statistically significant. The statistical analysis was performed with SPSS Statistics version 25.

Results

Patient characteristics can be found in Table 1. For the busulfan conditioning regimen, 1 mg/kg (orally) or 0.8 mg/kg (intravenously) four times a day was used.

In patients receiving phenytoin, the dose was 1.25 mg/kg and given every 6 h, starting 1 or 2 days before, or on the same day of the start of the busulfan regime, until the end of the busulfan regime. All patients took their phenytoin orally. Of the 43 cases that were given with prophylactic phenytoin, four patients (9.5%) had a seizure, of whom two had a cerebral non-Hodgkin lymphoma as a likely contributing cause to the seizure. The seizures occurred between days 3 and 9 after the start of the busulfan regime. Of the 96 patients that did not receive phenytoin, 3 patients (3.1%) had a seizure of whom one patient had cerebral lesions of unknown origin as contributing cause to the seizure. The seizures happened between 3 and 5 days after the start of the busulfan regime. No significant difference in the incidence of seizures was found between both groups ($p = 0.203$, Fisher's exact test). When considering only patients with seizures with an unknown cause (seizures not related to an intracranial lesion), we could not demonstrate significant differences in seizure occurrence between patients with and without prophylaxis (see Table 2).

We also assessed possible confounders in a logistic regression analysis with seizure occurrence as the dependent

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TABLE 1 Patient characteristics.

	Phenytoin ($N = 43$)	No phenytoin ($N = 96$)
Male sex	21 (49%)	54 (56%)
Age (years) mean ± SD	47 ± 15.9	50 ± 13.3
Diagnosis		
AML[a]	29	57
CML[b]	1	2
Myelofibrosis	1	20
ALL[c]	6	8
Other	6	9
Stemcell source		
Autologous	10	51
Allogeneic	33	45
Busulfan conditioning regime		
0.8 mg/kg (IV)	0	89
1 mg/kg (oral)	43	7
Mortality	20 (46%)	33 (34%)

[a]AML, Acute myeloid leukemia.
[b]CML, Chronic myeloid leukemia.
[c]ALL, Acute lymphoid leukemia.

TABLE 2 Incidence of epileptic seizures with unknown cause in both groups.

	Epileptic seizure	No epileptic seizure	Total
Phenytoin prophylaxis	2 (4.7%)*	41 (95.3%)	43
No phenytoin prophylaxis	2 (2.1%)*	94 (97.9%)	96
Total	4	135	139

*$p = 0.36$.

variable. The dosage of busulfan (which was different when given IV or orally), phenytoin prophylaxis or not, age, and sex did not relate to the occurrence of seizures.

Regarding the safety of phenytoin use, we found that all four patients treated with phenytoin with a seizure had phenytoin intoxication (levels were 21 μg/ml or higher). All other patients in the phenytoin group of whom the phenytoin levels were recorded had therapeutic (or higher) levels (average 15.9 μg/mL or higher), and still, four more patients had clinical signs of a phenytoin intoxication (confirmed by the levels) but without seizures.

Discussion

In our retrospective study, we could not demonstrate any positive effect of phenytoin on the prevention of seizure occurrence in patients treated with busulfan. In contrast, these patients were exposed to risks, like phenytoin intoxication.

Phenytoin's therapeutic range is between 10 and 20 μg/ml, and elevated levels may lead to severe side effects, such as cerebellar syndrome, while coma may occur with serum levels higher than 40 μg/ml (8, 12). In previous studies, the prevalence of seizures (without seizure prophylaxis) was 1–10% of patients treated with busulfan (4, 13). Our numbers were similar, as we found that 3.1% of patients with busulfan conditioning without phenytoin had an epileptic seizure. Thus, seizure risks do not seem to change over time. However, we found that the seizure risk in the phenytoin-treated group was similar to the non-treated group, leading to the conclusion that phenytoin has no benefit in preventing seizures in these patients. Our findings, therefore, support the decision to stop adding phenytoin to busulfan regimes.

Other anti-epileptic drugs than phenytoin could have presented a more positive picture. Phenytoin (in contrast to other, and newer, anti-epileptic drugs) has an unfavorable side effect profile and narrow therapeutic window, which can easily lead to high levels and intoxication, which, in turn, might cause seizures as well (8). Other anti-epileptic drugs have been assessed for the primary prevention of seizures in busulfan treatments. E.g., Levetiracetam might be a better candidate for primary seizure prevention, though the published studies are not placebo-controlled or randomized. The benefit-risk ratio of newer agents like levetiracetam may be better in these vulnerable patients (7, 14, 15) E.g., levetiracetam has far fewer drug-drug interactions, while showing lesser side effects (15). However, in our study, we show that only two out of the 96 patients who received no prophylaxis, experienced seizures. Providing a prophylactic drug to patients could be beneficial, but even if the effectivity of the anti-epileptic would be 100%, the number needed to be treated is high (in our population 96, to prevent two patients having a seizure). Given these low frequencies, a double-blind randomized trial will not be feasible. Therefore, it remains at the discretion of the treating medical team whether primary seizure prophylaxis will be given (preferably with a newer anti-epileptic drug like levetiracetam) or not.

Despite our important findings, our study has some limitations. First, this was a retrospective study performed in a single center, leading to possible bias in reporting and underreporting seizures and seizure-like events. Also, absolute seizure event numbers were low, both in prophylactically treated patients, as well as in non-treated patients. Of course, this is not beneficial for the power of this study, however, there is no large clinical benefit for the patients treated with phenytoin (we even saw some adverse effects). Secondly, the phenytoin levels were not measured in all the patients leading to missing data in patients without seizures and doing well on phenytoin, nor were busulfan levels measured to assess the effect of possible pharmacokinetic interaction, or to assess the effects of the change of formulation over time from intravenous to oral

administration. However, as we mainly focussed on phenytoin treatment and seizure prophylaxis, this was less relevant.

Conclusion

We found no benefit of phenytoin use in patients treated with busulfan, and we recommend a reconsideration of the standard practice of giving phenytoin as primary prophylaxis in busulfan-based conditioning regimens in hematopoietic stem cell transplantation.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by METC MUMC+. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

RG collected the data, performed statistical analysis, and drafted the manuscript. AD supervised the study and revised the manuscript for intellectual and scientific content. RR designed and supervised the study and revised the manuscript for intellectual and scientific content. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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BIRDs (Brief Potentially Ictal Rhythmic Discharges) watching during EEG monitoring

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Brief Potentially Ictal Rhythmic Discharges (BIRDs), initially described in neonates, have been shown to correlate with increased risk of seizures in both critically ill and non-critically ill adults. In critically ill patients, BIRDs are associated with acute brain injury and worse functional outcomes. In non-critically ill adults, BIRDs are seen in patients with epilepsy with a greater likelihood of having drug resistance. The location of BIRDs seems to better predict the seizure onset zone compared to other interictal epileptiform discharges. The definition of BIRDs includes Paroxysmal Fast Activity (PFA), and they have similar clinical significance regardless of the exact cut-off frequencies. Their potential as a biomarker for seizure activity and seizure onset zone has been suggested. In patients with status epilepticus, BIRDs also resolve or decrease when seizures resolve. Thus, if BIRDs are observed on scalp EEG, more extended EEG monitoring is recommended to estimate their seizure burden and to guide treatment. With the recent addition of BIRDs in the critical care EEG terminology, with future investigations, we may soon be able to reach a consensus about the definition of electrographic seizures and better understand their neurophysiology and clinical significance.

KEYWORDS

seizure, status epilepticus, critical care, drug resistant epilepsy, seizure onset zone, paroxysmal fast activity

Introduction

Continuous EEG monitoring (CEEG) is an essential diagnostic tool to assess subclinical seizure activity or non-convulsive status epilepticus in patients with persistent or fluctuating altered mental status that are otherwise unexplained. The clinical picture of these patients can range from an awake but confused patient to a comatose patient in the intensive care unit (ICU) without any prior history of epilepsy. The EEG patterns of critically ill patients are in many ways different from those of non-critically ill patients, especially in the setting of acute brain injury. The background of EEG is slower in critically ill patients, rhythmic or periodic patterns are common, and the seizure patterns of critically ill patients also often involve a non-evolving pattern. The first definition of seizures in critically ill patients by Young et al. (1) included generalized or focal repetitive epileptiform discharges at >3 Hz lasting for >10 s. This served as a framework for current consensus definitions of electrographic seizures from the Salzburg Consensus Criteria (2, 3). This has been adopted by the

American Clinical Neurophysiology Society (ACNS), and according to the updated 2021 ACNS Standardized Critical Care EEG Terminology, electrographic seizures are defined as epileptiform discharges averaging >2.5 Hz for ≥10 s or any pattern with definite evolution and lasting ≥10 s (4). If it lasts <10 s but has a clear clinical correlate, it is called an electroclinical seizure (4). The cut-off number of "10 seconds", originally derived from observation of typical seizure duration in epilepsy patients (except for absence or myoclonic seizures) (5, 6), is rather an arbitrary number. Ictal-appearing rhythmic discharges that last under 10 s without clinical correlation are not called seizures. These discharges were first described in neonates, then later described in critically ill adults under the name, brief potentially ictal rhythmic discharges (BIRDs) (7). Since then, further efforts have been made to define, characterize, and investigate its clinical significance, which will be reviewed here. The definition of BIRDs has been modified and adopted by the 2021 ACNS Critical Care EEG Terminology. It is defined as focal or generalized rhythmic activity >4 Hz (at least six waves at a regular rate) lasting ≥0.5 to <10 s, not consistent with a known normal pattern or benign variant, not part of burst-suppression or burst-attenuation, without definite clinical correlate (see Box 1 for full definition and categories) (4).

BIRDs in neonates

Brief rhythmic discharges were first described in neonates. Because rhythmic trains of stereotyped waveforms lasting for a few seconds are a very common finding in non-specifically abnormal neonatal EEGs, a 10-s cut-off had been adopted in some neonatal studies to avoid misclassifying these waveforms as "ictal." (8–13). However, the 10-s cut-off could also make the EEG readers disregard true ictal discharges. Shewmon discussed this problem and preferred to call them "brief ictal rhythmic discharges (BIRDs)" with an intentional ambiguity of the acronym "I" that it can either convey ictal or interictal, reflecting their conceptual fuzziness (14). He suggested that non-ictal rhythmic waveforms are generally distinguishable from true BIRDs based on (1) their common occurrence in infants with nonspecific encephalopathies and no seizures, (2) their limited range of durations in a given tracing (never longer than a few seconds), and (3) the company they keep (i.e., BIRDs tend to flock with unequivocal seizures of similar morphology) (14). Oliviera et al. tested the diagnostic and prognostic validity of BIRDs alone (i.e., when it is not accompanied by electrographic seizures) in neonates. Their study showed BIRDs by themselves were associated with a clinical history of hypoxic-ischemic encephalopathy and increased risk for the abnormal neurodevelopmental outcome and suggested including BIRDs in future studies of neonatal seizures (15). In a subsequent study by Nagarajan et al., 52 neonates were divided into three groups: (1) BERDs (here "E" stands for "EEG") only, (2) BERDs and seizures, (3) seizures only, and found no significant difference in mortality and neurodevelopmental outcomes or background EEG impairment among these three groups and suggested that BERDs should be considered as mini seizures (16).

BIRDs in critically ill adults

The occurrence of BIRDs in adults was first described in 2014 in critically ill patients. In this study, BIRDs were defined as very brief (<10 s) lateralized runs of rhythmic activity >4 Hz, with or without evolution. This study included 20 patients with BIRDs and 40 controls matched by age and the primary diagnosis. The prevalence of BIRDs was 2%. The most common frequency of BIRDs was theta (70%), typically lasting 1–3 s. In this study, none of the BIRDs showed obvious evolution. All patients with BIRDs had evidence of cerebral injury (primarily acute). The occurrence of a history of epilepsy was not significantly different from the control group. Patients with BIRDs were more likely to have seizures during CEEG than patients without BIRDs [15 of 20 (75%) vs. 10 of 40 (25%); $p < 0.001$]. Seizures often started with a morphology similar to that of BIRDs and within the same region. In all patients whose seizures were controlled with medications, BIRDs ceased after the seizures had been controlled (Figure 1). On the other hand, lateralized periodic discharges (LPDs) persisted after the seizures were controlled in most patients. Patients with BIRDs tended to have a worse outcome than controls [16 (80%) vs. 25 (63%)], but this was not statistically significant. Given the high association between BIRDs and seizures and timing of occurrence, it was strongly suggested that if BIRDs were present in the short EEG recording, continue monitoring or treat prophylactically (7). Limited by the small number of patients included in this study, further study was needed to help make the definitions more specific and help identify clinically relevant subtypes.

BIRDs in non-critically ill patients

BIRDs in non-critically ill patients were subsequently described in patients who were electively admitted to the epilepsy monitoring unit or had ambulatory EEG monitoring at home (17). In these alert and oriented patients, brief rhythmic discharges appeared with varying frequency and often in alpha or beta frequencies than theta. Generalized BIRDs were also observed and hence included in this study. BIRDs were defined as very brief (<10 s) runs of focal or generalized sharply contoured rhythmic activity >4 Hz with or without evolution. This study included 15 patients with BIRDs (1.2% prevalence) and 30 controls matched for age and etiology. Since all patients with BIRDs had epilepsy, all controls also had a history of epilepsy but no BIRDs on EEG. Patients with BIRDs were more likely to have drug-resistant epilepsy [10 of 15 (67%) vs. 5 of

BOX 1
Brief Potentially Ictal Rhythmic Discharges (BIRDs).

Definition: focal (including L, BI, UI, or Mf) or generalized rhythmic activity > 4 Hz (at least six waves at a regular rate) lasting ≥0.5 to <10 s, not consistent with a known normal pattern or benign variant, not part of burst-suppression or burst-attenuation, without definite clinical correlate, and that has at least one of the following features:

a. Evolution ("evolving BIRDs," a form of definite BIRDs)
b. Similar morphology and location as interictal epileptiform discharges or seizures in the same patient (definite BIRDs)
c. Sharply contoured but without (a) or (b) (possible BIRDs)

Note: Paroxysmal fast activity lasting ≥0.5 to <10 s qualifies as BIRDs, whether generalized (also known as generalized paroxysmal fast activity, or GPFA) or focal.

Note: Although they are termed "brief," technically all BIRDs are "very brief" because they are <10 s.

L, lateralized, BI, Bilateral Independent, UI, Unilateral Independent, Mf, Multifocal. (Adopted from American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version).

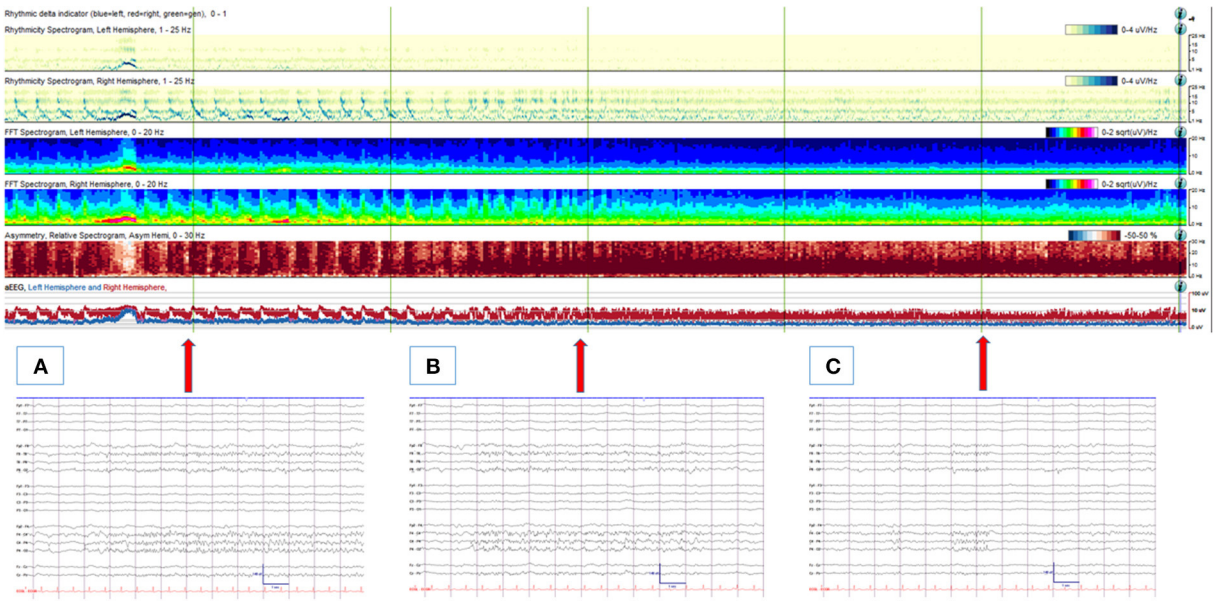

FIGURE 1
An 88-year-old man with an acute traumatic brain injury with right sided intraparenchymal hemorrhage, subdural hemorrhage and subarachnoid hemorrhage, who was noted to have frequent left facial twitching. **(Upper panel)** A quantitative EEG panel showing a total of 1-h duration. From the beginning of the record, frequent cyclic seizures are seen originating from the right hemisphere (with increased rhythmicity, power, asymmetry and amplitude from the right hemisphere with each seizure). With anti-seizure medication treatments, seizures resolve, and no more cyclic seizure patterns are depicted from the quantitative EEG analysis. **(Lower panel)** corresponding (arrows) raw EEG examples are shown. **(A)** An electrographic seizure from the right hemisphere (maximal from the parasagittal region). **(B)** Evolving BIRDs from the same area, lasting 9 s. **(C)** Non-evolving BIRDs from the same area. High- and low-pass filters were set at 1 and 70 Hz, respectively. The notch filter was off.

30 (17%); $p < 0.01$]. The mean duration of monitoring was similar between the two groups, and seizures were captured more commonly in the BIRDs group although this did not reach the statistical significance. In this study, emphasis was made to distinguish BIRDs from normal or benign variants since many benign variants could look like BIRDs by their morphology and duration in these non-critically ill patients (e.g., mu rhythm, wicket spikes, 14- and 6-Hz positive bursts, and rhythmic mid-temporal theta discharges). One of the distinguishing features of the BIRDs from benign variants was that BIRDs were activated by sleep (especially in stage 2 sleep), whereas most benign variants are known to be present in an awake and drowsy state. However, this distinguishing feature based on the state of alertness is often not applicable to critically ill patients, especially when there are no state changes or reactivity. The location and morphology of BIRDs were also similar to the location of interictal epileptiform discharges (IEDs) or seizures in the same patient (Figure 2). Based on these features, BIRDs were defined as focal or generalized rhythmic activity >4 Hz (at least six waves at a regular rate) lasting 0.5–10 s, not consistent with a known normal pattern or benign variant, and that has at least one of the following features: (a). evolution (definite BIRDs),

(b). similar morphology and location as interictal epileptiform discharges or seizures in the same patient (definite BIRDs). (c). sharply contoured but without a or b (possible BIRDs) (17). The American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 version modified and adopted this definition and category (Box 1) (4).

BIRDs as EEG biomarker for seizure activity and seizure onset zone

Many examples of BIRDs in the adult population could also be called paroxysmal fast activity (PFA) since it encompasses any frequencies above 4 Hz. However, with the term PFA, many of these discharges with slower frequency (i.e., theta or slower alpha frequencies) would be missed since PFA by its name means "fast." The definition of PFA and GPFA has varied in the literature, but according to the most recent EEG term glossary, PFA is defined as "fast frequencies in the beta range or above, occurring in trains" and GPFA as "bilateral synchronous bursts of spikes of 2–10 s duration, with a frequency between 10 and 25 Hz and maximal in the frontal regions that only occurs during sleep" (18). GPFA was historically considered a marker for Lennox-Gastaut syndrome or other epileptic encephalopathies (19–21). More recently, this was recognized in patients with normal cognition and generalized epilepsy (22–25). Most recent studies have described the association between the presence of GPFA and drug resistance and no specific association with a particular type of generalized epilepsy (25, 26). Focal PFA has also been described in patients with focal epilepsy, and their relationship to seizure onset zone and intractability has been suggested (27–29). The occurrence of BIRDs and asymmetric extreme delta brush in similar regions has been reported in patients with anti-N-methyl D-aspartate (NMDA)-receptor encephalitis (30, 31). To test if different frequencies of these rhythmic discharges have any different clinical significance, different frequencies of BIRDs (including PFA), other EEG and clinical features were compared in both critically ill and non-critically ill adults (32). In this study of 94 patients with BIRDs or PFA, 74 % had epilepsy, and over half (62%) had drug-resistant epilepsy. All patients with generalized BIRDs/PFA had a history of epilepsy (67% were drug-resistant), and only 14% had epileptic encephalopathy. Sixty-six percent had seizures captured during the same recording (89% among the critically ill and 52% in non-critically ill), and the scalp EEG seizure onset zone co-localized with BIRDs/PFA in all cases, including cases with contralateral epileptiform discharges. The rate of the seizures was similar regardless of the frequency or location of the BIRDs/PFA. All patients with evolving BIRDs/PFA had electrographic seizures in the same recording, and 50% of patients with non-evolving BIRDs/PFA had seizures. In 33 patients who were in status epilepticus, when seizures resolved with anti-seizure medication treatment, BIRDs/PFA also decreased or resolved. Based on these results, BIRDs/PFA were suggested to be a biomarker for seizure activity and seizure onset zone, and since BIRDs include the frequency spectrum of PFA, it was suggested to include PFA as a sub-type of BIRDs. A recent systematic review of scalp-detected high-frequency oscillations (HFOs) in epilepsy patients reported that scalp HFOs localized the epileptogenic zone better than spikes, correlated negatively with cognition and positively with disease activity and severity, and decreased after medical and surgical treatment (33). Since no upper limit of frequency was defined in BIRDs, further study of BIRDs including scalp-detected HFOs would be valuable.

Intracranial correlates of BIRDs

No studies thus far directly compared BIRDs to intracranial seizures. Only limited studies have attempted to systematically correlate the seizure-onset patterns on scalp EEGs with intracranial EEGs (iEEG) in epilepsy patients (34–37). A recent study compared electrocorticography (ECoG) from the responsive neurostimulation (RNS) device and simultaneous scalp EEG monitoring in drug-resistant epilepsy patients implanted with a responsive neurostimulator. In this study, the most common scalp EEG correlates for ictal-appearing long episodes that did not have scalp seizure correlates were BIRDs, including both evolving and non-evolving types (38).

Further studies, especially with simultaneous scalp EEG recordings, are needed to study the relationship between intracranial seizures and scalp EEG markers including BIRDs (both evolving and non-evolving types), to better understand the anatomical, pathological, electrophysiological, and clinical significance. It would also be interesting to study them in critically ill patients monitored with additional depth electrodes.

Clinical use of BIRDs

To guide clinicians in assessing seizure risk, a seizure-risk scoring system (2HELPS2B) has been developed, which consists of 5 continuous EEG (CEEG) features and just one clinical variable (a history of seizure) (39). This multi-center study included 5,427 CEEG cases (>6 h) from the Critical Care EEG Research Consortium database and used a machine learning method to produce accurate, risk-calibrated scoring systems. BIRDs were seen in 3.2% of patients with a high odds ratio (18.8) and a high proportion (69%) of seizures and thus given 2 points when present. All the other variables (history of seizure, lateralized periodic discharges or rhythmic delta activity, frequency of >2 Hz for any periodic or rhythmic pattern, "plus"

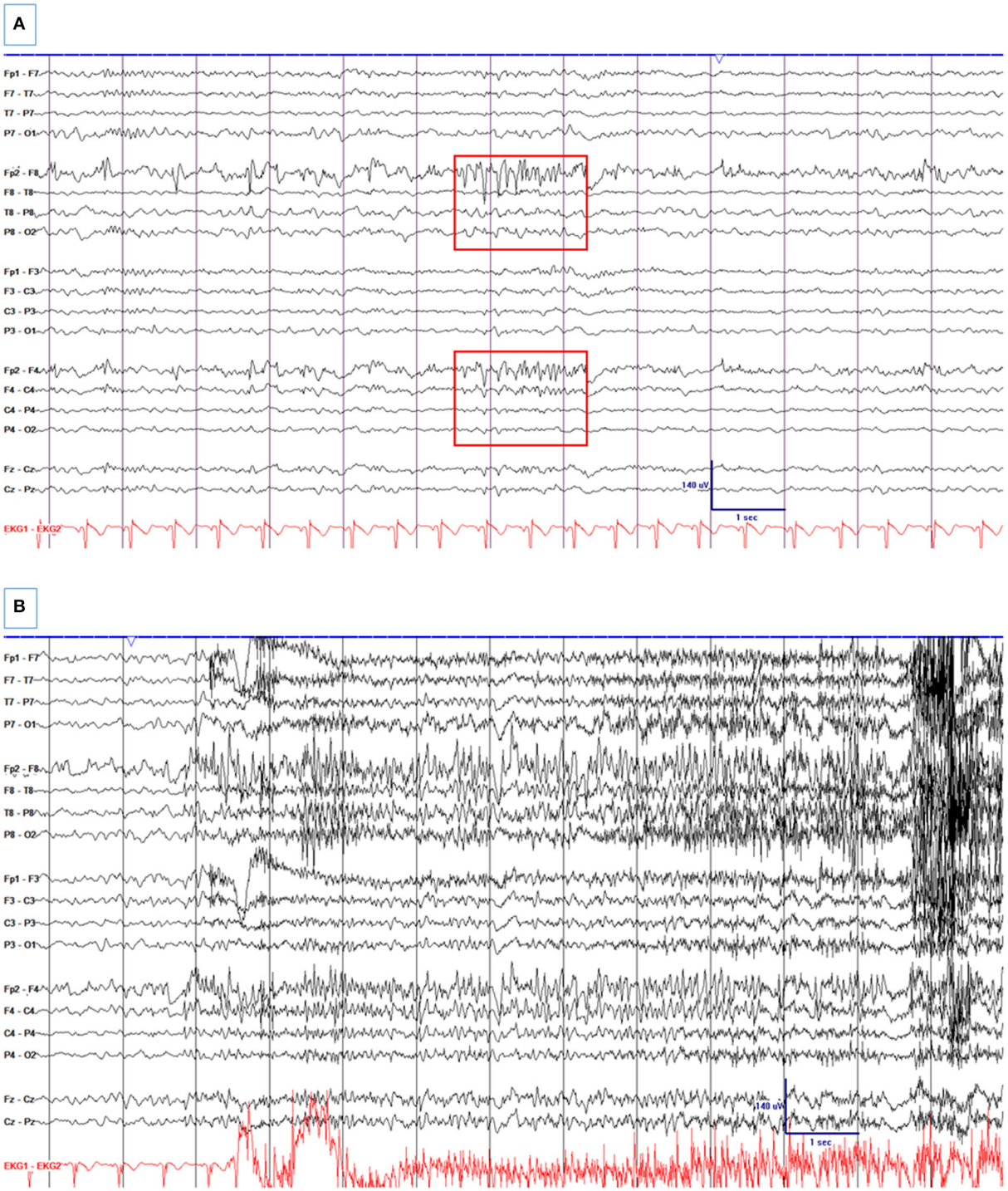

FIGURE 2
A 33-year-old woman with a remote history of traumatic brain injury at age two with a right frontal encephalomalacia and surrounding gliosis and drug-resistant epilepsy, who was electively admitted for pre-surgical evaluation. **(A)** Right frontal spikes and R frontal non-evolving BIRDs (Box 1). There is a right frontal breach rhythm. **(B)** A seizure from the right frontal region. High- and low-pass filters were set at 1 and 70 Hz, respectively. The notch filter was off.

features, sporadic epileptiform discharges) were given 1 point. The probable seizure risk was 5% for a score of 0, 12% for 1, 27% for 2, 50% for 3, 73% for 4, 88% for 5, and >95% for a score of 6 or 7. This study was performed before the proposed categories of BIRDs (possible vs. definite, evolving vs. non-evolving) (17), so no distinction was made for these sub-categories of BIRDs. This scoring system was also shown to identify low-risk patients accurately and quickly with only 1-h screening EEG (40).

Since PFA has similar clinical significance to BIRDs (regardless of their frequencies), whether seen in critically ill patients or non-critically ill patients with epilepsy, their presence should alert the clinicians of the high likelihood of ongoing seizures or increased seizure burden of those patients. Its high correlation with seizure onset zone will also help guide the surgical planning of drug-resistant epilepsy patients, especially with further investigation of its characteristics with anatomy and pathology.

Discussion

BIRDs are associated with a high risk of seizures and better predict the seizure onset zone compared to other interictal epileptiform discharges, thus potentially serving as a biomarker of seizure activity and seizure onset zone. The definition of BIRDs includes Paroxysmal Fast Activity (PFA), and they have similar clinical significance regardless of the exact cut-off frequencies. In patients with status epilepticus, BIRDs also resolve or decrease when seizures resolve. Thus, if BIRDs are observed on scalp EEG, longer EEG monitoring is recommended to estimate their seizure burden and to guide treatment.

EEG waveforms often appear rhythmic, and some factors make them appear sharply contoured (e.g., breach rhythm); therefore, it is essential to avoid overcalling BIRDs. In the non-critically ill, the morphology of BIRDs often resembles benign variants. So, it is important to distinguish them and not to call them BIRDs when they are, in fact, benign variants. When there are no state changes or reactivity in the critically ill, distinguishing them is challenging based on their presence in different states of alertness (41). Due to this problem, if such waveforms are seen, it is recommended to call them "possible BIRDs" in the absence of co-existing IEDs or seizures in the same patient and avoid overtreating these patterns. If the waveforms evolve, or if there are co-localizing IEDs or seizures in the same patient, then they meet the criteria for definite BIRDs, in which case they deserve treatment with anti-seizure medications. Non-evolving BIRDs also have a high correlation with seizures, so in their presence, longer monitoring is strongly suggested, and a prophylactic dose of ASMs should be considered to prevent impending seizures.

Whether to maintain or eliminate the "10-second" (clearly an arbitrary) cut-off for electrographic seizures was discussed among the authors of the critical care EEG terminology 2021 version and the Critical Care EEG Monitoring Research Consortium (CCEMRC) members both online and in person. No consensus was reached at the time as there was no convincing new literature to change it (4). Now that BIRDs are added to the official EEG terminology with the revised 2021 version of critical care EEG terminology (Box 1), with further investigations, we may be able to reach a consensus about the definition of electrographic seizures and better understand its pathologic, anatomic, and neurophysiological significance.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Acute symptomatic seizures and status epilepticus in older adults: A narrative review focusing on management and outcomes

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A clear narrative of acute symptomatic seizures (ASyS) in older adults is lacking. Older adults (≥60 years) have the highest incidence of seizures of all age groups and necessitate a tailored approach. ASyS has a bimodal peak in infancy and old age (82.3–123.2/100,000/year after 65 years of age). ASyS can represent half of the new-onset seizures in older adults and can progress to acute symptomatic status epilepticus (ASySE) in 52–72% of the patients. Common etiologies for ASyS in older adults include acute stroke and metabolic disturbances. For ASySE, common etiologies are acute stroke and anoxic brain injury (ABI). Initial testing for ASyS should be consistent with the most common and urgent etiologies. A 20-min electroencephalogram (EEG) is less sensitive in older adults than in younger adults and might not help predict chronic epilepsy. The prolonged postictal phase is an additional challenge for acute management. Studies note that 30% of older adults with ASyS subsequently develop epilepsy. The risk of wrongly equating ASyS as the first seizure of epilepsy is higher in older adults due to the increased long-term challenges with chronic anti-seizure medication (ASM) treatment. Specific challenges to managing ASyS in older adults are related to their chronic comorbidities and polypharmacy. It is unclear if the prognosis of ASyS is dependent on the underlying etiology. Short-term mortality is 1.6 to 3.6 times higher than younger adults. ASySE has high short-term mortality, especially when it is secondary to acute stroke. An acute symptomatic etiology of ASySE had five times increased risk of short-term mortality compared to other types of etiology.

KEYWORDS

acute symptomatic seizure, acute symptomatic status epilepticus, older adults, management, outcomes

Introduction

Definition

The International League Against Epilepsy (ILAE) defines acute symptomatic seizures (ASyS) as seizures occurring in close temporal relationship with an acute central nervous system (CNS) insult of varying etiologies (1). The definition also includes seizures occurring in a preexisting background of epilepsy and fulfills other criteria for ASyS. Differentiating ASyS from unprovoked seizures is essential due to

prognostic implications. ASyS differs from remote symptomatic seizures and progressive symptomatic seizures as the prognosis is different. For seizures to be considered ASyS, ILAE has proposed the following: seizure occurrence 1 week after stroke, head trauma, and anoxic brain injury (ABI), 1 day for metabolic causes, 7–48 h from the last alcoholic drink, and active intracranial infection or inflammation. Studies on optimal laboratory cutoff values to better delineate toxic–metabolic causes are lacking. Seizures due to anti-seizure medication (ASM) non-adherence are considered provoked seizures (1).

Older adults with epilepsy have the highest incidence of epilepsy of all age groups, with at least 25% of newly diagnosed seizures occurring after 60 years of age (2, 3). They constitute a separate treatment group compared to other adults due to the high incidence of comorbidities, associated polypharmacy, and age or disease-related changes in pharmacodynamics and pharmacokinetics (4).

There is a lack of consensus on who is considered an older adult in general and in those with seizures. We define older adults as ≥60 years of age for this review unless otherwise mentioned. Josephson et al. suggested using an age threshold of 65–70 years to define "elderly-onset epilepsy." However, such a recommendation is lacking in ASyS or current older adults with "younger-onset epilepsy" (5).

Epidemiology

Studies note that 34% of all afebrile seizures are ASyS (incidence 39 persons/100,000/year) (6). Men are more susceptible than women (42 vs. 27/100,000/year). Mirroring the incidence of epilepsy, ASyS also has two peaks, i.e., infancy and >74 years (7, 8). The rates start increasing gradually after 45 years of age: 55/100,000/year for 55–65 years; 82.3/100,000/year for 65–75 years; and 123.2/100,000/year for 75+ years. Older male adults are 1.6 to 2.6 more likely to have ASyS than older female adults (8).

According to Holt-Seitz et al. (9) ASyS represented half of the new-onset seizures in older adults. Nearly half were due to cerebrovascular disease (CVD), and 20% were due to metabolic disturbances (8). The rising incidence of CVD and metabolic disturbances with age (renal and hepatic dysfunction and diabetes) is likely responsible for the increased incidence of ASyS.

Acute symptomatic seizures represent 52–72% of cases of status epilepticus [SE; acute symptomatic status epilepticus (ASySE)] (10). ILAE definition of SE does not differentiate between the etiology of epilepsy and that of SE. For example, in a patient with a remote symptomatic cause of epilepsy such as CVD, the new SE might be triggered by a metabolic insult. This lack of differentiation is significant in older adults due to the potential for long-term polypharmacy (11). However, we assume that the definition of ASyS that includes "seizures occurring in a preexisting background of epilepsy" can be extrapolated to SE.

Etiology

Cerebrovascular disease is the most common etiology of ASyS in older adults and accounts for 28–58% of ASyS (Table 1). ASyS are two times as likely with hemorrhagic CVD as compared to ischemic CVD (12). Cortical location predicts the risk of seizures after hemorrhagic and ischemic CVD (12). Regional ischemia leading to excitatory neurotransmitter release and local irritation due to acute mass effect from cerebral hemorrhage is the proposed pathophysiological mechanism underlying CVD-related AsyS (12). Other etiologies include metabolic (6–14%), traumatic brain injury (TBI) (7–10%), CNS infections (2–6%), and toxin-related (5–12%). Post-traumatic ASyS commonly occurs in the setting of acute subdural hematoma (13).

Acute stroke was responsible for 35% of ASySE in older adults (15). Other common etiologies in decreasing frequency were hypoxia (17%), metabolic disorders (14%), and alcohol-related (11%) (15).

Clinical presentations and diagnostic workup

Clinical presentations and differential diagnosis

Older adults can have atypical seizure presentations, such as epileptic aura, subtle confusion, aphasia, or prolonged postictal altered mental status. Non-motor manifestations, including somnolence and clumsiness, might be more common than convulsive seizures (17). Focal impaired awareness seizures originating from the frontal lobe are more common in the elderly than other types (18). Due to these atypical presentations, clinicians should consider seizures in the differential diagnosis of other common presentations in older adults, such as transient ischemic attacks, syncope, and falls.

Convulsive syncope is a seizure triggered by syncopal mechanisms caused by loss of vascular supply to the brain (19). The population incidence of convulsive syncope is unknown but is commonly seen in clinical practice. It can present as a transient myoclonic activity when the patient collapses with loss of consciousness. Surprisingly, head deviation, automatisms, and visual and auditory hallucinations, usually associated with focal onset seizures, are common (60–80%) in convulsive syncope (20) and can further lead to diagnostic dilemmas.

TABLE 1 Etiology of acute symptomatic seizures in older adults.

Proportion of ASyS cases by etiology for older adults*	Traumatic brain injury	CVD	Central nervous system infection	Metabolic	Toxic
Hauser et al. (14)	-	28%	-	-	-
DeLorenzo et al. (15)	-	35%	-	14%	11%
Ramsay et al. (3)	6.9%	35.8%	-	-	-
Sibia et al. (16)	4.40%	58.14%	6.16%	6.16%	5.28%
Annegers et al. (8)	10.2%	40.8%	2%	8.2%	11.6%

*Definition of older adults varies between age ≥ 60 years (3, 16) and ≥ 65 years (8, 14).

Diagnostic testing

The American Academy of Neurology has published practice guidelines for the management of the first unprovoked seizure (21). However, a similar guideline is not available for first or recurrent provoked or ASyS.

Neuroimaging

The initial testing for ASyS in older adults should be consistent with the most common and urgent etiologies. Focal deficits with and after a seizure should prompt evaluation for CVD, including CT head to rule out acute intracranial hemorrhage and MRI brain for acute ischemic stroke. Neuroimaging is also helpful to evaluate underlying neoplastic or infectious processes. One study focusing on older adults has found CT head with the new-onset seizures to show an acute pathology in 35% of patients (9).

Electrophysiologic studies

Initial electroencephalogram (EEG) was abnormal in 73% (61 out of 84) of older adults with new-onset seizures. Notably, 64% showed focal slowing but only 39% had epileptiform discharges. However, these included patients with all types of seizures and were not limited to AsyS (9). Routine EEG was less sensitive in older adults and might not help distinguish an ASyS with no clear etiology from an unprovoked seizure with possible epilepsy (22). Prolonged EEGs or serial EEGs should be considered if the long-term risk of seizures and diagnosis of epilepsy is to be ascertained (23). The yield of detecting interictal epileptiform discharges increased by 50% when ambulatory EEG was performed, as compared to routine EEG (3). Prolonged EEG can help detect non-convulsive SE in older adults who present with acute confusional states (24). However, Rossetti et al. demonstrated that prolonged EEG, despite increasing seizure detection, did not change the outcomes as compared to routine EEG in critically ill patients without recent seizures (25).

For patients with suspected convulsive syncope, capturing the episode on EEG or prolonged cardiac electrophysiological tests (event monitor, loop recorder) might be required for a definitive diagnosis. A simultaneous tilt-table and EEG might help confirm the diagnosis in a small number of patients (26). Clinicians should direct management toward finding and treating the cause of syncope.

Laboratory studies

One of the commonest etiologies is an acute metabolic disturbance. Relevant testing, including serum glucose, electrolytes, renal, and hepatic function tests, would guide appropriate diagnosis and treatment. The other common etiologies are infections, i.e., systemic or CNS (meningitis and encephalitis). Fever and non-reactive leukocytosis should lead to further workup, including urine analysis, chest X-ray, and lumbar puncture. Toxicology testing, including alcohol level, should be performed at presentation. Alcohol (induced or withdrawal) is a common cause of ASyS and ASySE. Elevated serum alcohol levels can diagnose alcohol-induced ASyS. However, for the diagnosis of alcohol-withdrawal seizures, reliable history of consistent alcohol use and recent abstinence and low serum alcohol level are needed. A clinical institute withdrawal assessment for alcohol scale (CIWA-Ar) score can measure alcohol withdrawal symptoms and prompt appropriate prevention of alcohol-withdrawal seizures (27).

Outcomes and management

Outcomes

Short-term and long-term mortality of ASyS

The short-term risk of death with ASyS is high (around 20% in the first month post-ASyS). However, it is higher in older adults (28.4–40.5%) as compared to younger adults (11.2 vs. 17.7%). Thus, within the same population, the risk of death was 1.6 to 3.6 times for older adults (28). Similarly, short-term mortality due to ASySE is two times the rate in older adults compared to younger adults. This difference persists after excluding myoclonic SE due to ABI (29).

Despite increased short-term mortality of ASyS, studies show that long-term mortality is similar to ASyS and unprovoked seizures (30). ASyS does not predict functional outcomes at 6 months for patients with intracerebral hemorrhage in a prospective trial (31). However, these studies are not specific to older adults.

Mortality of ASyS by etiology

Cerebrovascular disease and ABI were the most common causes of ASyS in those with short-term mortality (28). Population-based studies fail to reveal if the increased risk of death is due to ASyS or the underlying etiology.

Similarly, ASySE in older adults has poor short-term outcomes (11). Acute symptomatic etiology was the commonest type of etiology for SE (52–58%) and also had a >6 times risk of poor outcome (death or new neurological impairment) as compared to other types of etiologies (11, 32). Two-thirds of patients with ASySE had a poor outcome, and 57% had inpatient mortality. CVD was the predominant acute symptomatic etiology (33). Similarly, Hui et al. (34) found that the acute symptomatic etiology of SE had five times increased risk of short-term mortality (49% mortality rate), with CVD the most common reason. In a study of convulsive SE in older adults, acute symptomatic etiology was the commonest cause, seen in 60% of the patients. Out of 33 patients, nine (27%) patients progressed to refractory SE. However, acute symptomatic etiology did not increase the likelihood of progressing to Refractory Status Epilepticus (RSE). CVD followed by metabolic disturbance was the most likely reason. None of the patients with CVD died. However, acute symptomatic etiology was associated with increased short-term mortality, seen in five out of six patients (35). Thus, in most studies, acute symptomatic etiology of ASySE and CVD as the specific etiology suggests poor outcomes in older adults.

Mortality in older adults with ASySE and acute ischemic CVD (39%) is much greater than in ischemic CVD alone (14%) or SE due to remote ischemic CVD (5%) (36). This finding demonstrates that the high mortality is due to "synergistic effects of SE and ischemic brain injury" (36). The increased mortality was not explained by the increased severity of CVD as measured by the size of the CVD. However, 63% of patients with acute ischemic CVD and 75% of patients with acute ischemic CVD + SE had negative CT or MRI imaging. This finding suggests that some of these patients possibly had a prolonged postictal focal deficit, which is commonly seen in older adults (37). It is unclear if the severity of ischemic CVD as measured by NIHSS is correlated with worse outcomes in concurrent SE (36).

There is conflicting evidence on whether acute stroke treatment with Tissue Plasminogen Activator (TPA) or thrombectomy increases the risk of ASyS. Two studies found that thrombolysis and thrombectomy increase the risk of poststroke seizures (38, 39) but were not replicated in a case–control study (40).

Risk of recurrence

The risk of subsequent unprovoked seizures after ASyS is about 30% and does not meet the criteria for a diagnosis of epilepsy (41, 42). Although ASyS has high short-term mortality, the risk of developing epilepsy is significantly lower than unprovoked or remote symptomatic seizures (43). A 10-year follow-up study found that the risk of future seizure recurrence is 3.3 times higher in ASySE as compared to ASyS. The risk is further modified by the underlying etiologies of ASyS, with ABI conferring the highest risk, followed by metabolic and structural causes (42). Thus, treatment with ASM in older adults with ASySE might be warranted, but not with ASyS.

It is unclear if seizure recurrence risk after ASyS is more in older adults than in young adults or if there is risk stratification with different etiologies. More than three seizures at presentation and epileptiform activity on initial EEG were predictors of subsequent unprovoked seizures and epilepsy (9).

A meta-analysis noted that ASyS increases the risk of poststroke epilepsy. Although this finding is not specific to older adults, most CVDs occur in older adults, so the conclusion can potentially be extrapolated to the older adult cohort (44). ASyS due to CVD carries the highest weight in the SeLECT score that provides risk-stratification of postischemic stroke epilepsy (45). A large majority of participants in the SeLECT study were ≥60 years and provided ample evidence of seizure risk in this cohort. Similarly, ASyS is a risk factor for the development of epilepsy in posthemorrhagic CVD as measured by the CAVE score (46).

For all adults with TBI, the risk of recurrent seizures increases if seizures occur within 1 week of injury, with severe and penetrating injury, prolonged loss of consciousness, intracerebral hemorrhage, and subdural hemorrhage requiring surgical evacuation (49).

Physicians often encounter outpatient scenarios where patients are inappropriately started on ASMs due to ASyS in an acute setting. The abovementioned risk factors in addition to patient comfort and projected consequences of a seizure (even if low risk) such as injuries in job setting and loss of driving privileges should be considered to decide continuation vs. gradual weaning off of the ASM.

Management

Initial treatment of ASyS is directed toward the management of underlying etiologies. Patients with ischemic CVD presenting within a thrombolytic or endovascular window should receive cerebral revascularization treatment accordingly. In the 2019 American Heart Association guideline for the early management of ischemic CVD, IV Alteplase is reasonable in patients presenting with seizures at symptom onset if the residual deficits are attributed to CVD (50).

For patients with metabolic disturbances, correction of electrolyte and glucose disturbances is the most effective

TABLE 2 Antiseizure management for acute symptomatic seizures (ASyS).

Management of ASyS	Traumatic brain injury	Cerebro vascular disease	Central nervous system infection	Neoplastic	Metabolic	Alcohol
Primary prophylaxis	Yes	No	No	No	No	Yes[a]
Short-term ASM	Yes	Possible[b]	Yes	Possible[d]	Possible[e]	Yes
Long-term ASM	Possible[e]	Possible[c]	Possible[d]	Possible[d]	No	No

[a]ASM prophylaxis can be considered for severe alcohol withdrawal. [b]In selected cases such as ischemic stroke with hemodynamically relevant stenosis, brain edema, or vasospasms after subarachnoid hemorrhage (47). [c]ASM can be considered in ischemic CVD based on SeLECT score (45) and in hemorrhagic CVD based on CAVE score (46). [d]ASM should be continued if there are persistent structural abnormalities due to neoplasm or CNS infection or stroke. [d]ASM can be considered if there is a delay in metabolic derangement correction. [e]In patients with SDH requiring surgical evacuation, multiple brain contusions, early seizures, and dural penetrating injuries (48).

management for ASyS. Due to polypharmacy and multiple comorbidities, older adults may be prone to these disturbances. Investigating and treating underlying metabolic etiologies long-term is crucial to preventing future episodes. ASM is indicated to prevent recurrent seizures if there is an expected delay in correcting some metabolic derangement and hypoxia. Older adults are also prone to systemic and CNS infections due to immunosenescence (51, 52). New-onset seizures, especially in the setting of encephalopathy, should prompt early investigation and treatment of these infections. For patients with toxin ingestion or medication-induced (e.g., digoxin) ASyS, the culprit drug or toxin cessation and antidote administration (if available) are the most effective ways to treat seizures. Drug cessation and close monitoring of levels can help normalize epileptiform activity on EEG (53).

Anti-seizure medication is indicated for ASySE and might be necessary for treating ASyS that persist despite treatment of the underlying cause. Unfortunately, studies to guide the long-term management of ASM in the setting of ASyS are lacking. Patients who have interictal epileptiform discharges and persistent structural abnormalities or who present with SE are at a higher risk of developing epilepsy. The indication and duration of ASM in ASyS differ depending on the underlying etiology (Table 2) (43, 48, 50, 54–56). A 1–3 month duration has been proposed for short-term ASM use (43). For patients with ASyS due to posterior reversible encephalopathy syndrome (PRES), 3 months of ASM treatment have been proposed (57).

Primary seizure prophylaxis is not recommended for patients with acute ischemic CVD(50)or with intracranial neoplasm (54, 55). The Brain Trauma Foundation recommends 7-day anti-seizure medication prophylaxis after a TBI (56). Benzodiazepines or phenobarbital may be considered for seizure prophylaxis in severe alcohol withdrawal as determined by the CIWA-Ar score (43).

Few observational studies have found preventive benefits against ASyS with statins (58, 59). However, prospective, randomized studies are lacking to strongly recommend statin use at this time. The management of ASyS is summarized in Table 2.

Choice of ASM

Choosing an ASM in the setting of ASyS in older adults is challenging. Physicians need to consider underlying etiologies of ASyS, concurrent medications, comorbidities, and altered drug metabolism.

Strong hepatic enzyme inducers such as carbamazepine, phenytoin, and phenobarbital and enzyme inhibitor such as valproic acid should be used with caution due to potential interaction with multiple drugs used in older adults (60). Similarly, these ASMs should be avoided in patients with neoplasms due to drug–drug interaction with chemotherapeutic agents (61). They are also known to be atherogenic due to the potential of increasing serum cholesterol and, hence, are a suboptimal choice for poststroke seizures (61), a common reason for ASyS in older adults. Levetiracetam can improve cognitive outcomes after hemorrhagic CVD (62). It is comparable with phenytoin for the efficacy of primary and secondary seizure prophylaxis in TBI (43).

Patients with metabolic derangement secondary to renal or hepatic dysfunction require further consideration. Hepatically and renally metabolized or cleared ASM should be avoided or dose adjusted accordingly. Older adults can have physiologically decreased creatinine clearance (CL_{CR}). Specifically, for levetiracetam, dose adjustment is required for $CL_{CR} < 80$ ml/min/1.73 m^2 (63). Similarly, a maximum dose of 300 mg/day is recommended for lacosamide for severe renal impairment ($CL_{CR} < 30$ ml/min) (64). An additional dose of up to 50% once a day on baseline is recommended for levetiracetam and lacosamide in end-stage renal disease after hemodialysis on dialysis days (63, 64).

Randomized trials on ASMs targeting older adults are limited. However, two systematic reviews and meta-analyses suggest that lamotrigine, levetiracetam, and lacosamide are first-choice ASMs based on their high efficacy and reasonable

tolerance in older adults (65, 66). Overall, older adults require lower doses to be seizure-free. For example, a median lamotrigine daily dose of 100 mg was sufficient for seizure freedom in many patients (67). A reasonable strategy for ASMs in older adults is "Start low, go slow, and stay low."

Special considerations in the management of ASyS in the older adults

Differentiating between ASyS and unprovoked seizures can be challenging. However, the diagnostic dilemma has worse outcomes in older adults. The risk outcome of diagnosing a seizure as "unprovoked" when it was ASyS is more with older adults as they might be started on unnecessary chronic ASMs. This action can add to the medication burden in patients with polypharmacy (68). ASMs are frequently associated with adverse effects in older adults, including falls, cognitive impairment, and long-term complications like osteoporosis (69). In addition, they increase the risk of hospitalization (70).

Older adults can have prolonged postictal symptoms, including altered mental status, lasting hours to days (37). Thus, even if the etiology is known to be acute symptomatic, this prolonged postictal state could be confused with non-convulsive SE and could lead to needless treatment with benzodiazepines, ASMs, and anesthetic medications. This intervention further leads to an increased risk of intubation and increased length of stay which are known to have worse short-term and long-term outcomes (11). Obtaining an emergent EEG is of paramount importance in these patients to distinguish the postictal state from non-convulsive SE. Even in patients with established epilepsy, failure to distinguish between ASyS and unprovoked seizures will lead to an unnecessary increase in the dose of baseline ASMs.

Conclusion

Diagnosis and management of ASyS is an emerging field with many unanswered questions in older adults, including patient selection and risk factors for primary prophylaxis, short-term and long-term outcomes, and ASM management. Some novel clinical endeavors such as post-ASyS clinics and the multicenter Post-Acute Symptomatic Seizure Investigation and Outcomes Network (PASSION) project will help to further clarify many unknowns in this field (71).

Author contributions

WK and RM were responsible for the conception and design of the paper, drafting, critical revision, and final approval of the article to be published.

Conflict of interest

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The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Epileptic seizure first aid practices of publics in Northwest Ethiopia 2021: Unsafe practices of nearly three-fourths of the community

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Background: Religious and sociocultural beliefs influence how people with epilepsy (PWE) are treated and cared for. Many communities in Africa and other developing countries, including Ethiopia, believe that epilepsy is caused by evil spirits and should be treated with herbal plants by traditional doctors and religious leaders. The combination of these sociocultural beliefs and the level of community awareness of epilepsy affect first aid practices in the management of epileptic seizures.

Objective: This study aimed to assess epileptic seizure first aid practice of public and its associated factors in Northwest Ethiopia, south Gondar zone, Amhara, Ethiopia 2021.

Methods: A community-based cross-sectional study was conducted using a previously adapted standard questionnaire. A multistage cluster sampling technique was applied. A total of 756 participants were approached and 741 respondents completed the questionnaire with a response rate of 98.02%. Data were entered into Epi data version 4.4.2 and then exported to Statistical Package for Social Science (SPSS) version 24 for analysis. Descriptive and analytical statistical procedures and bivariable and multivariable binary logistic regressions with odds ratios and 95% confidence interval (CI) were employed. The level of significance of the association was determined at $p < 0.05$.

Results: Overall, 71.7% (95%CI: 68.3, 74.9) of the south Gondar community had unsafe practice measures in managing patients with seizure episodes. Individuals who were illiterate [adjusted odd ratio (AOR) = 1.99,

95%CI: 1.00.3.97] and participants who did not take training related to epilepsy (AOR = 2.07, 95%CI: 1.35, 3.17) and had poor knowledge about (AOR = 1.51, 95%CI: 1.06, 2.14) and a negative attitude toward epilepsy (AOR = 2.20, 95%CI: 1.50, 3.22) had unsafe practices compared to their counterparts. Conversely, participants who reached secondary education had safe practice measures (AOR = 0.4, 95%CI: 0.26, 0.63) in the management of epileptic seizures.

Conclusions: In this study, large numbers of the south Gondar community had unsafe practice measures in managing people with epileptic seizure episodes. Greater emphasis should be laid on individuals who were illiterate, in the provision of health education and/or training for the community to help them to acquire good knowledge about epilepsy and develop a positive attitude toward epilepsy.

KEYWORDS

seizure, epilepsy, unsafe practice, south Gondar zone, community

Introduction

An epileptic seizure is defined as a brief episode of signs and/or symptoms associated with abnormally excessive or synchronized brain neuron activity (1). Two or more spontaneous seizures occurring more than 24 h apart are considered clinically indicative of epilepsy (2). The need for care and treatment of people with epilepsy (PWE) are influenced by religious and cultural beliefs (3).

Epilepsy affects at least 50 million people globally (4), with the majority living in developing countries (5). The burden of epilepsy in low-income countries is double compared to developed countries (6). In a study conducted in some African countries (Kenya, Tanzania, Uganda, Ghana, and South Africa), the prevalence of epilepsy was between 7 and 15 per 1,000 people (7), 0.9/1,000 in Sudan (8), and 6.5/1,000 in Saudi Arabia (9). Similarly, the incidence of epilepsy in Qatar was 174 per 100,000 people (10). Likewise, the adjusted prevalence estimates for lifetime and active epilepsy in a study conducted in rural Kenya were 41/1,000 and 11/1,000, respectively (11). Moreover, in the Zay society of Ethiopia, the prevalence rates of epilepsy are found to be 29.5/1,000 (12).

People with epilepsy are highly stigmatized in most parts of the world (13, 14) and have different levels of awareness, attitudes, and first aid practice measures regarding epilepsy in various cultures. Nevertheless, PWE generally encounter social stigma, there are public misconceptions about the treatment and first aid measures at the time of seizure attacks (15). Even though the psychosocial and economic impacts of epilepsy are considered in high-income countries, the treatment gaps in low-income countries remain large, ranging from 60 to 98% (16). In Ethiopia, more than 85% of PWE are untreated. Only 4% of the untreated cited cost as justification for not receiving treatment, and 90% were unaware of the availability of treatment (17). Epilepsy remains a major public health problem, not only because of its health implications, but also because of its social, cultural, psychological, and economic effects in developing countries (18, 19). PWE also experience physical, intellectual, psychological, and social limitations (20). In severe cases, it results in disability and death due to burns, drowning, and even depression-induced suicide (21). This is usually associated with public misbeliefs (22) and inadequate public knowledge and a negative attitude about epilepsy, myths, and misconceptions (23–25).

A cross-sectional study of people living with epilepsy in sub-Saharan Africa, India, and Zimbabwe showed that PWE had limited opportunities in education, employment, and healthcare compared to the other population without epilepsy (26–28). Research conducted in Karachi, Pakistan, and Southeastern Nigeria on the practices of school teachers and secondary school students toward children with epilepsy showed persistent unsafe practices toward the management of epileptic seizures (29, 30). Surprisingly, there is an unsafe practice of epilepsy even among medical students as indicated by a study conducted in Southern Nigeria (31). Similarly, a study by World Health Organization (WHO) on epilepsy first aid management practice of the population in suburban Senegal revealed that nearly 23.4% of PWE had unsafe treatment practices (32). According to the result of previous studies, the magnitude of unsafe practices ranges from 6 to 68.1% (33–36).

First aid is crucial to prevent people from getting harmed during seizure episodes. Lack of knowledge and misunderstandings about first aid measures related to epileptic seizures cause the chance of not taking effective measures

Abbreviations: PWE, People with epilepsy; IRB, Institutional review board; SPSS, Statistical Package for Social Sciences; US, United States; WHO, World Health Organizations.

or taking dangerous measures while managing a seizure episode (37).

Factors that affect first aid practices in the community in the management of epileptic seizures include sociodemographic variables (age, sex, residence, marital status, educational status, and occupational status), the presence of patients with epilepsy in a family, the presence or absence of epilepsy, whether participants have received training related to epilepsy, knowledge about epilepsy, and attitudes toward epilepsy.

Despite its enormous impact, to the best of our knowledge, there are no published studies on first aid practices of the public in the management of epileptic seizures and their associated factors in the south Gondar zone, Amhara region as a whole. Therefore, this study adds to the body of knowledge about epileptic seizure first aid practices and their associated factors. Moreover, assessing first aid practices among public in the management of epileptic seizures would hopefully serve as a stepping stone for future large-scale community-based studies, and would be used as an indicator to health managers for appropriate planning and intervention programs.

Thus, this study aimed to assess epileptic seizure first aid practices among public and their associated factors in Northwest Ethiopia in 2021.

Materials and methods

Study settings and period

A community-based cross-sectional study was conducted in the southern Gondar zone from February to April 2021. Based on the 2007 Census conducted by the Central Statistical Agency of Ethiopia (CSA), the southern Gondar zone has 468,238 households and a total population of 2,051,738. Of these, 1,041,061 are men and 1,010,677 are women. Debre Tabor town, a city in the southern Gondar zone, is located 666 km north of the capital city Addis Ababa. This zone has 21 districts and 406 subdistricts (Kebeles). There are 97 health centers and 10 hospitals in the community. Healthcare services for epilepsy and mental health issues exist in every hospital.

Sample size determination and sampling procedures

In this study, the sample size was determined by using the single population proportion formula taking assumptions of a 95% confidence interval (CI), a 5% margin of error, and the magnitude of unsafe practices (66.5%) from a study conducted in the Oromia regional state, Ethiopia. The final sample size was 756 after adding 10% of the non-response rate to the sample size.

A multistage cluster sampling technique was used. First, the author randomly selects five districts from the total of 21 districts (Woreda) and three subdistricts (Kebeles) for each selected district. The source population include all households in the study area. All households found in the Kebeles were considered as the study population. Each person in the selected households for which actual data were collected was considered as the study unit. All people who lived permanently (at least 6 months) and were 18 years or older in the 20 selected Kebeles were included, excluding those who were seriously ill at the time of data collection.

To establish a sampling frame, a household survey was conducted by 40 health extension worker (HEW) data collectors 8 days before the actual data collection, and the household numbering was done in the selected Kebeles. The survey found a total of 8,789 people who ever helped people with seizures. Next, proportional allocation of the sample was made to identify representative samples from each Kebele based on the number of individuals who ever helped people with seizures. Then, a simple random sample technique (computer-generated random numbers) was employed. In situations there was more than one eligible study participant in a household, a lottery method was used to select only one.

Study variables

The dependent variable was the community practice of first aid for patients with epilepsy during seizure episodes (unsafe/safe). Sociodemographic factors (like age, sex, place of residence, marital status, educational status, and employment status) the presence of members with epilepsy in a family, the presence of absence of epilepsy, participation or not in epilepsy-related training, knowledge about epilepsy, and their attitude toward epilepsy were independent variables.

Data collection tools and procedures

Data were collected *via* face-to-face interviews using the previously adapted standard questionnaire that had two subsections. The first part dealt with the factors associated with the practice of seizure first aid measures. These factors included sociodemographic characteristics, familiarity with epilepsy, participation or not in epilepsy-related training, community knowledge about epilepsy, and their attitude toward epilepsy. The questions that measured the knowledge of the respondents about epilepsy had a sensitivity and specificity of 100 and 72%, respectively, and the entered data reliability was 0.87 (Cronbach's α). The attitude of the community toward epilepsy was measured using a six-point Likert scale questionnaire with an internal consistency value (Cronbach's α 0.79) (1 = I disagree very much, 2 = I disagree pretty much, 3 = I disagree a little, 4 = I agree a little, 5 = I agree pretty much, and 6 = I agree very much, that an item for which a "disagree" response (scored

negatively has been reversed) indicates a positive attitude (38). In the second part, seizure first aid practice measures were categorized as safe/unsafe practices toward practice measures. The questionnaire was translated into Amharic by a bilingual translator. It was retranslated to the original version (English) to ensure consistency. Two HEWs as data collectors and two BSc nurse supervisors were selected for each selected Kebele. Data collectors and supervisors were trained by a principal investigator for 1 day, about the methods of data collection, its tools, and how to handle ethical issues. A pretest was conducted on 38 (5%) of the samples outside the study area before the actual data collection to find any potential problems with the data collection tools. Data collection was regularly monitored by a principal investigator and supervisors. Every day the collected data were checked for completeness and consistency before being promptly entered from paper to computer.

Operational definitions

Practice

A 10-item questionnaire with yes/no options was used to assess the first aid practices of the community. Practice questions were graded with 1 point for each correct response and 0 point for each incorrect response. The total score is between 0 and 10. In this context, "safe practice" was defined as having a score greater than or equal to 50% on true questions about first aid practice measures, and an "unsafe practice" was defined as having a score <50% (19).

Training

Taking training was defined as whether the respondents took formal training or in any form of health education in health campaigns about the general information related to epilepsy, which has yes/no choices.

Knowledge

The knowledge of participants about epilepsy was assessed using a 10-item questionnaire with yes/no options. One point was awarded for each correct response to the true knowledge questions, while 0 point was awarded for each incorrect response. The total score is between 0 and 10. In this regard, good knowledge was defined when the respondents scored ≥50% in the true questions related to the knowledge about epilepsy, and "poor knowledge" was defined when respondents scored <50% on true knowledge questions (19).

Attitude

The part on attitude comprised 20 questions and response options on a six-point Likert scale consisting of I disagree very much (1), I disagree pretty much (2), I disagree a little (3), I agree a little (4), I agree pretty much (5), and I agree very much (6), that the items for which a "disagree" response (scored negatively have been reversed) indicates a positive attitude. Means were used as measures of the respondent's attitude. Participants whose score is equal to or greater than the mean have been considered to have a positive attitude whereas those whose score is less than the mean have been considered to have a negative attitude toward epilepsy related to the true attitude questions (38).

Data processing and analysis

Data were coded, entered into Epi data version 4.2, and then exported to Statistical Package for Social Science (SPSS) version 24. To determine the association of independent variables with outcome variables, bivariable and multivariable binary logistic regression analyses were performed. Variables with $p < 0.05$ in bivariable analysis were taken to multivariable analysis for further analysis to control for confounding factors. The results were presented using frequencies, proportions, and odds ratio (OR) with a 95% CI, and variables with $p < 0.05$ were declared to be significantly associated with unsafe practices.

Model fitness was examined using Hosmer and Lemeshow's test ($p = 0.45$). Using the variance inflation factor and tolerance, multicollinearity was checked to determine the correlation between the independent variables. The variance inflation factor in this instance was 10, and the tolerance level was higher than 0.1, indicating that there was no dependence between the independent variables.

Ethical considerations

Ethical clearance was obtained from the ethical review committee of Debre Tabor University, to obtain a permission letter from the south Gondar zone health department. The confidentiality of respondents was maintained using the anonymous data collection tool, and the questionnaire was provided with written consent. Selected personnel were informed that they can quit at any time, even if they had agreed to participate at first, and that their decision was not causing them any problems.

Results

Sociodemographic characteristics

A total of 741 respondents participated in this study with a response rate of 98.02%. Approximately half of the respondents were women 376 (50.7%) and urban residents 457 (61.7%).

TABLE 1 Sociodemographic characteristics of the community living in south Gondar zone, Amhara, Ethiopia 2021 ($n = 741$).

Characteristics	Category	Frequency	Percent
Sex	Male	365	49.3
	Female	376	50.7
Age	18–35	534	72.1
	36–45	122	16.4
	≥46	85	11.5
Residence	Rural	284	38.3
	Urban	457	61.7
Ethnicity	Amhara	711	96
	Oromia	20	2.7
	Tigray	10	1.3
Religion	Orthodox	610	82.3
	Muslim	94	12.8
	Catholic	10	1.3
	protestant	12	1.6
	Adventist	15	2.0
Educational status	Illiterate	168	22.7
	Primary school (1–8th grade)	138	18.6
	Secondary school (9–12th grade)	160	21.6
	College and above	275	37.1

The mean age of the respondents was 30.1 years with a standard deviation (SD) of ± 12.5 years, with the majority of participants 534 (70.1%) included in the age group of 18–35 years. Most of participants were orthodox followers 610 (82.3%) and Amhara by ethnicity 711 (96.0%). Regarding their educational status, ∼168 (22.7%) of them did not know how to write and read (Table 1).

Familiarity, training, knowledge, and attitude of the community about epilepsy

In this study, 18 (2.4%) of participants had families with epilepsy, and nine (1.2%) of the respondents were living with epilepsy. Approximately 137 (18.5%) of them received epilepsy training, 59.9% of participants had poor knowledge about epilepsy, and 40.1% of participants had a negative attitude toward epilepsy.

Seizure first aid practice of the community

In this study, the first aid practice of the community in managing people with episodes of epileptic seizures has been investigated. Of all participants, 641 (86.5%) take the patients to the holy water, 540 (72.9%) take the patient to prayer, 286 (38.6%) of the community took to the traditional healer, and 650 (87.7%) of the respondents refused to take them to the hospital. Similarly, 273 (36.8%) of participants insert clothing into the patient's mouth, and 318 (42.9%) of them restrain the patient from movement because they believed that this will reduce the seizure intensity. Approximately 460 (62.1%) of participants smoke the match in the belief that it treats epilepsy, 465 (62.8%) of them provide food and water to the patient while having a seizure episode, 185 (25.0%) of the respondents keep the patient away from harmful or sharp objects, and ∼438 (59.1%) of them sprinkle water on the patient's body and believed that it is always the best treatment.

Overall, 71.7% (95%CI: 68.3, 74.9) of the south Gondar community had unsafe practice measures in managing patients with seizure episodes.

Factors associated with seizure first aid practice

Bivariable and multivariable binary logistic regression analysis were conducted to show the relationship between independent variables and first aid practices. In the bivariable analysis, respondents who were rural residents, participants who had poor knowledge about epilepsy and a negative attitude toward epilepsy, respondents who did not take any training related to epilepsy, and participants who were illiterate were significantly associated with unsafe practice measures at $p < 0.05$. In contrast, participants who were young and reached secondary education were associated with safe practices. These variables were taken to multivariable analysis to control for confounding effects. In multivariable analysis, respondents who were illiterate, who had poor knowledge about epilepsy and a negative attitude toward epilepsy, as well as respondents who did not take any training related to epilepsy affected practice measures negatively. Conversely, participants who reached secondary education had safe practices in managing patients with seizure episodes.

When controlling for other variables, the odds of having unsafe practices among participants were 1.99 times higher among those who were illiterate compared to those who were in college and above [adjusted odd ratio (AOR) = 1.99, 95%CI: 1.00, 3.97] whereas individuals who reached secondary education had safe practice (AOR = 0.4, 95%CI: 0.26, 0.63). Similarly, participants who did not take training related to epilepsy had unsafe practices while managing patients on seizure episodes compared to those respondents who took training about epilepsy (AOR = 2.07, 95%CI: 1.35, 3.17). The likelihood of having an unsafe practice in managing seizures was greater among participants who had poor knowledge (AOR = 1.51,

95%CI: 1.06, 2.14) and a negative attitude (AOR = 2.20, 95%CI: 1.50, 3.22) compared to respondents who had good knowledge and a positive attitude toward epilepsy, respectively (Table 2).

Discussion

This study is based on the result of a previous research work, which showed that a greater number of communities in the northwest Ethiopia had poor knowledge and a negative attitude toward epilepsy (39). This study aimed to assess the first aid practice measures taken by the community in managing people with epileptic seizure episodes. This has been investigated in relation to sociodemographic variables and other factors that potentially affect their level of practice.

The magnitude of unsafe practices in the management of epileptic seizures in the south Gondar community was 71.7% (95%CI: 68.3, 74.9). Individuals who were illiterate and participants who did not take training related to epilepsy and had a poor knowledge about (AOR = 1.51, 95%CI: 1.06, 2.14) and a negative attitude toward epilepsy (AOR = 2.20, 95% CI: 1.50, 3.22) showed unsafe practices compared to their counterparts. Conversely, participants who reached secondary education had safe practice measures in the management of epileptic seizures.

In this study, 86.5% of participants took patients to holy water, 72.9% of them took patients to prayer, and 38.6% of the communities took patients to the traditional healer. Surprisingly, 87.7% of respondents refused to be taken to the hospital. This mismanagement is worse than that in the studies conducted in Mekelle, Cameron, India, and Nigeria. In a study conducted in Mekelle, 70.3% of respondents preferred to be taken to the holy water, 64.01% preferred to be taken to the hospital, 44.8% recommended to be taken to traditional healers, and 32.1% preferred to be taken to prayer (40). In a study conducted in Cameron, ∼67.4% was taken to the hospital and 22.0% recommended prayers (41). In a study conducted in India, ∼74.0% of participants calls a doctor in response to an epileptic seizure (42). Another research in Cameron found that 65.7% of them were taken to the doctor and 29.7% of participants were taken to prayer, and only 8.6% were taken to a traditional healer (43). In a study in Nigeria, the majority (87.4%) of participants agreed with hospital management of PWE (31). This difference might be due the differences in cultural background of participants. Moreover, the study in Mekelle was conducted among secondary students, while the current study was conducted on the general population. This calls the need for community education related to epilepsy. Similarly, in the Sudanese study, around 86.2% (44) of participants recommended medical treatment that was practiced safely compared to the current study. Here, the study was conducted in both rural and urban societies, while in the Sudanese study included only the residents of Khartoum. This suggests the need to disseminate information about epilepsy to the community as a whole, especially rural communities. Likewise, the Nigerian study was conducted among medical students. This enabled them to get the information through their course, and revealed

TABLE 2 Factors associated with public first aid practice measures of an epileptic seizure, Northwest Ethiopia, 2021 ($n = 741$).

Characteristics	Category	Practice		COR (95%CI)	AOR (95%CI)	*P* value
		Safe	Unsafe			
Age	18–35	190	344	***0.24 (0.12, 0.48)**	0.48 (0.2, 1.15)	0.100
	36–45	10	112	1.49 (0.59, 3.76)	1.99 (0.72, 5.52)	0.186
	≥46	10	75	1	1	
Residents	Rural	60	224	***1.82 (1.29, 2.58)**	0.78 (0.50, 1.22)	0.269
	Urban	150	307	**1**	1	
Educational status	Illiterate	19	149	***2.68 (1.55, 4.64)**	****1.99 (1.00.3.97)**	0.049
	Primary school	39	99	0.87 (0.55, 1.37)	0.72 (0.44, 1.19)	0.202
	Secondary school	82	78	***0.33 (0.22, 0.49)**	***0.41 (0.26, 0.63)**	0.000
	College and above	70	205	1	**1**	
Training	Yes	60	77	1	1	0.001
	No	150	454	***2.36 (1.61, 3.47)**	****2.07 (1.35, 3.17)**	
Knowledge	Good	109	188	**1**	**1**	0.024
	Poor	101	343	***1.97 (1.42, 2.72)**	****1.51 (1.06, 2.14)**	
Attitude	Positive	145	299	1	1	0.000
	Negative	65	232	***1.73 (1.23, 2.43)**	****2.20 (1.50, 3.22)**	

*Factors were significantly associated with pubic first aid practices of an epileptic seizure in bivariable analysis.
**Factors were significantly associated with pubic first aid practices of an epileptic seizure in multivariable analysis.
COR, crude odd ratio; AOR, adjusted odd ratio.

the necessity for community health education on epilepsy. In this study, ~62.1% of participants smoke match sticks, which is a relatively safe practice compared to the Mekelle (81.9%) (40) study. Moreover, 36.8% of participants dangerously put clothes in patients' mouth, which seems to be better than the studies conducted in Cameron (41.6%) (43) and Nigeria (62.2%) (36) but worse than the studies conducted in Mekelle (22.8%) (40) and Addis Ababa (8.6%) (45). Approximately 318 (42.9%) of them restrain the patient from the movement as they believed that this will reduce the seizure intensity. This practice was relatively safe compared to studies in Nigeria (54.9%) (36) and India (47%) (42). This might be due to a variation in sociocultural background of the study participants. Moreover, 465 (62.8%) of them provide food and water to patients during a seizure episode. This was an unsafe practice compared to the studies in Mekelle (27.2%) (40) and Addis Ababa (41.7%) (45). Approximately 185 (25.0%) of the respondents move the patient away from harmful or sharp objects, which was a relatively unsafe practice compared to the studies conducted in Mekelle (59.0%) (40), Addis Ababa (58.3%) (45), Khartoum State Sudan (88.8%) (44), and India (61.0%) (42).

Overall, 71.7% (95%CI: 68.3, 74.9) of the south Gondar community had unsafe practice measures in managing patients with seizure episodes.This was unsafe practice compared to the studies in Jima Ethiopia (6.0%) (33), Lay Armachiho Ethiopia (55.3%) (34), Goncha Siso Enesie Woreda Ethiopia (63.2%) (35), and Nigeria (68.1%) (36). This discrepancy might be due to differences in study participants and cultural differences. In the Jima study, participants were epileptic, but in the current study all respondents were from the communities. In this case, PWE have a chance to receive continuous psychological education during their routine hospital visits, which helps them access safer practices compared to the general population. Similarly, in the current study, the community had unsafe practice measures compared to other studies conducted in Sululta Woreda Ethiopia (66.5%) (46) and Addis Ababa Ethiopia (59.1%) (45). This might be a difference in the deep-rooted sociocultural beliefs and practices about the causes and treatment of epilepsy. Moreover, in the current study, participants were from both urban and rural societies, whereas the Addis Ababa study included only teachers.

In relation to the factors that affect first aid practice, participants without epilepsy training and/or health education showed unsafe practices compared to those who did. This was in agreement with studies conducted in Nigeria (36), Addis Ababa (45), Lay Armachiho Ethiopia (34), and Sululta Woreda Ethiopia (46). In other words, training and/or health education will enable society to have better knowledge, which in turn helps to safely manage people in seizure episodes. Participants who were illiterate had unsafe practices and those who reached secondary education had safe practices in managing patients with seizure episodes, which were in line with a previous study conducted in Lay Armachiho Ethiopia (34). This might be that people who are illiterate did not have access to the information from different reading materials and did not gain knowledge that actually their level of practice become unsafe. Moreover, participants who had poor knowledge about epilepsy and negative attitudes toward epilepsy showed unsafe practices in the management of epileptic seizures. This finding was in agreement with the study done in Goncha Siso Enesie Woreda Ethiopia (35). It is theoretically agreed that people who had no information, i.e., poor knowledge and a negative attitude, will have unsafe practices compared with their counterparts.

Conclusion

The findings of this study indicated that the majority of people in the south Gondar zone community have unsafe practices in the management of epileptic seizures. Factors such as illiteracy, lack of epilepsy-related training, and poor knowledge of and a negative attitude toward epilepsy were significantly associated with unsafe practices in first aid management of epileptic seizures.

This requires an emphasis on participants without epilepsy-related training and/or health education, those who are illiterate, and those with poor knowledge about and a negative attitude toward epilepsy. Moreover, this result revealed that there is still a gap in community health education that needs the direct engagement of health institutions to promote the awareness of communities about epilepsy and improve their attitude and practice. It is recommended that further qualitative studies, such as interviews with key informants (priests, traditional healers, etc.), are needed to explore the thoughts and motivations of religious and traditional healers on how to practice first aid in the management of epileptic seizures.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical approval was obtained from IRB of Debre Tabor University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Implications of stimulus-induced, rhythmic, periodic, or ictal discharges (SIRPIDs) in hospitalized patients

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Background: Stimulus-induced electroencephalographic (EEG) patterns are commonly seen in acutely ill patients undergoing continuous EEG monitoring. Despite ongoing investigations, the pathophysiology, therapeutic and prognostic significance of stimulus-induced rhythmic, periodic or ictal discharges (SIRPIDs) and how it applies to specific pathologies remain unclear. We aimed to investigate the clinical implications of SIRPIDs in hospitalized patients.

Methods: This is a retrospective single-center study of hospitalized patients from May 2016 to August 2017. We included patients above the age of 18 years who underwent >16 h of EEG monitoring during a single admission. We excluded patients with cardiac arrest and anoxic brain injury. Demographic data were obtained as well as admission GCS, and discharge modified Rankin Score (mRS). EEGs were reviewed for background activity in addition to epileptiform, periodic, and rhythmic patterns. The presence or absence of SIRPIDs was recorded. Our outcome was discharge mRS defined as good outcome, mRS 0–4, and poor outcome mRS, 5–6.

Results: A total of 351 patients were included in the final analysis. The median age was 63 years and 175 (50%) were women. SIRPIDs were identified in 82 patients (23.4%). Patients with SIRPIDs had a median initial GCS of 12 (IQR, 6–15) and a length of stay of 12 days (IQR, 6–15). They were more likely to have absent posterior dominant rhythm, decreased reactivity, and more likely to have spontaneous periodic and rhythmic patterns and higher frequency of burst suppression. After adjusting for baseline clinical variables, underlying disease type and severity, and EEG background features, the presence of SIRPIDs was also associated with poor outcomes classified as MRS 5 or 6 (OR 4.75 [2.74–8.24] $p \leq 0.0001$).

Conclusion: In our cohort of hospitalized patients excluding anoxic brain injury, SIRPIDs were identified in 23.4% and were seen most commonly in patients with primary systemic illness. We found SIRPIDs were independently associated with poor neurologic outcomes. Several studies are indicated to validate these findings and determine the risks vs. benefits of anti-seizure treatment.

KEYWORDS

seizures, SIRPIDs, critically ill, electroencephalography, stimulus induced, GPDs, LPDs

1. Introduction

Stimulus-induced electroencephalographic (EEG) patterns are commonly seen in acutely ill patients undergoing continuous EEG monitoring (1–3). The American Clinical Neurophysiology Society (ACNS) has defined these patterns as stimulus-induced rhythmic delta activity, periodic discharges, spike, and wave discharges, ictal-interictal continuum patterns, brief ictal rhythmic discharges, and seizures (4). Collectively these patterns are referred to as stimulus-induced rhythmic, periodic, or ictal-appearing discharges (SIRPIDs) (4). SIRPIDs have been reported with an incidence of 10–34% (1–3, 5, 6), and can be seen in patients with acute brain injuries (e.g., trauma, stroke, and infections), anoxic brain injury, epilepsy, neurodegenerative diseases and toxic-metabolic disturbances (6, 7). Despite ongoing research, the pathophysiology, therapeutic and prognostic significance of SIRPIDs continues to be uncertain and it is unclear how it applies to specific pathologies. In a large cohort, SIRPIDs were not associated with an increased risk of seizures (8). However, small cohorts examining the association of SIRPIDs with mortality and functional outcomes have shown conflicting results and have included patients with anoxic brain injury/post-cardiac arrest pathology (1–3, 5, 6). Given anoxic brain injury/post-cardiac arrest patients represent a unique pathophysiology and entity, often with a worse prognosis, we aimed to focus our study on patients excluding anoxic brain injury as an etiology for decreased consciousness. The goal of this study was to describe the relationship of SIRPIDs with neurologic outcomes in a cohort of acutely ill patients undergoing EEG monitoring.

2. Methods

This is a retrospective cohort study of patients admitted to a single center between May 2016 and April 2017. The study was approved by the Institutional Review Board. Informed consent was not required. The results are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies (9). The data that support the findings of this study are available from the senior author upon reasonable request. We included patients who were above the age of 18 years and who underwent $\geq$16 h of EEG monitoring where the duration of consecutive artifacts is <30% of the total length. We excluded patients with cardiac arrest.

2.1. Patient demographics

Data were extracted including age, gender, primary admitting diagnosis, GCS score on admission, history of epilepsy, hospital length of stay, in-hospital mortality, use of anti-seizure medications (ASMs) during hospital stay, and use of anesthetic drugs, discharge location.

2.2. EEG

The EEG recordings were obtained using the international 10-20 system. Per institutional protocol, all EEGs were reviewed and reported by two clinical neurophysiologists. All EEG findings were reported using the American Clinical Neurophysiology Society nomenclature (ACNS) (10). The relevant EEG data were subsequently abstracted from the clinical EEG reports. Reports were reviewed for the best background activity (alpha, beta, theta, delta, or burst suppression) and unilateral vs. focal slowing, presence of sleep architecture, sharp waves, generalized periodic discharges (GPD), lateralized periodic discharges (LPDs), generalized rhythmic delta activity (GRDA), lateralized rhythmic delta activity (LRDA), bilateral independent periodic discharges (BIPD), brief ictal rhythmic discharges (BIRDS), seizures (electrographic and clinical), and SIRPIDs. If SIRPIDs were present, further data were collected to ascertain which pattern type i.e., stimulus-induced (SI) patterns, SI-GPD, SI-LPD, SI-GRDA, SI-LRDA, SI-BIPD, and SI-seizures.

2.3. Outcomes

We examined discharge neurologic status as measured by the modified Rankin Scale (mRS); 0—no symptoms, 1—no significant disability, 2—slight disability, 3—moderate disability, 4—moderately severe disability, 5—severe disability, and 6—death (11). We defined poor neurologic outcome as mRS of 5 to 6. mRS was abstracted from a physician and physical and occupational therapy clinical examinations by reviewers who were blinded to the EEG findings as previously described (12).

2.4. Statistical analysis

For descriptive statistics, we calculated mean, median, and interquartile ranges. Fisher's exact test was used for the comparison of dichotomized and categorical variables, and the Mann-Whitney U-test was used for continuous variables. Significance was set at 0.05, and two-sided *p*-values were reported. We performed a multivariate logistic regression analysis to assess the relationship between SIRPIDs and discharge outcomes. We adjusted for baseline variables including age, sex, and underlying diagnosis. We adjusted for the Glasgow Coma Scale (GCS) as a marker for disease severity. We also adjusted for the presence of spontaneous epileptiform abnormalities (LPDs, GPDs, LRDA, sporadic discharges that were not stimulus-induced), the presence of burst suppression (more than 50% of the record consisting of attenuation or suppression with alternating bursts) (4), and poor EEG background (absent PDR, or absent sleep architecture or absent reactivity) (4). Odds ratios and 95% confidence intervals (OR [95% CI]) were calculated to quantify the association of SIRPIDs with outcomes. The goodness-of-fit for logistic regression models was assessed using the Hosmer–Lemeshow test.

3. Results

A total of 351 patients were included in the final analysis. Baseline characteristics are presented in Table 1. The median age of the cohort was 63 (IQR, 52–74 years,), and 175 (49.8%) were women, of which 82 (23.4%) patients had SIRPIDs. Patients with SIRPIDs were older (median age 70 years (Q1–Q3, 60–79) vs. 63 years (Q1–Q3, 52–74) in patients without SIRPIDs). Patients admitted with a primary systemic illness, and those with a history of epilepsy were more likely to have SIRPIDs. Patients with SIRPIDs were more likely to have

absent PDR and decreased reactivity on EEG. Patients with SIRPIDs were also more likely to have spontaneous periodic and rhythmic patterns, and a higher frequency of burst suppression compared to patients without SIRPIDs. There was no significant difference in the frequency of clinical seizures between patients with SIRPIDs vs. without. Interestingly, patients with SIRPIDs were more likely to have electrographic status epilepticus. The distribution of stimulus-induced pattern types is shown in Figure 1. GPDs were the most common stimulus-induced pattern.

3.1. Outcomes

The distribution of discharge mRS scores across the cohort is shown in Figure 2. On univariate analysis presence of SIRPIDs was in poor neurologic outcome (OR 4.76 [2.74–8.24] $p \leq 0.0001$). After adjusting for baseline variables, and other EEG features (presence of epileptiform abnormalities, burst suppression, and poor background), SIRPIDs continued to be significantly associated with poor outcomes defined as mRS of 5–6 (OR 2.41 [1.27–4.60], $p = 0.007$).

3.2. Sensitivity/Subgroup analyses

Sensitivity analysis was performed in patients with epileptiform abnormalities such as seizures, periodic discharges, or rhythmic delta activity. In the subgroup of patients with epileptiform abnormalities, SIRPIDs continued to be associated with poor outcomes, even after adjusting for baseline variables (OR 2.94 [160–5.42] $p = 0.0005$). We performed an additional sensitivity analysis including anti-seizure medications (ASMs) in the regression model. After adjusting for ASM use, SIRPIDs continued to be significantly associated with poor outcomes (OR 2.45 [CI 1.29–4.63], $p = 0.0006$).

4. Discussion

In our cohort of hospitalized patients, SIRPIDs were seen in 24% of patients and occurred more commonly in patients with primary systemic illness. We found that SIRPIDs were independently associated with poor discharge outcomes (8). In light of our findings, larger studies are indicated to confirm our findings and determine the optimal treatment strategies including anti-seizure medication treatment vs. minimizing frequent stimuli that result in SIRPIDs.

The prevalence of SIRPIDs (23.4%) in our study is comparable to prior literature (1–3, 5, 13). Previously published studies have conflicting findings on the association of SIRPIDs with outcomes. A study of post-cardiac arrest patients found SIRPIDs were associated with poor prognosis if they were seen in conjunction with intermittent or unreactive EEG background activity (14). In another study of post-cardiac arrest patients' absence of reactivity to external stimuli or absence of a posterior dominant rhythm were associated with death or persistent coma at discharge, while SIRPIDs were not significantly associated with outcomes (5). In a larger series of 416 patients, age, anoxic brain injury, and lack of EEG reactivity were independently associated with in-hospital mortality, while SIRPIDs were not (3). A potential explanation for our different findings from prior work is that we excluded patients with cardiac arrest, while all prior studies have either specifically focused on post-cardiac arrest patients or included anoxic brain injury, a disease subgroup with a distinct prognostic profile.

The median GCS of patients with SIRPIDs was 12 (6–10, 12–15) demonstrating SIRPIDs can be seen across a spectrum of disease severities, and not limited to severe brain injury as previously thought (1, 5). SIRPIDs were seen most commonly in patients with primary systemic illnesses, 24/82 (29%), and may be secondary to the underlying metabolic process. We also found that the most common stimulus-induced pattern was generalized periodic discharges (SI-GPDs) which were seen in 43 (52%) of patients with stimulus-induced patterns. Given the majority of our patients with SIRPIDs were those with primary systemic illnesses, it is not unexpected that the most common SI pattern observed in our study was SI-GPDs. GPDs are commonly associated with metabolic derangements (15) and a majority of patients with GPDs have a toxic-metabolic illness or sepsis and may have a coexisting brain injury (16–19). Therefore, another treatment consideration is correcting metabolic derangements, in addition to or as an alternative to anti-seizure treatments.

We found SIRPIDs were more likely to be present if the EEG also showed spontaneous periodic and rhythmic patterns. Periodic and rhythmic patterns have been shown to be associated with increased metabolic stress and secondary brain injury that may worsen outcomes (20–22). The exact mechanism underlying stimulus-induced ictal patterns is not entirely understood, and studies have suggested a component of hyperactivity within the thalamocortical system (23) and an additional hypothesis that relates to the dorsal midbrain anticonvulsant zone (DMAZ) which seems to play a role in brainstem networks related to seizures (24). Further work is needed to understand the underlying mechanisms of SIRPIDs, and to determine whether they exert metabolic stress similar to spontaneous ictal patterns.

Interestingly, we found our patients with SIRPIDs were more likely to have electrographic status. Similar to the association with outcomes there are variable reports on the association of SIRPIDs with seizures, with some studies showing no association between SIRPIDs and seizures (1, 25), while others have found SIRPIDs associated with focal motor and non-convulsive seizures (2, 3, 15, 24). However, these studies had a smaller number of patients with SIRPIDS and did not account for anti-seizure treatment and whether increasing ASMs in response to SIRPIDs may reduce the subsequent risk of electrographic seizures.

There were several limitations of this study including its retrospective nature and being a single-center study. with a small sample size. We did not account for ASM use in our analysis, as it is difficult to disentangle the indication for ASM (clinic seizures vs. spontaneous EEG findings vs. SIRPIDS). While we adjusted for multiple confounders, there may be residual unmeasured confounding.

5. Conclusion

In summary, in a cohort of acutely ill patients, the presence of SIRPIDs was significantly associated with poor outcomes defined. The decision to treat continues to be challenging and further prospective studies will be needed to determine if antiseizure medications or minimizing stimuli is the best treatment approach.

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TABLE 1 Baseline characteristics and outcomes.

	All patients ($N = 351$)	Patients with SIRPIDS ($N = 82$)	Patients without SIRPIDS ($N = 269$)	p-value
Age (median, Q1–Q3)	63 (52–74)	70 (60–79)	62 (49–72)	<0.0001
Gender, Female (%)	175 (49.8%)	49 (60%)	126 (47%)	0.044
History of stroke	84 (24.7%)	23 (28%)	64 (24%)	0.466
History of hypertension	175 (49.8%)	49 (60%)	126 (47%)	0.044
History of epilepsy	85 (24.4%)	11 (13%)	74 (28%)	0.0082
History of brain surgery	41 (11.7%)	5 (6%)	36 (13%)	0.079
History of CNS malignancy	38 (10.8%)	5 (6%)	33 (12%)	0.1544
History of dementia	19 (5.4%)	4 (5%)	15 (9%)	1
Initial GCS (median, Q1–Q3)	14 (8–15)	12 (6–15)	14 (9–15)	0.0329
Clinical seizures	38 (11%)	9 (11%)	29 (11%)	1
Use of ASMs	307 (87%)	74 (90%)	233 (87%)	0.4506
DC on ASMs	221 (63%)	41 (50%)	179 (67%)	0.0089
Length of stay (median, Q1–Q3)	14 (8–25.5)	12 (6–15)	12 (7–20)	<0.0001
Primary diagnosis				
CVA	71 (20.2%)	22 (27%)	49 (18%)	0.115
TBI	42 (11.9%	9 (11%)	33 (12%)	0.8476
NeuroID/Inflam	22 (6.2%)	7 (9%)	15 (6%)	0.301
NeuroOnc	39 (11.1%)	3 (4%)	36 (13%)	0.0147
Other Neuro	42 (11.9%)	9 (11%)	33(8%)	0.848
Primary Systemic	68 (19.3%)	24 (29%)	44 (16%)	0.0159
Seizure/Status	67 (19%)	8 (10%)	59 (22%)	0.0154
DC mRS				<0.0001
0	14 (4%)	1 (1%)	13 (5%)	
1	11 (3%)	0	11 (4%)	
2	12 (3%)	1 (1%)	11 (4%)	
3	39 (11%)	4 (5%)	35 (13%)	
4	112 (32%)	15 (18%)	97 (36%)	
5	102 (29%)	36 (44%)	66 (25%)	
6	61 (17%)	25 (30%)	36 (13%)	
EEG characteristics				
Burst suppression on EEG	45 (13%)	24 (29%)	21 (8%)	<0.0001
PDR on EEG	126 (36%)	12 (15%)	114 (42%)	<0.0001
Sleep architecture	113 (32%)	15 (18%)	98 (36%)	0.0019
EEG reactivity	170 (48%)	31 (38%)	139 (52%)	0.032
EEG sporadic sharps	237 (67%)	69 (84%)	168 (62%)	0.0002
GPDs	100 (28%)	52 (63%)	48 (18%)	<0.0001
LPDs	135 (38%)	40 (49%)	95 (35%)	0.0376
GRDA	106 (30%)	33 (40%)	73 (27%)	0.028
LRDA	65 (19%)	23 (28%)	42 (16%)	0.0147
BiPDs	50 (14%)	20 (24%)	30 (11%)	0.006
EEG status	25 (7%)	11 (13%)	14 (5%)	0.0239
Electrographic seizures	66 (19%)	23 (28%)	43 (62%)	0.0229
Electrographic status	25 (7%)	11 (13%)	14 (5%)	0.0239

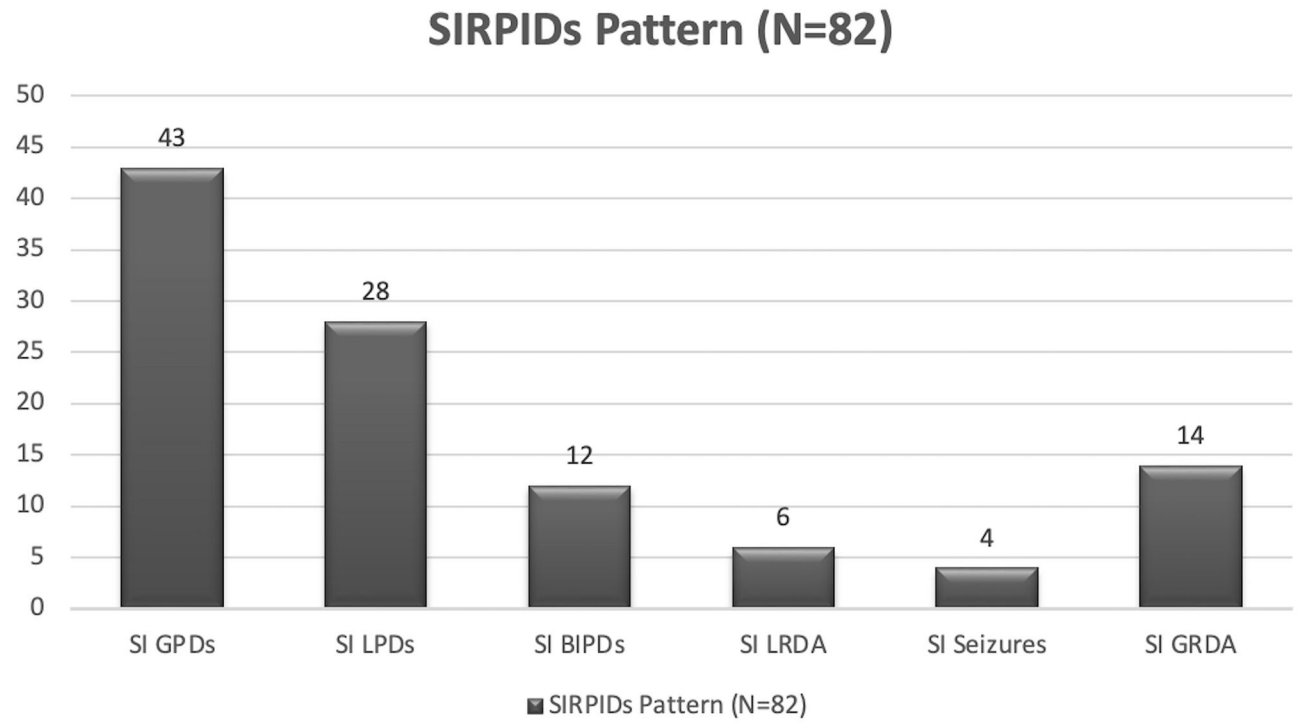

FIGURE 1
SIRPIDs EEG patterns.

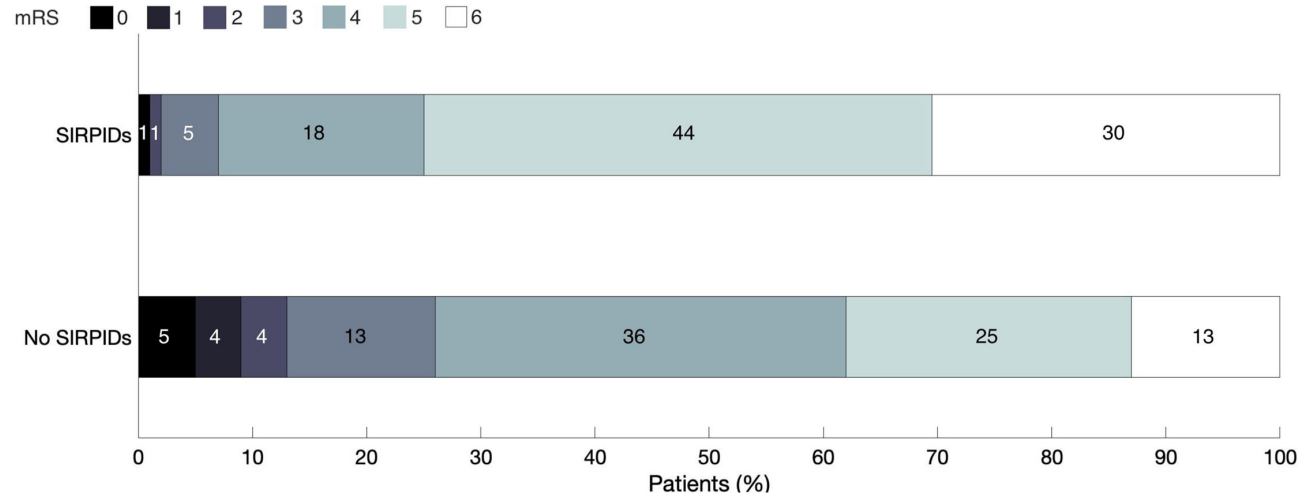

FIGURE 2
Distribution of discharge modified Rankin Scale scores across the cohort.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

The first draft of the manuscript was written by PM and IS and all authors commented on, edited, and revised previous and final versions of the manuscript. All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by all authors. All authors read and approved the final manuscript.

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Conflict of interest

SZ is a clinical neurophysiologist for Corticare, unrelated to this work. MW is cofounder of Beacon Biosignals unrelated to this work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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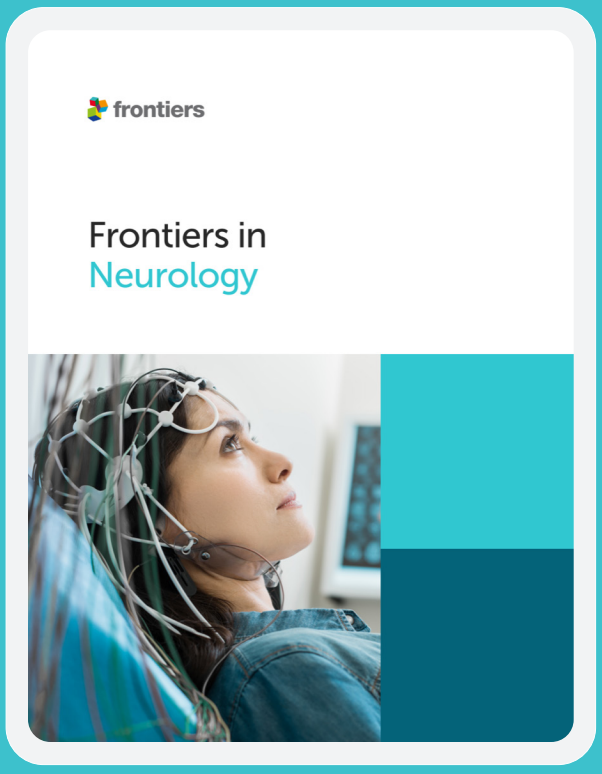

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