Continuous EEG monitoring in the follow-up of convulsive status epilepticus patients: A proposal and preliminary validation of an EEG-based seizure build-up score (EaSiBUSSEs)

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Personal View

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Short running title: EEG-based seizure build-up score in status epilepticus

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Abstract

Continuous electroencephalography (EEG) is a major tool for monitoring patients admitted to the intensive care unit after refractory convulsive status epilepticus, following control of convulsive movements. We review the values of different EEG patterns observed in critically ill patients for prognosis and seizure risk, together with proposed criteria for non-convulsive status epilepticus diagnosis (Salzburg Criteria), the EEG scores for prognosis (Epidemiology-based Mortality score in Status Epilepticus, EMSE) and for seizure risk (2HELPS2B). These criteria and scores, based partially on continuous EEG, are not tailored to repetitively monitor the progressive build-up leading to seizure or status epilepticus recurrence. Therefore, we propose a new EEG-based seizure build-up score in status epilepticus (EaSiBUSSEs), based on the morphology and the prevalence of the EEG patterns observed in the follow-up of convulsive status epilepticus patients. It displays subscores from the least (no interictal activity) to the most associated with seizures (focal or generalized status epilepticus). We then evaluated the performance of the EaSiBUSSEs in a cohort of eleven patients who were admitted to intensive care unit for convulsive status epilepticus and who underwent continuous EEG recording. The receiver operating curve revealed good accuracy in identifying patients who would have seizures in the next 24 hours, with excellent intra- and inter-rater reliability. We believe that this score is simple to perform, and suitable for repeated monitoring of EEG following refractory convulsive status epilepticus, with quantitative description of major EEG changes leading to seizures.

Keywords: continuous EEG monitoring, diagnosis, prognosis, score, seizure risk, status epilepticus

Introduction

Continuous electroencephalography (cEEG) has been increasingly used for brain monitoring in the critical care setting for (i) detection of non-convulsive seizures (NCS) or non-convulsive status epilepticus (NCSE), in particular for patients with unexplained consciousness disorders or delirium; (ii) titration of continuous intravenous (IV) antiepileptic drug therapy in patients with refractory status epilepticus (SE); (iii) outcome assessment of patients with severe brain injury or neurological deterioration; and (iv) early detection of delayed cerebral ischemia during vasospasm after subarachnoid hemorrhage [24].

Recent meta-analysis indicates a high prevalence of NCS and NCSE detected by cEEG (17.9% and 9.1% respectively), compared to those detected by routine electroencephalography (EEG) (3.1% and 6.2% respectively) in critically ill adults with mixed causes of admission [29].

Nowadays, most professional societies recommend cEEG for the management of refractory SE [4,9,15]. To avoid bias in EEG interpretation and to facilitate communication, the American Clinical Neurophysiology Society proposed the Standardized Critical Care EEG Terminology (SCCET) [16]. All EEG patterns observed in intensive care units (ICU) are thus classified by their localization (generalized, lateralized, bilateral independent and multifocal patterns) and morphology (periodic discharges [PDs, also known as periodic epileptiform discharges], rhythmic delta activity [RDA] and spike-and-wave or sharp-and-wave [SWs]). Sub-classifications are defined by modifiers, such as the prevalence, the frequency, or the presence of additional *plus* features (in which case the pattern appears more ictal than the usual term without the *plus*).

Here, we reviewed the available literature on EEG-based criteria, or scores used for patients with SE (Figure 1), to diagnose non-convulsive SE or to evaluate prognostic value and seizure risk. We then proposed and evaluated a new score to quantify the pro-epileptiform potential of

EEG patterns in the context of daily repeated monitoring of pathological activities related to SE during the ICU stay.

EEG findings associated with SE diagnosis

The definition of SE proposed by the International League Against Epilepsy (ILAE) distinguishes two time points: t1, when a seizure is likely to be prolonged leading to continuous seizure activity—5 min for generalized tonic-clonic SE, 10 min for other SE—; t2, when a seizure may cause long-term consequences—30 min for generalized tonic-clonic SE and 60 min for focal SE with impairment of consciousness [46].

This diagnostic classification of SE distinguished four axes: semiology, etiology, EEG correlates and age. None of the ictal EEG patterns is specific for any particular form of SE. Therefore, there are no consensus EEG criteria for the diagnosis of each SE type [46,47]. The diagnosis of convulsive SE, when clinically typical, does not require EEG recording. In contrast, a correct diagnosis of NCSE is not possible without EEG recording. The "Salzburg EEG criteria for NCSE" have been proposed as a practical guide for NCSE diagnosis [2,25,27]. Their diagnostic accuracy was evaluated in a recent retrospective study from EEG recording of patients admitted for neurological symptoms, with a sensitivity of 97.7% and a specificity of 89.6% [27].

Together, these arguments strengthen the idea that cEEG combined with continuous video recording could have a high potential for identifying seizures or the occurrence (or recurrence) of SE, in patients admitted to the ICU for refractory SE or any other neurological reason [29,49].

EEG findings associated with prognosis

We found no formal consensus regarding which EEG patterns are associated with ongoing neuronal injury, which situations need to be treated and how to prevent poor prognosis [19].

Nevertheless, several studies have evaluated the relationship between various EEG patterns and mortality or outcome, in large populations [1,11,17,28,31–33,35,40,42,45,48] as well as in etiology-selected patient groups [3,5,8,10,36,38].

Prognostic value of EEG patterns

Periodic discharges have been demonstrated to be associated with poorer outcome, but on different levels, depending on their lateralization [5,28,42], their etiology [17] and other clinical characteristics (age, comorbidities, history of SE, drug toxicities) [28]. Lateralized periodic discharges [LPDs] are the most widely studied EEG pattern. These discharges are often observed in structural brain lesions such as stroke, central nervous system (CNS) infections and tumors [19]. Patients with LPDs have mortality rates ranging from 5% to 50% [5,17,28,33,40,42,48], and poor outcomes ranging from 30% to 64% [5,17,28,33,40,48]. Both generalized PDs [GPDs] and bilateral independent PDs [BiPDs] are commonly associated with post-anoxic coma and other (sub)acute injuries [19]. Patients with GPDs have very high rates of mortality, ranging from 27% to 85% [3,5,11,28,33,38] and half of them [33], or even 64% of those with CNS infections [5], become functionally dependent. Patients with BiPDs have mortality rates ranging from 25% to 75% [5,28,33,38,42], and poor outcomes ranging from 39% to 75% [5,28,33]. These disparities in mortality rates could firstly be explained by underlying etiologies. For example, the lowest mortality score was reported in patients without acute or progressive brain injury [40], while the highest score corresponded to patients with post-anoxic refractory SE [3]. Other factors may strongly influence mortality: age over 65 years (Odds ratio, OR 2.55), systemic infection (OR 2.23), anoxic encephalopathy (OR 2.28) and occurrence of SE (OR 2.59) [28].

Focal and generalized non-rhythmic slowing show less association with poor outcomes. Patients with focal and generalized non-rhythmic slowing have lower mortality rates, ranging

from 7% to 30% [17,22,31]. In contrast, non-medically induced burst-suppression appears to be the worst EEG pattern, associated with mortality rates ranging from 59% to 98% according to etiology [3,17].

Sporadic epileptiform discharges were recorded in 28 out of 180 patients during a 24-hour period after clinical SE [17]. Of them, 18% died and 29% presented a poor outcome at time of discharge. This EEG pattern was not predictive of outcome, in contrast to other patterns (burst-suppression or PDs).

An EEG background attenuation was recorded in 47 out of 180 patients after convulsive status epilepticus. Of them, 15 (32%) died and 21 (45%) presented a poor outcome at hospital discharge [17]. In critically children, 64% of those with EEG background attenuation died [45].

Convulsive seizures and NCS are frequently reported in critical care patients. The prevalence of seizures in patients undergoing cEEG in ICU is 13% to 59% [5,7,8,11,18,23,28,33,41,49]. The presence of clinical or electrographic seizures is associated with poorer outcomes. Indeed, among 180 patients admitted for treatment of convulsive SE, 96 presented 'After Status epilepticus Ictal Discharges' (ASIDs) on EEG monitoring with a high rate of mortality (41%) and poor outcome (53%) [17]. A high rate of mortality (47%) was also found in patients with post-anoxic refractory SE [3]. Nevertheless, beyond the occurrence of seizures, the *seizure burden* (i.e. the maximum percentage of any hour that is occupied by an electrographic seizure [35], or the duration, in hours, of seizures on cEEG [10]) and the ictal fraction (i.e. the total seizure duration out of the cEEG recording duration [36]) may have significant prognostic value. A study conducted on 38 newborns showed that the mean seizure duration and the duration of the longest seizure were not related to the outcome, contrary to the ictal fraction when it exceeded 17% (10 minutes per hour) [36]. Another study conducted on 259 children admitted to ICU, identified a *seizure burden* threshold of 20% per hour (12 minutes) above which, the probability and the magnitude of neurological decline rose sharply whatever the

diagnosis [35]. In adults with spontaneous subarachnoid hemorrhage (n=402), the *seizure burden* was associated with unfavorable functional and cognitive outcome and every hour of seizure was associated with an OR of 1.10 to 3-month disability and mortality [10].

Quantitative assessment of prognostic value according to EEG patterns: epidemiology-based mortality score

An epidemiology-based mortality score in SE (EMSE) was recently proposed to better evaluate outcome. Using a combination of four items (etiology, age, comorbidity and EEG), this score could explain mortality in 90% of cases, and predicted both poor and good outcome better than the previous SE severity score [26]. The EEG item was classified into three subgroups with corresponding mortality risk points: (i) normal EEG, non-specific EEG abnormalities (focal or generalized slowing) or interictal epileptiform discharges [0 point]; (ii) LPDs, GPDs or ASIDs [40 points] and (iii) non-medically induced burst suppression [60 points] [26]. Later studies have confirmed effectiveness of the EMSE in assessing SE prognosis [13,20,34].

Taken together, these findings indicate that non-medically induced burst-suppression is the worst EEG pattern, followed by PDs then by sporadic epileptiform discharges and focal and generalized non-rhythmic slowing. Ictal events occurring after a SE, in particular those with a high *seizure burden* are associated with a poor outcome. EMSE is an efficient prognostic score.

EEG findings associated with seizure risk

In order to study the risk of seizures based on EEG findings, it is crucial to correctly recognize interictal EEG patterns and to differentiate them from ictal ones. In practice, electroencephalographers often meet three situations: (i) EEG patterns are unequivocally ictal (typical EEG features with temporally and spatially organized epileptiform activities; or clinical and EEG manifestations promptly improving after intravenous antiepileptic drug) [2], (ii) EEG

patterns are clearly non-ictal, and (iii) ambiguous, unclear EEG features, which are difficult to classify into ictal or non-ictal patterns, in particular those with sequences of periodic discharges or rhythmic activities. With the use of long-term cEEG in ICU, new EEG patterns of unclear or unknown significance have increasingly been reported. Consequently, they are still not included in treatment strategies [51]. Some EEG patterns are described in the SCCET: lateralized RDA [LRDA], generalized RDA [GRDA] and stimulus-induced rhythmic, periodic, or ictal discharges [SIRPIDs], while other ones (brief (potentially ictal) rhythmic discharges [B(I)RDs] and ictal-interictal continuum [IIC] are not covered by the terminology [16]. The IIC was described as fluctuating, rhythmic and/or periodic activity, without clear onset or offset [51]. We now examine the risk of seizures associated with the different patterns.

Seizure risk from EEG patterns

Among the periodic patterns, LPDs are most consistently associated with seizures, with an incidence of clinical or electrographic seizures ranging from 44% to 92% [7,8,12,18,28,33,37,39,40,42,44,48] according to etiology, seizure type or level of consciousness. Seizures occur in 16% to 58% of patients with GPDs, and are therefore less common in patients with GPDs compared to those with LPDs [7,11,28,33,39,44]. The association between these both patterns and seizures increases with pattern prevalence, higher frequencies (above 2 Hz), and presence of *plus* features [39].

Focal or generalized slowing are not associated with increased risk of seizures [12,44]. Among 558 critically ill patients, those with focal non-rhythmic EEG slowing (n=136) had less seizures (20%) than those with LPDs (n=49 and 57%) [12]. In another series of 112 patients with generalized slowing as the initial EEG pattern, none of them showed seizures [44].

Sporadic epileptiform discharges were reported to be associated with seizures in less than 31% of the cases [22,41,44].

Lateralized rhythmic delta activity (LRDA), mostly reported in intracerebral and subarachnoid hemorrhages, carries a similar risk of seizures as LPDs (63% *versus* 57%) in a study conducted on 558 critically ill patients [12]. As for LPDs and GPDs, LRDA are associated with a higher risk of seizures when the patterns show higher frequencies (above 2 Hz) and *plus* features. On the contrary, GRDA were not associated with seizures, even if showing *plus* features, higher frequencies or prevalence [39].

Stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs) correspond to rhythmic, periodic or ictal-appearing activities that are elicited by patient stimulation [19]. There is an ongoing debate about whether SIRPIDs should be classed as ictal or interictal activities. In order to determine whether SIRPIDs represent an ictal phenomenon or not, a SPECT study in a patient presenting SIRPIDs did not show any increase of brain perfusion; SIRPIDs in this patient might therefore not be an ictal pattern [52]. Conversely, disappearance of SIRPIDs was observed in another patient after receiving benzodiazepines, suggesting that SIRPIDs might behave like seizures [21]. A recent study in a large cohort of patients examined whether the seizure risk changed when the periodic or the rhythmic activities were induced by stimulation. Their preliminary findings indicated no significant difference in the incidence of seizures and showed 20% of patients with LRDA elicited by stimulation versus 28% of patients with spontaneous LRDA; similarly, the risk of seizure was 17% for patients with GPD, elicited or not by stimulation. Therefore rhythmic and periodic patterns observed after stimulation seem not to represent an additional risk for seizures [39].

Brief (ictal or interictal) rhythmic discharges (B(I)RDs) are defined as rhythmic discharges lasting less than 10 s. Up to 75% of patients with B(I)RDs are reported to have seizures [50].

Quantitative assessment of seizure risk according to EEG patterns: 2HELPS2B score

The largest series of patients on cEEG monitoring has contributed to major descriptions of different EEG patterns [39]. A quantitative evaluation tool of seizure risk according to EEG patterns was then proposed: the 2HELPS2B score [43]. This score is the sum of points according to one clinical and five EEG variables: prior seizure [1 point], brief (ictal) rhythmic discharges (B[i]RDs) [2 points], presence of LPDs, LRDA, BiPDs [1 point], sporadic epileptiform discharges [1 point], frequency greater than 2 Hz of periodic or rhythmic pattern [1 point] and presence of *plus* features [1 point]. The estimated seizure risk was 5% with a score of 0, 12% with a score of 1, 27% with a score of 2, 50% with a score of 3, 73% with a score of 4, 88% for a score of 5, and greater than 95% with a score of 6 or 7 [43]. The same team recently tested this score in a subpopulation of patients with acute brain injury and found that the 2HELPS2B score was not superior to EEG, but was superior to clinical factors in evaluating seizure risk [30]. However, it could be queried whether LPDs or LRDA really predict the same seizure risk as sporadic epileptiform discharges do, given that they all count for 1 point.

These findings together indicate that PDs highly increase the risk of seizures, followed by sporadic epileptiform discharges, while focal and generalized slowing do not. Among new EEG patterns of uncertain significance, B(I)RDs and LRDA increase the risk of seizures while SIRPIDs and GRDA do not. The prevalence of events, the EEG pattern frequency, and the *plus* features contribute to seizure risk. The 2HELPS2B is an effective score to evaluate seizure risk even if some questions remain unanswered.

EEG findings associated with seizure build-up after SE

There is a need for a specific score in order to monitor EEG activity after refractory SE, which should respond to multiple purposes: (i) to quantitatively describe major EEG changes leading to seizure(s), (ii) to monitor therapeutic trials evaluating the drugs to block seizure recurrence

or to allow a neuroprotective effect, and (iii) to further examine the relationship between the "seizure build-up" and the kinetics of various biomarkers assessing brain injuries [14].

In patients with refractory convulsive SE receiving anesthetics, the question of seizures or SE recurrence is of major importance. Continuous electroencephalography is crucial to monitor ictal events, notably while doses of anesthetics are being reduced. Non-convulsive seizures and NCSE occur frequently after post-convulsive SE (33.5% and 20.2% respectively) [29], with a large variability in localization and morphology of ictal and inter-ictal patterns [6]. In super-refractory SE, the dynamics of seizure or SE recurrence can be even more complex. Seizures may not reoccur suddenly but be preceded by a continuum between non-ictal and ictal events, which fluctuate both spatially and temporally (personal observations).

The current scores for cEEG described above are not tailored to repeatedly monitor the progressive build-up leading to seizure or SE recurrence. The ESME EEG subscore does not distinguish epileptiform from non-epileptiform events [26]. The 2HELPS2B score includes additional items based on EEG patterns and their features. This score is however not easily applied for repeated assessments because of fixed items such as 'previous seizure' [43]. Secondly, this score attributes the same value to different patterns: the sporadic epileptiform discharges and the LPDs or LRDA all count for 1 point, despite the fact that they have been associated with unequal seizure risk in previous studies [8,12,22,28,37,39–41,43,44]. Thirdly, it does not take into account the prevalence of the EEG pattern, despite a higher risk of seizures having been reported when the patterns have higher prevalence [39]. Finally, it does not assess the different impact of an isolated 'previous seizure' when compared with a higher seizure burden.

We therefore propose an EEG-based seizure build-up score in status epilepticus (EaSiBUSSEs) to quantify the pro-epileptiform potential of several EEG patterns observed after convulsive SE in patients undergoing cEEG monitoring in ICU. We defined seven EEG subscores based on

morphology and prevalence of EEG patterns, rising from the least associated with seizure (no interictal activity) to the most associated and severe one (focal or generalized SE). We provide a detailed description of each score (Figure 2) and corresponding EEG examples (Figures 3 and 4).

This seizure build-up score was designed from robust findings of previous studies which have evaluated the association of EEG patterns with seizure risk in critically ill patients. The risk of NCS or NCSE is higher in patients undergoing cEEG monitoring after refractory convulsive SE cessation than in those after traumatic brain injury or intracerebral hemorrhage [7]. There is no literature to the best of our knowledge suggesting that the seizure risk related to periodic or rhythmic activities could change according to the primary etiological diagnosis and the referral indication of cEEG monitoring. On the other hand, a study conducted on a large cohort of patients showed an association between EEG patterns and seizure risk by using multivariate logistic regression models, whatever the primary etiological diagnosis including status epilepticus [39]. We therefore assume to apply their findings in our population with status epilepticus to build the EaSiBUSSEs.

Normal EEG or EEG with focal or generalized slowing is associated with a seizure risk ranging from 0% to 20% [score 1] [12,39,44]; sporadic epileptiform discharges from 0% to 31% [scores of 2 or 3, depending on their low or high prevalence] [22,41,44]; PDs from 16% to 92% [8,11,28,33,39,40,44,48], while LRDA shares similar seizure risk with LPDs [12] [scores of 4 or 5, depending on their low or high prevalence].

We did not take into account the side of lateralization of PDs because all PDs were associated with seizures in overlapping ranges (LPDs: 44% to 92%; GPDs: 16% to 58%, and BiPDs: 10% to 58%) [39].

We allocated the same subscore 6 for both continuous PDs or LRDA without spatial or temporal organization, with occasional brief rhythmic discharges (BRDs) (6a), and for infrequent

seizures (seizure burden <20%) (6b). We allocated the same subscore 7 for both continuous PDs or LRDA without spatial or temporal organization, with frequent BRDs (7a), and for frequent seizures (seizure burden ≧20%) (7b). We attributed the same subscore for these patterns because we consider that they need the same clinical monitoring and might be treated equally. We distinguished subscores 6 and 7 according to the seizure burden, with a threshold of 20%, which was validated in children admitted to ICU and provided a prognostic value [35,36].

GRDA and the rhythmic or periodic patterns induced by stimulation were not included in this score, because they were not associated with increased seizure risk [39].

Evaluation of the EaSiBUSSEs for clinical use

In order to enhance the understandability and facilitate the use of the EaSiBUSSEs, we provided a decision-making flowchart to the electroencephalographers (Supplementary Fig.1). We then evaluated the EaSiBUSSEs in 11 patients admitted in ICU for refractory convulsive SE and underwent at least 72 hours of cEEG recording. EEG were independently and blindly scored with EaSiBUSSEs by two neurophysiologists, on time windows of 3 hours. Analyses were performed on more than 950 hours of EEG records over a total of 103 days. To assess intra- and inter-rater reliability, we measured the intraclass correlation. To assess clinical relevance, we measured the capability of EaSiBUSSEs to identify patients who would present a seizure in the next 24 hours. We computed the area under the receiving operating characteristics (ROC) curve and reported the values of sensitivity and specificity. Analyses were performed using the R software V.3.5.0.

EEG scores were reproducible using EaSiBUSSEs with an excellent intra- and inter-rater consistency of 0.916 [CI 95% 0.896-0.932] and 0.935 [CI 95% 0.902-0.957], respectively. ROC curve revealed also good accuracy at detecting seizure recurrence in the next 24 hours for

EaSiBUSSEs (AUC=0.903; CI 95% 0.835-0.972), with a sensitivity of 93.6%, specificity of 72.0%, positive predictive value of 75.9% and negative predictive value of 92.3% when using the cut-off of 5.

Conclusion

Continuous electroencephalography is crucial for monitoring patients admitted in ICU with brain injury. It is particularly relevant in the management of patients with refractory SE. It is the only way to diagnose persistence or recurrence of NCS or NCSE in anesthetized and curarized patients. Simple and effective EEG scores are needed to summarize the excessive amount of EEG data with large variety of patterns. Several scores or criteria are now available for NCSE diagnosis (Salzburg Criteria), for prognosis (EMSE) and for seizure risk (2HELPS2B).

Here, we propose a new score to monitor EEG activity after refractory convulsive SE and to quantitatively describe major EEG changes leading to seizure: the EaSiBUSSEs score. We believe that this score is simple to perform and better suited for repeated monitoring of the progressive build-up leading to seizure or SE recurrence, by quantifying the pro-epileptiform potential of several EEG patterns. It may be also useful for other purposes (e.g., therapeutic trials or research on brain injury markers). Using the terminology of SCCET, it will facilitate the communication between medical professionals. We validated in a small cohort of patients its accuracy for detecting seizure recurrence. Further studies are needed to examine the performance of EaSiBUSSEs in critically ill patients after convulsive status epilepticus.

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References

[1] Alvarez V, Drislane FW, Westover MB, Dworetzky BA, Lee JW. Characteristics and role in outcome prediction of continuous EEG after status epilepticus: A prospective observational cohort. Epilepsia 2015;56:933–41.

[2] Beniczky S, Hirsch LJ, Kaplan PW, Pressler R, Bauer G, Aurlien H, et al. Unified EEG terminology and criteria for nonconvulsive status epilepticus. Epilepsia 2013;54 Suppl 6:28–9.

[3] Beretta S, Coppo A, Bianchi E, Zanchi C, Carone D, Stabile A, et al. Neurologic outcome of postanoxic refractory status epilepticus after aggressive treatment. Neurology 2018;91:e2153–62.

[4] Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 2012;17:3–23.

[5] Carrera E, Claassen J, Oddo M, Emerson RG, Mayer SA, Hirsch LJ. Continuous electroencephalographic monitoring in critically ill patients with central nervous system infections. Arch Neurol 2008;65:1612–8.

[6] Chen J, Xie L, Hu Y, Lan X, Jiang L. Nonconvulsive status epilepticus after cessation of convulsive status epilepticus in pediatric intensive care unit patients. Epilepsy Behav 2018;82:68–73.

[7] Claassen J, Mayer SA, Kowalski RG, Emerson RG, Hirsch LJ. Detection of

electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology 2004;62:1743–8.

[8] Claassen J, Jetté N, Chum F, Green R, Schmidt M, Choi H, et al. Electrographic seizures and periodic discharges after intracerebral hemorrhage. Neurology 2007;69:1356–65.

[9] Claassen J, Taccone FS, Horn P, Holtkamp M, Stocchetti N, Oddo M, et al. Recommendations on the use of EEG monitoring in critically ill patients: consensus statement from the neurointensive care section of the ESICM. Intensive Care Med 2013;39:1337–51.

[10] De Marchis GM, Pugin D, Meyers E, Velasquez A, Suwatcharangkoon S, Park S, et al. Seizure burden in subarachnoid hemorrhage associated with functional and cognitive outcome. Neurology 2016;86:253–60.

[11] Foreman B, Claassen J, Abou Khaled K, Jirsch J, Alschuler DM, Wittman J, et al. Generalized periodic discharges in the critically ill: a case-control study of 200 patients. Neurology 2012;79:1951–60.

[12] Gaspard N, Manganas L, Rampal N, Petroff OAC, Hirsch LJ. Similarity of lateralized rhythmic delta activity to periodic lateralized epileptiform discharges in critically ill patients. JAMA Neurol 2013;70:1288–95.

[13] Giovannini G, Monti G, Tondelli M, Marudi A, Valzania F, Leitinger M, et al. Mortality, morbidity and refractoriness prediction in status epilepticus: Comparison of STESS and EMSE scores. Seizure 2017;46:31–7.

[14] Hanin A, Lambrecq V, Denis JA, Imbert-Bismut F, Rucheton B, Lamari F, et al. Cerebrospinal fluid and blood biomarkers of status epilepticus. Epilepsia 2020;61:6–18.

[15] Herman ST, Abend NS, Bleck TP, Chapman KE, Drislane FW, Emerson RG, et al. Consensus statement on continuous EEG in critically ill adults and children, part I: indications. J Clin Neurophysiol 2015;32:87–95.

[16] Hirsch LJ, LaRoche SM, Gaspard N, Gerard E, Svoronos A, Herman ST, et al. American

Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. J Clin Neurophysiol 2013;30:1–27.

[17] Jaitly R, Sgro JA, Towne AR, Ko D, DeLorenzo RJ. Prognostic value of EEG monitoring after status epilepticus: a prospective adult study. J Clin Neurophysiol 1997;14:326–34.

[18] Jette N, Claassen J, Emerson RG, Hirsch LJ. Frequency and predictors of nonconvulsive seizures during continuous electroencephalographic monitoring in critically ill children. Arch Neurol 2006;63:1750–5.

[19] Johnson EL, Kaplan PW. Population of the ictal-interictal zone: The significance of periodic and rhythmic activity. Clin Neurophysiol Pract 2017;2:107–18.

[20] Kang BS, Kim DW, Kim KK, Moon HJ, Kim Y-S, Kim HK, et al. Prediction of mortality and functional outcome from status epilepticus and independent external validation of STESS and EMSE scores. Crit Care 2016;20:25.

[21] Kaplan PW, Duckworth J. Confusion and SIRPIDs regress with parenteral lorazepam. Epileptic Disord Int Epilepsy J Videotape 2011;13:291–4.

[22] Koren JP, Herta J, Pirker S, Fürbass F, Hartmann M, Kluge T, et al Rhythmic and periodic EEG patterns of "ictal-interictal uncertainty" in critically ill neurological patients. Clin Neurophysiol 2016;127:1176–81.

[23] Koren J, Herta J, Draschtak S, Pötzl G, Fürbass F, Hartmann M, et al. Early Epileptiform Discharges and Clinical Signs Predict Nonconvulsive Status Epilepticus on Continuous EEG. Neurocrit Care 2018;29:388–95.

[24] Kubota Y, Nakamoto H, Egawa S, Kawamata T. Continuous EEG monitoring in ICU. J Intensive Care 2018;6:39.

[25] Leitinger M, Beniczky S, Rohracher A, Gardella E, Kalss G, Qerama E, et al. Salzburg Consensus Criteria for Non-Convulsive Status Epilepticus--approach to clinical application.

Epilepsy Behav 2015;49:158–63.

[26] Leitinger M, Höller Y, Kalss G, Rohracher A, Novak HF, Höfler J, et al. Epidemiology-based mortality score in status epilepticus (EMSE). Neurocrit Care 2015;22:273–82.

[27] Leitinger M, Trinka E, Gardella E, Rohracher A, Kalss G, Qerama E, et al. Diagnostic accuracy of the Salzburg EEG criteria for non-convulsive status epilepticus: a retrospective study. Lancet Neurol 2016;15:1054–62.

[28] Li H-T, Wu T, Lin W-R, Tseng W-EJ, Chang C-W, Cheng M-Y, et al. Clinical correlation and prognostic implication of periodic EEG patterns: A cohort study. Epilepsy Res 2017;131:44–50.

[29] Limotai C, Ingsathit A, Thadanipon K, McEvoy M, Attia J, Thakkinstian A. How and Whom to Monitor for Seizures in an ICU: A Systematic Review and Meta-Analysis. Crit Care Med 2019;47:e366–73.

[30] Moffet EW, Subramaniam T, Hirsch LJ, Gilmore EJ, Lee JW, Rodriguez-Ruiz AA, et al. Validation of the 2HELPS2B Seizure Risk Score in Acute Brain Injury Patients. Neurocrit Care 2020;33:701-7.

[31] Nei M, Lee JM, Shanker VL, Sperling MR. The EEG and prognosis in status epilepticus. Epilepsia 1999;40:157–63.

[32] Ong C, Gilmore E, Claassen J, Foreman B, Mayer SA. Impact of prolonged periodic epileptiform discharges on coma prognosis. Neurocrit Care 2012;17:39–44.

[33] Orta DSJ, Chiappa KH, Quiroz AZ, Costello DJ, Cole AJ. Prognostic implications of periodic epileptiform discharges. Arch Neurol 2009;66:985–91.

[34] Pacha MS, Orellana L, Silva E, Ernst G, Pantiu F, Quiroga Narvaez J, et al. Role of EMSE and STESS scores in the outcome evaluation of status epilepticus. Epilepsy Behav 2016;64:140–2.

[35] Payne ET, Zhao XY, Frndova H, McBain K, Sharma R, Hutchison JS, et al. Seizure

burden is independently associated with short term outcome in critically ill children. Brain 2014;137:1429–38.

[36] Pisani F, Copioli C, Di Gioia C, Turco E, Sisti L. Neonatal seizures: relation of ictal video-electroencephalography (EEG) findings with neurodevelopmental outcome. J Child Neurol 2008;23:394–8.

[37] Punia V, Garcia CG, Hantus S. Incidence of recurrent seizures following hospital discharge in patients with LPDs (PLEDs) and nonconvulsive seizures recorded on continuous EEG in the critical care setting. Epilepsy Behav 2015;49:250–4.

[38] Ribeiro A, Singh R, Brunnhuber F. Clinical outcome of generalized periodic epileptiform discharges on first EEG in patients with hypoxic encephalopathy postcardiac arrest. Epilepsy Behav 2015;49:268–72.

[39] Rodriguez Ruiz A, Vlachy J, Lee JW, Gilmore EJ, Ayer T, Haider HA, et al. Association of Periodic and Rhythmic Electroencephalographic Patterns With Seizures in Critically Ill Patients. JAMA Neurol 2017;74:181–8.

[40] Sainju RK, Manganas LN, Gilmore EJ, Petroff OA, Rampal N, Hirsch LJ, et al. Clinical Correlates and Prognostic Significance of Lateralized Periodic Discharges in Patients Without Acute or Progressive Brain Injury: A Case-Control Study. J Clin Neurophysiol 2015;32:495–500.

[41] Shafi MM, Westover MB, Cole AJ, Kilbride RD, Hoch DB, Cash SS. Absence of early epileptiform abnormalities predicts lack of seizures on continuous EEG. Neurology 2012;79:1796–801.

[42] Snodgrass SM, Tsuburaya K, Ajmone-Marsan C. Clinical significance of periodic lateralized epileptiform discharges: relationship with status epilepticus. J Clin Neurophysiol 1989;6:159–72.

[43] Struck AF, Ustun B, Ruiz AR, Lee JW, LaRoche SM, Hirsch LJ, et al. Association of

an Electroencephalography-Based Risk Score With Seizure Probability in Hospitalized Patients. JAMA Neurol 2017;74:1419–24.

[44] Swisher CB, Shah D, Sinha SR, Husain AM. Baseline EEG pattern on continuous ICU EEG monitoring and incidence of seizures. J Clin Neurophysiol 2015;32:147–51.

[45] Topjian AA, Gutierrez-Colina AM, Sanchez SM, Berg RA, Friess SH, Dlugos DJ, et al. Electrographic status epilepticus is associated with mortality and worse short-term outcome in critically ill children. Crit Care Med 2013;41:215–23.

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

[47] Trinka E, Kälviäinen R. 25 years of advances in the definition, classification and treatment of status epilepticus. Seizure 2017;44:65–73.

[48] Walsh JM, Brenner RP. Periodic lateralized epileptiform discharges--long-term outcome in adults. Epilepsia 1987;28:533–6.

[49] Westover MB, Shafi MM, Bianchi MT, Moura LMVR, O'Rourke D, Rosenthal ES, et al. The probability of seizures during EEG monitoring in critically ill adults. Clin Neurophysiol 2015;126:463–71.

[50] Yoo JY, Rampal N, Petroff OA, Hirsch LJ, Gaspard N. Brief potentially ictal rhythmic discharges in critically ill adults. JAMA Neurol 2014;71:454–62.

[51] Zafar SF, Subramaniam T, Osman G, Herlopian A, Struck AF. Electrographic seizures and ictal-interictal continuum (IIC) patterns in critically ill patients. Epilepsy Behav 2020;106:107037.

[52] Zeiler SR, Turtzo LC, Kaplan PW. SPECT-negative SIRPIDs argues against treatment as seizures. J Clin Neurophysiol 2011;28:493–6.

Figures legends

Figure 1: Fields of application of cEEG after status epilepticus.

Figure 2: Definition and model of the EEG-based seizure build-up score in status epilepticus (EaSiBUSSEs).

Seven EEG subscores were defined from the pattern least associated with seizure risk (no interictal activity) to the most severe one (focal or generalized SE). They depict the morphology and prevalence of EEG patterns in EEG epochs. The grey boxes represent the background activity. The green lines represent the focal or generalized slowing, the black lines the sporadic epileptiform discharges, the blue lines the PDs (BiPDs, LPDs and GPDs) and LRDA, the purple lines the BRDs and the red lines the seizures. The seizure burden is estimated as the total duration of seizures out of the total duration of cEEG recording.

Abbreviations: BiPDs = bilateral independent periodic discharges; BRDs = brief rhythmic discharges; GPDs = generalized periodic discharges; LPDs = lateralized periodic discharges; LRDA = lateralized delta rhythmic activity

Figure 3: Raw EEG examples of each subscore from 1 to 5.

Each EEG example (8 electrodes, longitudinal bipolar montage, low frequency filter 0.53 Hz, high frequency filter 70 Hz) corresponds to a 30s-epoch extracted from a 3h-analysed period, for display purpose.

Subscore **1** = Interictal EEG with generalized slowing in a 58-year-old man who presented a nonconvulsive status epilepticus, **2** = Occasional low-amplitude focal epileptiform discharge in a 20-year-old man, who presented an anti-$NMDA_R$ encephalitis, **3** = Abundant sporadic epileptiform discharges in a 26-year-old man with a history of myoclonic astatic epilepsy, **4** =

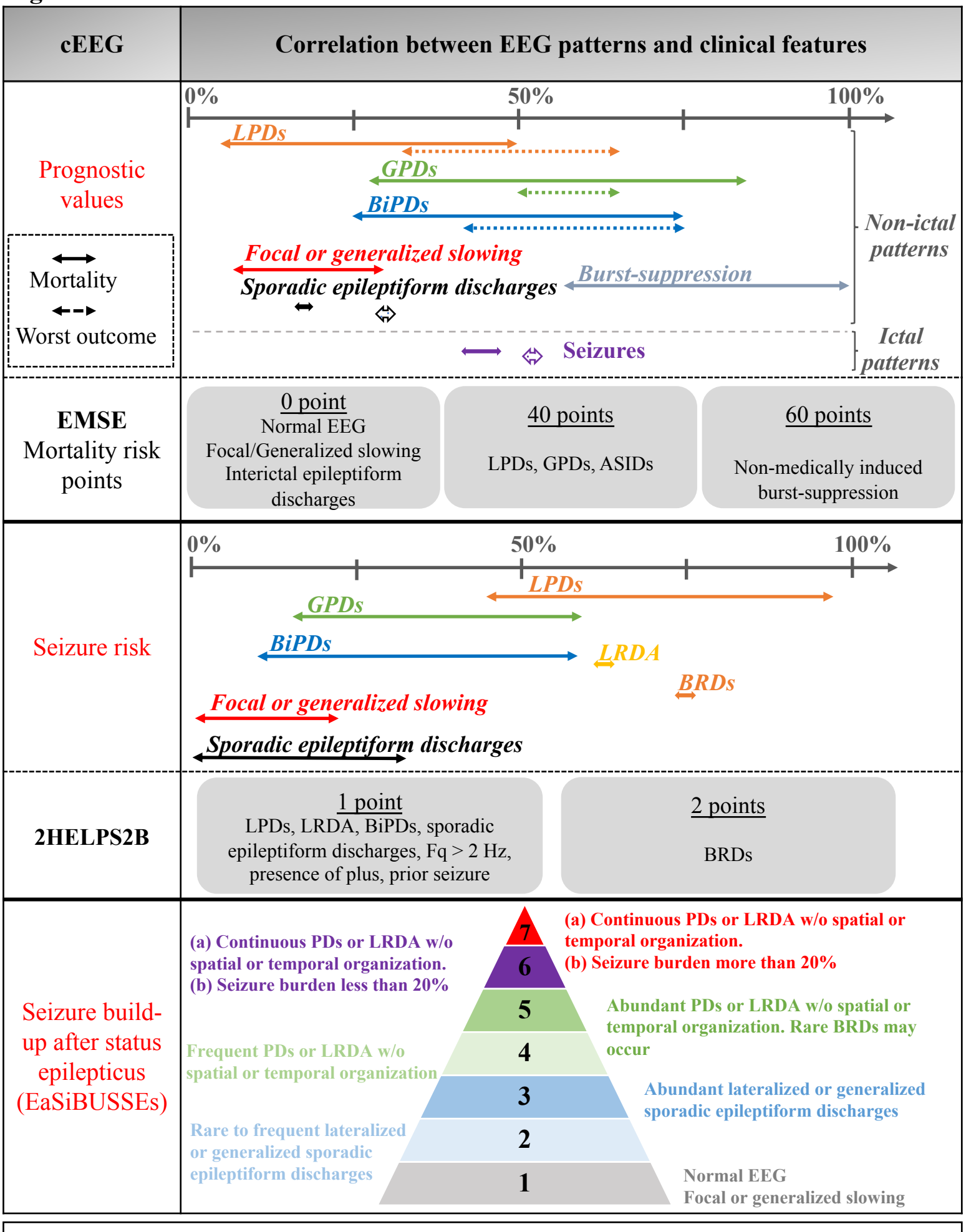
Frequent PDs in a 75-year-old man with a New-Onset-Refractory-Status-Epilepticus, whose EEG demonstrates intermittent PDs, **5** = Abundant focal occipital PDs without spatial or temporal organization, in a 24-year-old patient with mitochondrial disease.

Figure 4: Raw EEG examples of each subscore from 6 to 7.

Each EEG example (8 electrodes, longitudinal bipolar montage, low frequency filter 0.53 Hz, high frequency filter 70 Hz) corresponds to a 30s-epoch extracted from a 3h-analysed period, for display purpose.

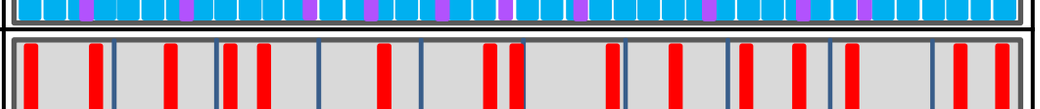
Subscore **6a** = Continuous PDs, interrupted by a brief period of rhythmic discharges (red line) in a 58-year-old man with altered mental status, **6b** = A focal electrographic seizure which begins in the left temporal region, without clinical correlate, in a 20-year-old man, who presented an anti-$NMDA_R$ encephalitis. The seizure burden is less than 20% (i.e. 3 seizures of 80 seconds in a 3-h period), as reported by left Compressed Spectral Array (seizures are apparent as increase in power in high frequencies, represented by warmer colors), **7a** = Continuous PDs, interrupted by a longer period of rhythmic discharges (red line), evolving into a seizure, in a 20-year-old man with new-onset-refractory status epilepticus, **7b** = Frequent electrographic seizures arising from the left hemisphere, following LPDs, in a 27-year-old man with new-onset-refractory status epilepticus. The seizure burden is more than 20%, as shown by left Compressed Spectral Array (detection of 30 seizures of 150 seconds in a 3-h period).

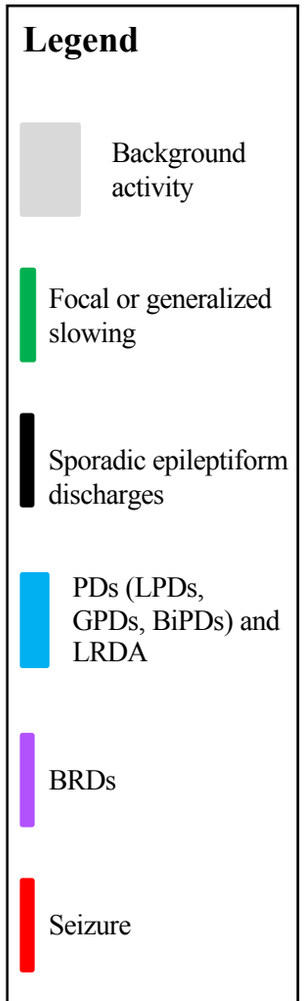
Figure 1



Rare < 1%; Occasional 1-9%, Frequent 10-40%; Abundant 50-89%, Continuous ≧90%

ASIDs: after status epilepticus ictal discharges; BiPDs: bilateral independent periodic discharges; BRDs: brief rhythmic discharges; Fq: frequency; GPDs; generalized periodic discharges; LPDs: lateralized periodic discharges; LRDA : lateralized rhythmic delta activity; PDs: periodic discharges; w/o: without

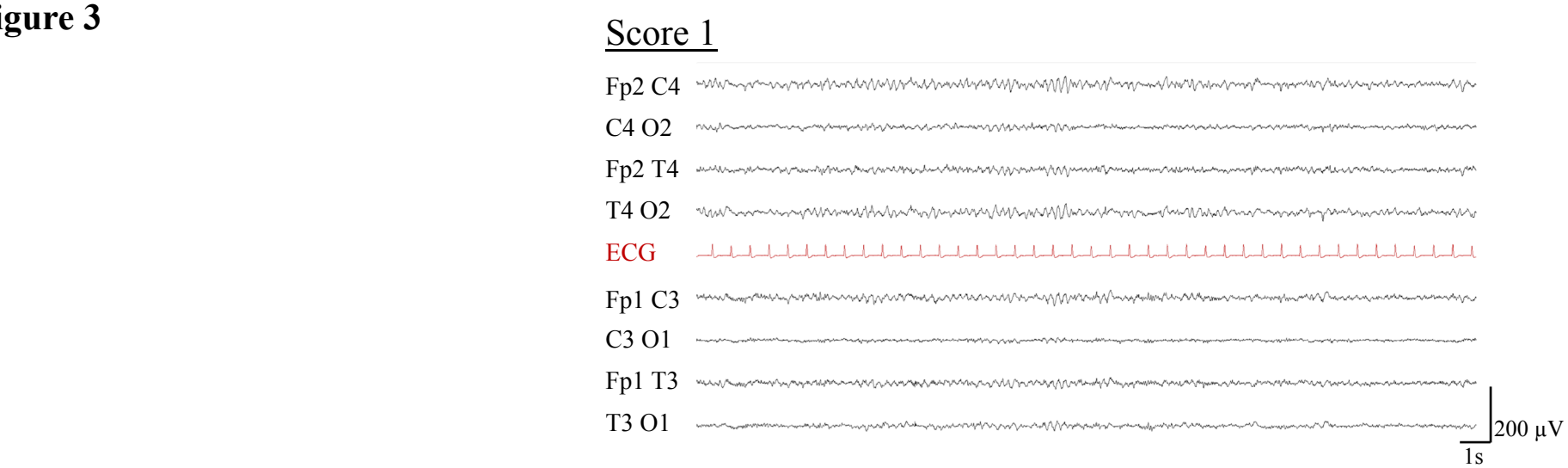
Score	Definition		Model
1	Background EEG with no interictal or ictal epileptiform discharges		
	Background EEG activity with non-specific EEG abnormalities (including focal or generalized slowing)		
2	Background EEG activity with lateralized or generalized, sporadic (rare < 1%, occasional 1-9% to frequent 10-49%) interictal epileptiform discharges (including spikes, polyspikes)		
3	Background EEG with lateralized or generalized, abundant (50-89%) interictal epileptiform discharges (including spikes, polyspikes)		
4	Background EEG activity with frequent (10-49%) periodic discharges (LPDs, GPDs, BiPDs) or LRDA without spatial or temporal organization, from 0.1 to 1.5/s	Scattered activities	
		Grouped activities	
5	Background EEG activity with abundant (50-89%) periodic discharges (LPDs, GPDs, BiPDs) or LRDA, without spatial or temporal organization from 0.1 to 1.5/s. Rare (<1%) BRDs, above 1.5/s, without spatial or temporal organization may occur	Scattered activities	
		Grouped activities	
6	(a) Continuous (≧ 90%) periodic discharges (LPDs, GPDs, BiPDs) or LRDA, without spatial or temporal organization from 0.1 to 1.5/s; with occasional (1-9%) BRDs, above 1.5/s; no background activity		
	(b) Seizure burden less than 20%		
7	(a) Continuous (≧ 90%) periodic discharges (LPDs, GPDs, BiPDs) or LRDA, without spatial or temporal organization from 0.1 to 1.5/s, with frequent (10-49%) BRDs, above 1.5/s; no background activity		
	(b) Seizure burden more than 20%		



*The GRDA and SIRPIDs were not included in this score, because they were shown not to be associated with seizures[43]

Figure 2

Figure 3


Score 1
Fp2 C4
C4 O2
Fp2 T4
T4 O2
ECG
Fp1 C3
C3 O1
Fp1 T3
T3 O1
200 µV
1s
Score 2
Fp2 C4
C4 O2
Fp2 T4
T4 O2
ECG
Fp1 C3
C3 O1
Fp1 T3
T3 O1
100 µV
1s
Score 3
Fp2 C4
C4 O2
Fp2 T4
T4 O2
ECG
Fp1 C3
C3 O1
Fp1 T3
T3 O1
200 µV
1s
Score 4
Fp2 C4
C4 O2
Fp2 T4
T4 O2
ECG
Fp1 C3
C3 O1
Fp1 T3
T3 O1
200 µV
1s
Score 5
Fp2 C4
C4 O2
Fp2 T4
T4 O2
ECG
Fp1 C3
C3 O1
Fp1 T3
T3 O1
200 µV
1s

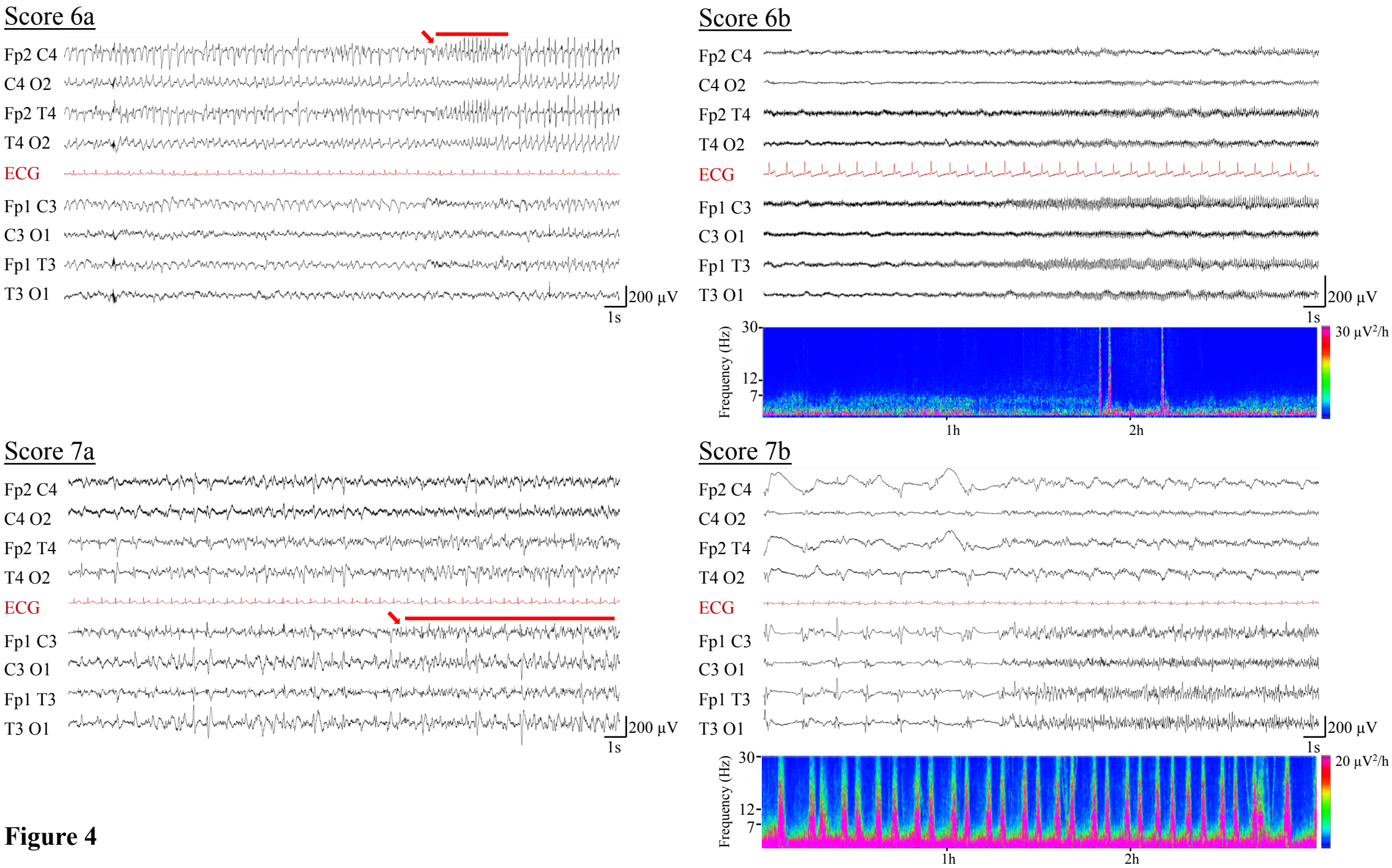
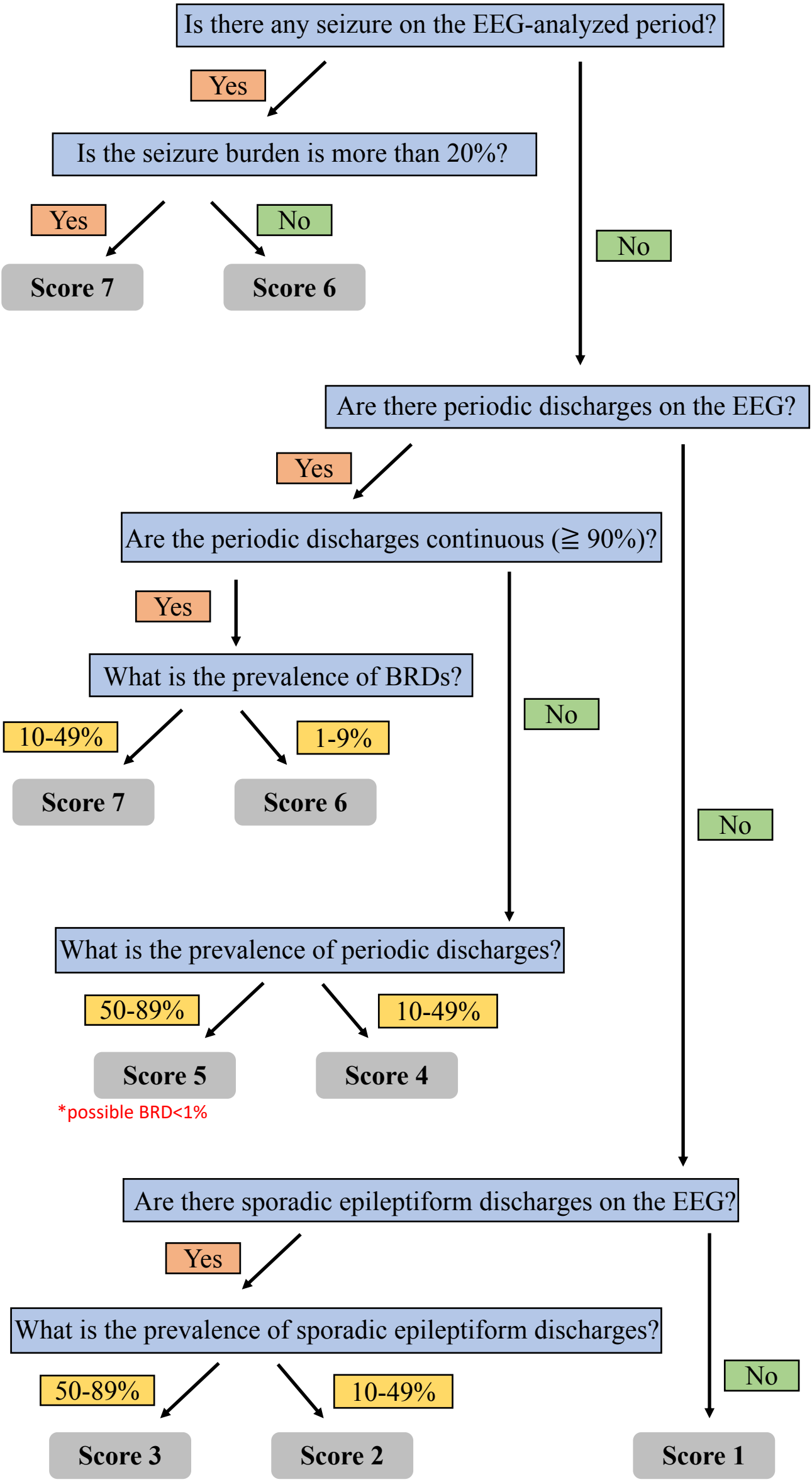

Score 6a
Fp2 C4
C4 O2
Fp2 T4
T4 O2
ECG
Fp1 C3
C3 O1
Fp1 T3
T3 O1
200 µV
1s
Score 6b
Fp2 C4
C4 O2
Fp2 T4
T4 O2
ECG
Fp1 C3
C3 O1
Fp1 T3
T3 O1
200 µV
1s
Frequency (Hz)
30
12
7
1h
2h
30 µV²/h
Score 7a
Fp2 C4
C4 O2
Fp2 T4
T4 O2
ECG
Fp1 C3
C3 O1
Fp1 T3
T3 O1
200 µV
1s
Score 7b
Fp2 C4
C4 O2
Fp2 T4
T4 O2
ECG
Fp1 C3
C3 O1
Fp1 T3
T3 O1
200 µV
1s
Frequency (Hz)
30
12
7
1h
2h
20 µV²/h

Figure 4



Supplementary Fig.1: Decision-making tree for EaSiBUSSEs