

# Validation of an algorithm of time-dependent electro-clinical risk stratification for electrographic seizures (TERSE) in critically ill patients

F.A. Cissé<sup>a,b</sup>, G.M. Osman<sup>c,d</sup>, B. Legros<sup>a</sup>, C. Depondt<sup>a</sup>, L.J. Hirsch<sup>d</sup>, A.F. Struck<sup>e</sup>, N. Gaspard<sup>a,d,\*</sup>

<sup>a</sup> Department of Neurology, Université Libre de Bruxelles – Hôpital Erasme, Bruxelles, Belgium

<sup>b</sup> Department of Neurology, CHU de Conakry, Conakry, Guinée

<sup>c</sup> Department of Neurology, Henry Ford Hospital, Detroit, MI, USA

<sup>d</sup> Department of Neurology and Comprehensive Epilepsy Center, Yale University, New Haven, CT, USA

<sup>e</sup> Department of Neurology, University of Wisconsin, Madison, WI, USA

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## HIGHLIGHTS

- Electroclinical risk stratification identifies 95% of acutely ill patients with electrographic seizures.
- Electroclinical risk stratification reduces continuous EEG monitoring recording time by 67%.
- Accounting for evolving brain injury will be required to further improve prediction accuracy.

## ABSTRACT

**Objective:** The clinical implementation of continuous electroencephalography (CEEG) monitoring in critically ill patients is hampered by the substantial burden of work that it entails for clinical neurophysiologists. Solutions that might reduce this burden, including by shortening the duration of EEG to be recorded, would help its widespread adoption. Our aim was to validate a recently described algorithm of time-dependent electro-clinical risk stratification for electrographic seizure (ESz) (TERSE) based on simple clinical and EEG features.

**Methods:** We retrospectively reviewed the medical records and EEG recordings of consecutive patients undergoing CEEG between October 1, 2015 and September, 30 2016 and assessed the sensitivity of TERSE for seizure detection, as well as the reduction in EEG time needed to be reviewed.

**Results:** In a cohort of 407 patients and compared to full CEEG review, the model allowed the detection of 95% of patients with ESz and 97% of those with electrographic status epilepticus. The amount of CEEG to be recorded to detect ESz was reduced by two-thirds, compared to the duration of CEEG that was actually recorded.

**Conclusions:** TERSE allowed accurate time-dependent ESz risk stratification with a high sensitivity for ESz detection, which could substantially reduce the amount of CEEG to be recorded and reviewed, if applied prospectively in clinical practice.

**Significance:** Time-dependent electro-clinical risk stratification, such as TERSE, could allow more efficient practice of CEEG and its more widespread adoption. Future studies should aim to improve risk stratification in the subgroup of patients with acute brain injury and absence of clinical seizures.

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## 1. Introduction

Electrographic seizures (ESz) occur in 15–20% of acutely ill patients (Claassen et al. 2004; Rodriguez Ruis et al. 2017) and are associated with detrimental hemodynamic and metabolic effects

\* Corresponding author at: ULB – Hôpital Erasme, Service de Neurologie, Route de Lennik, 808, 1070 Bruxelles, Belgium.

E-mail address: [nicolas.gaspard@erasme.ulb.ac.be](mailto:nicolas.gaspard@erasme.ulb.ac.be) (N. Gaspard).

(Claassen et al. 2013a; Witsch et al. 2017) and worse functional outcome (Payne et al. 2014; De Marchis et al. 2015). Most ESz in the critically ill lack obvious clinical manifestation and their detection requires continuous EEG monitoring (CEEG) (Claassen et al. 2004; Rodriguez Ruis et al. 2017). Many professional societies now recommend that CEEG be performed to detect ESz in critically ill patients (Claassen et al. 2013b; Herman et al. 2015a; 2015b). The same guidelines also recommend that patients be monitored for at least 24 hours, or more if they are comatose or EEG risk

patterns are observed, as the identification of the first ESz might be delayed by several hours, or even days, after CEEG onset. (Claassen et al. 2004) The implementation of these guidelines is hampered by the cost and substantial burden of work that CEEG entails for EEG technologists and clinical neurophysiologists. For instance, the review of a 24-hour raw CEEG might take on average between 20 and 80 minutes, possibly more for more complex cases (Haider et al. 2016). One promising avenue to reduce this burden is to limit the duration of CEEG recording and related review time while maintaining an acceptable ESz detection rate. Based on prior works on seizure forecasting (Westover et al. 2014), we have recently proposed to combine clinical and EEG features in a time-dependent electro-clinical risk stratification for ESz (TERSE) algorithm that allows to determine the shortest duration of CEEG which achieves a high (95%) detection rate of patients with ESz on an individual patient basis. (Struck et al. 2017a) The model (Fig. 1), which includes two simple pre-CEEG clinical features (coma and history of seizures) and the identification of EEG risk patterns, appears promising but requires validation in an independent cohort. Additionally, the amount of EEG review time that can be spared, i.e. the net impact of the algorithm on the burden of work, remains to be assessed. Finally, while acceptable, the sensitivity of TERSE is not perfect and it is unclear why the risk stratification fails in some cases.

The aims of this study were thus (a) to provide validation of TERSE in an independent cohort of critically ill patients, (b) to estimate the amount of EEG review time that can be spared by applying this algorithm, and (c) to investigate the clinical and EEG features of false negative cases.

## 2. Material and Methods

### 2.1. Study population

Following institutional review board approval, we retrospectively identified in a prospective EEG database all acutely ill adult (age ≥ 16 years) patients who underwent CEEG at an academic

medical center (Hôpital Erasme, Bruxelles, Belgium) between October 1, 2015 and September, 30 2016. All patients were admitted to an intensive care or acute care (stroke) unit. We excluded patients with cardiac arrest, or if they received CEEG of < 24-hour duration, or if CEEG was interrupted for > 2 hours (consecutive or not).

### 2.2. Clinical variables

We retrieved the following variables from the medical records: demographic data (age, sex); past medical history, including a history of epilepsy prior to the current admission; occurrence of acute clinical seizures prior to CEEG, either since admission or within 24 hours prior to admission; coma at the time of CEEG, defined as the absence of purposeful response to noxious stimulation (Glasgow Coma Scale motor score ≤ 4); and time from admission to CEEG. Primary diagnoses were classified into the following categories: ischemic stroke, non-traumatic intracerebral hemorrhage (ICH), spontaneous subdural hematomas (SDH), subarachnoid hemorrhage (SAH), traumatic brain injury, CNS infection, CNS neoplasm, toxic metabolic encephalopathy, auto-immune encephalitis, posterior reversible encephalopathy syndrome (PRES) and other miscellaneous causes.

For further analysis, patients were classified in one of the four following groups: (1) “no coma/no seizure” (i.e. no history of epilepsy and no acute seizure); (2) “seizure/no coma” (i.e. history of epilepsy or acute seizure); (3) “coma/no seizure”; (4) “coma + seizure”, as previously described (Struck et al. 2017aa).

### 2.3. Clinical EEG recordings

Continuous EEG were performed as clinically indicated using 21 electrodes placed according to the 10–20 international system and reviewed by experienced clinical neurophysiologists (BL, CD and NG) certified in the American Clinical Neurophysiology Society (ACNS) Critical Care EEG Terminology (Hirsch et al. 2013). We follow the ACNS recommendations for the duration of CEEG recording (Herman et al. 2015b).

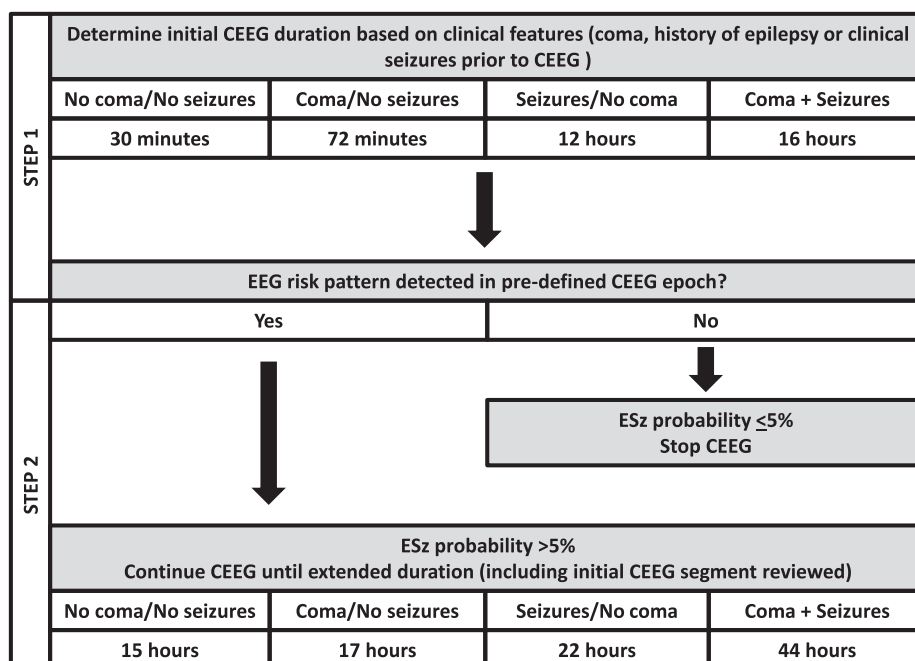


Fig. 1. Time-dependent electro-clinical risk stratification for electrographic seizures (TERSE). Please refer to the Methods section for details. Abbreviations: CEEG = continuous electroencephalography; ESz = Electrographic seizures.

#### 2.4. EEG review process and TERSE algorithm

For the purpose of this study, all CEEG were reviewed by at least one investigator (FAC or NG) according to the TERSE algorithm. The TERSE algorithm is a two-step algorithm (Fig. 1). In the first step, the length of the initial CEEG segment to be reviewed is determined according to the clinical group to which the patient belongs. These pre-determined review times are 30 minutes, 72 minutes, 12 hours, and 16 hours, for the “no coma/no seizure”, “coma/no seizure”, “seizure/no coma”, and “coma + seizure” groups, respectively. During this initial epoch, the EEG recording is reviewed for ESz and for electrographic risk patterns carrying a significant risk of ESz, including sporadic epileptiform discharges, lateralized periodic discharges (LPDs), lateralized rhythmic delta activity (LRDA), lateralized spike-and-wave discharges (LSW), bilateral independent periodic discharges (BIPDs), and brief potentially-ictal rhythmic discharges (BIRDs). (Gaspard et al. 2013; Hirsch et al. 2013; Yoo et al. 2014; Osman et al. 2018). If no ESz and no electrographic risk pattern are observed during this initial review time, no further CEEG data needs to be recorded. If, on the contrary, at least one risk pattern is observed, the CEEG is further pursued and reviewed for ESz for a total duration (extended review time) of 15 hours, 17 hours, 22 hours, and 44 hours, respectively, depending on the clinical group to which the patient belongs. No further extension is allowed beyond this total duration, even if additional risk patterns are observed during the extended review period.

The primary outcome measure was the ESz detection rate using the TERSE algorithm. We calculated sensitivity by comparing the detection rate of TERSE seizure detection to a gold standard, which was seizure detection by reviewing full-length CEEG recordings, irrespectively of any duration pre-specified by TERSE. One investigator (FAC or NG) assessed the presence of ESz, the latency to the first ESz from CEEG onset, and categorized them into ESz (Hirsch et al. 2013) or electrographic status epilepticus (ESE), defined either as an ESz lasting longer than 10 min (Trinka et al., 2015) or as the presence of recurring ESz occupying more than 20% of any 1-hour EEG epoch. (Payne et al., 2014) Secondary outcome measures included ESE detection rate and CEEG recording time saved by TERSE, for each clinical group. To determine the amount of CEEG to be recorded saved using TERSE, we subtracted for each patient the duration of CEEG reviewed with TERSE (TERSE CEEG duration) from the duration of CEEG reviewed without TERSE, either to the detection of the first seizure, if seizures occurred, or to the end of the recording, if no seizure occurred (full CEEG duration).

#### 2.5. Features of false negative patients

In order to identify the features of cases in which TERSE fails to correctly predict the occurrence of ESz, we combined clinical and EEG data of all patients with ESz in this study and of all patients with ESz who were included in our initial study (Struck et al., 2017a). We then categorized cases of the pooled series as false negative cases, in which TERSE did not allow the detection of ESz, and true positive cases, in which the risk stratification model and the review time predicted by the model did lead to the detection of ESz. Finally, we compared the clinical and EEG features between the false negative and true positive cases.

#### 2.6. Statistical analysis

Continuous variables were described as mean +/- standard deviation (SD) or median [interquartile range (IQR)], depending on their distribution. Categorical variables were described as count (frequency). Statistical tests were performed using Matlab (Mathworks, Natick, MA). Results with  $p < 0.05$  were considered statisti-

cally significant. Odds ratios were calculated to compare risk factors for ESz; statistically significant factors were identified using Fisher's exact test and Mann-Whitney's U test, as appropriate.

### 3. Results

#### 3.1. Clinical and EEG risk patterns associated with ESz

Of 491 identified patients, we excluded 60 with cardiac arrest and 24 with CEEG duration < 24 hours. We thus included 407 patients. Table 1 summarizes the demographics and clinical data. Electrographic seizures occurred in 63/407 (15%) patients, including 35/63 (55%) with ESE (24 with ESz lasting > 10 min and 11 with recurring ESz occupying >20% of a 1-hour epoch). The median overall latency to the first seizure was 26 min and was non-significantly longer in comatose patients (175 vs. 15 min;  $p = 0.26$ ; Table 1). Details of the association of clinical and EEG risk patterns with ESz are also provided in Table 1. Electrographic seizures occurred more frequently in comatose patients (30% vs. 12%; OR = 3.0) and in those with a history of clinical seizures (29% vs. 8%; OR 3.8). All EEG risk patterns (except BIPDs, but there were only 8 patients with this pattern), were associated with a higher risk of ESz, ranging from 24% in patients with sporadic epileptiform discharges to 75% in patients with BIRDs or LRDA.

#### 3.2. Seizure occurrence and sensitivity of TERSE

Performance data of TERSE are summarized in Table 2. Using TERSE, ESz were detected in 60/63 cases, overall, yielding an overall sensitivity of 95% (ranging from 80 to 100% across clinical subgroups), with a lower sensitivity observed in the lower risk groups (coma/no seizure and no coma/no seizure). Electrographic SE was detected in 34/35 (97%) cases. A secondary analysis, including the 24 patients who were excluded because of shortened CEEG recordings (median 13 h; range 5 to 22 h), yielded similar results, with a sensitivity of 61/64 (95%).

#### 3.3. Potential reduction in CEEG duration

The mean potential reduction in CEEG duration required to detect ESz by using TERSE compared to full CEEG duration was 21 hours (ranging from 12 to 41 hours across clinical subgroups), representing a mean percent reduction of 67 (ranging from 26% to 80%), across clinical subgroups (Table 2). The impact of TERSE on required CEEG duration was larger in the lowest risk groups.

#### 3.4. Clinical and EEG features of false negative cases

We combined patients with ESz ( $N = 63$ ) from this study with those from our prior study ( $N = 151$ ; see clinical details in Supplementary Table 1), thus obtaining a total cohort of 214 patients with ESz (Table 3). Of these 214 patients, TERSE predicted a duration of CEEG too short to detect ESz in 12 (6%), which were thus considered to be false negative cases (additional details provided in Supplementary Table 2). Compared to the true positive cases ( $N = 202$ ; Table 3), in which TERSE succeeded in predicting a sufficient duration of CEEG, the false negative cases less frequently had a history of seizures (17% vs. 62%;  $p = 0.004$ ) and tended to more frequently have an acute brain injury (83% vs. 55%;  $p = 0.07$ ). Their EEG was more likely to show focal or lateralized slowing (75% vs. 30%;  $p = 0.02$ ) or attenuation (42% vs. 16%;  $p = 0.04$ ) but tended to less often show EEG risk patterns. The latency to the first ESz was also significantly longer in this group (1062 vs. 35minutes;  $p < 0.001$ ). The longest latency was 2855 minutes.

**Table 1**  
Demographic, clinical and EEG data.

	Whole cohort (N = 407)	Electrographic seizures (N = 63)	No electrographic seizures (N = 344)	OR [95% CI]	p-value
<b>Clinical variables</b>					
Age (y)	64 [50–76]	67 [53–74]	63 [48–76]	N/A	0.41
Gender (male)	201 (49%)	30 (48%)	171 (50%)	0.9 [0.5–1.6]	0.79
Coma	70 (17%)	21 (33%)	49 (14%)	3.0 [1.6–5.5]	<0.001
History of seizures	123 (31%)	36 (57%)	89 (26%)	3.8 [2.2–6.6]	<0.001
History of epilepsy	45 (11%)	9 (14%)	36 (10%)	1.4 [0.7–3.1]	
Acute clinical seizures	101 (25%)	31 (49%)	70 (20%)	3.8 [2.2–6.6]	
Acute brain injury	242 (59%)	34 (54%)	208 (60%)	0.8 [0.4–1.3]	0.33
Time to CEEG (days)	0 [0–2]	0 [0–2]	0 [0–2]	N/A	0.89
<b>EEG variables</b>					
Sporadic epileptiform discharges	130 (37%)	31 (49%)	99 (29%)	2.4 [1.4–4.1]	0.002
LPDs	32 (8%)	20 (32%)	12 (3%)	12.9 [5.9–28.2]	<0.001
BIPDs	8 (2%)	2 (3%)	6 (2%)	1.9 [0.4–9.4]	0.36
LRDA	20 (5%)	15 (24%)	5 (1%)	9.5 [3.7–24.4]	<0.001
BIRDs	4 (1%)	3 (5%)	1 (0%)	17.2 [1.8–167.6]	0.01
Latency to first seizure (min)	N/A	26 [0–337]	N/A	N/A	0.26*
Not in coma		15 [0–251]			
In coma		175 [0–384]			

Data are presented as count (frequency) or median [interquartile range]. Percentages are column percentages. Abbreviations: CEEG = continuous electroencephalography monitoring; EEG = electroencephalography; LPDs = lateralized periodic discharges; BIPDs = bilateral independent periodic discharges; GPDs = generalized periodic discharges; LRDA = lateralized rhythmic delta activity; BIRDs = brief potentially-ictal rhythmic discharges; OR = odds ratio; N/A = not applicable. \*Comparing latency to first seizure between patients in coma and patients not in coma.

**Table 2**  
Performance of TERSE.

	Whole cohort (n = 407)	No coma/No seizure (n = 238)	Coma/No seizure (n = 44)	No coma/Seizure (n = 99)	Coma/Seizure (n = 26)
Electrographic seizures	63 (15%)	22 (9%)	5 (11%)	28 (28%)	8 (31%)
Initial CEEG epoch with risk EEG pattern	174 (43%)	85 (36%)	15 (34%)	56 (57%)	18 (69%)
Seizure detection rate	60/63 (95%)	20/22 (91%)	4/5 (80%)	28/28 (100%)	8/8 (100%)
Full CEEG duration (h)	23.5 [9–23.5]	24 [24–25]	48 [48–48]	24 [24–44]	48 [31–48]
TERSE CEEG duration (h)	12 [0.5–15]	0.5 [0.5–15]	1 [1–17]	22 [12–22]	44 [16–44]
% reduction	60 [15–97] %	69 [38–98] %	98 [65–98] %	25 [0–50] %	8 [2–67] %

Data are presented as count (frequency) or mean +/- standard deviation. Abbreviations: CEEG = continuous EEG monitoring.

**Table 3**  
Clinical and EEG features of patients with electrographic seizures, with false negative cases compared to true positive cases.

	All cases (N = 214)	False negative cases (N = 12)	True positive cases (N = 202)	p-value
<b>Clinical variables</b>				
Gender (male)	111 (52%)	6 (50%)	105 (52%)	0.92
Age (years)	66 [52–76]	66 [61–70]	66 [52–76]	0.91
Coma	61 (30%)	5 (42%)	56 (28%)	0.48
History of seizures	128 (62%)	2 (17%)	126 (62%)	0.004
Acute clinical seizures	114 (56%)	2 (17%)	112 (55%)	
History of epilepsy	35 (17%)	0 (0%)	35 (17%)	
Acute brain injury	121 (55%)	10 (83%)	111 (55%)	0.07
<b>EEG variables</b>				
Sporadic epileptiform discharges	66 (33%)	3 (25%)	63 (31%)	0.76
LPDs	61 (30%)	1 (8%)	60 (30%)	0.19
BIPDs	4 (2%)	0 (0%)	4 (2%)	0.67
LRDA	32 (15%)	1 (8%)	31 (15%)	0.76
BIRDs	10 (5%)	0 (0%)	10 (5%)	0.38
Focal/lateralized slowing	69 (32%)	9 (75%)	60 (30%)	0.02
Focal/lateralized attenuation	38 (18%)	5 (42%)	33 (16%)	0.04
Latency to first seizure (minutes)	37 [0–332]	1062 [776–1390]	35 [0–332]	<0.001

Data are presented as count (frequency) or median [interquartile range]. Abbreviations: LPDs = lateralized periodic discharges; BIPDs = bilateral independent periodic discharges; GPDs = generalized periodic discharges; LRDA = lateralized rhythmic delta activity; BIRDs = brief rhythmic discharges; OR = odds ratio. \*Comparing latency to first seizure between patients in coma and patients not in coma.

#### 4. Discussion

In this retrospective study of prospectively identified acutely ill patients undergoing CEEG, we confirmed the accuracy of TERSE, a

relatively simple algorithm that allows the identification of 95% of patients with ESz, while minimizing recording (and therefore review) time. The prevalence of ESz and of clinical and EEG risk factors used in TERSE in the cohorts used to design (Struck et al.,

2017a) and validate the algorithm (this study) is similar to the prevalence reported in recent large multi-center studies of CEEG (Alvarez et al., 2017; Rodriguez Ruis et al. 2017; Struck et al., 2017b). This suggests that our findings can be generalized to the population of acutely ill patients who benefit from CEEG on a routine basis. We should note, however, that TERSE was not intended for patients with post-anoxic brain injury, a population characterized by specific EEG patterns not included in TERSE, and in which CEEG is used not only for ESz detection but also for prognostication purposes. (Cloostermans et al., 2012; Sivaraju et al., 2015) An algorithm similar to TERSE but specific to post-anoxic brain injury can likely be designed but would need to take these differences into account. Also, we excluded patients from the primary analysis because of shortened CEEG recordings, as data from these cases did not reflect the 15% seizure risk usually observed in large cohorts of CEEG and the recommended monitoring durations, thus risking overestimating both the sensitivity of TERSE and its time-saving capability. As expected, including them in a secondary analysis only led to a marginal increase in sensitivity.

While showing excellent performance, the model was unable to correctly predict the CEEG duration necessary to detect seizures in 5% of patients. The analysis of these false negative cases indicates that they are clinically characterized by the presence of an acute brain injury (although this was not significant), the lack of clinical seizures prior to CEEG (leading to shorter recoding time since that is a feature of the algorithm). Thus, clinical factors used in TERSE might not be sensitive enough. For instance, seizures prior to CEEG might be missed if no bystander is present. Coma is a surrogate and crude measure of the severity of the acute brain injury or medical insult, and is known to be associated with the risk of ESz. However, severe acute brain injuries might not always cause coma and more discriminant scales or additional clinical features, perhaps specific to each etiology, might be required. False negative cases were also characterized by a lower, albeit non-significantly, prevalence of EEG risk patterns, and a higher prevalence of focal non-epileptiform patterns. It is thus possible that these EEG patterns (focal attenuation and polymorphic slowing), which are not associated with ESz at the whole population level, and thus were not included in TERSE, might still indicate a higher seizure risk in some selected subpopulations. A modified version of TERSE, designed for acute brain injury and including these EEG patterns, might achieve a better sensitivity. Quantitative analysis of EEG features might also be required to improve ESz prediction and risk stratification. False negative cases were also characterized by a long latency to the first seizure compared to true positive cases. A possible explanation is that acute brain injury, whether it is due to hemorrhage, ischemia or trauma, is a dynamic phenomenon with a potential for substantial evolution during the first days after the injury. Hematoma expansion, re-bleeding, delayed ischemia and increased cytotoxic or vasogenic edema all can lead to the progression of the initial injury and possibly to the delayed occurrence of ESz. (Claassen et al., 2007; Kim et al., 2017; Rosenthal et al., 2018) Prolonged CEEG with concomitant repeated assessment of the injury by neurological examination or with imaging would be required to formally confirm this hypothesis. Another major limitation of our work is the retrospective review of CEEGs that were acquired for clinical purposes. Although their duration followed the ACNS guidelines (Herman et al., 2015b), it is possible (if not likely) that seizures might occur beyond this recommended duration in a small proportion of cases. (Claassen et al., 2004)

We estimated that TERSE could reduce by approximately two-third the time and effort required of clinical neurophysiologists reading CEEG. Given an average review time of 35–60 minutes per 24-h EEG epoch (Moura et al., 2014; Haider et al., 2016), this reduction could amount up to 25–40 min per 24-h CEEG. This is an average value and it is possible that this reduction might be lower in

real life as the impact of using TERSE is more pronounced in low risk patients, whose EEG are easier to review by definition. The 95% prediction rate also compares favorably with the sensitivity of alternative approaches, such as simplified EEG montages (Kolls and Husain, 2007; Young et al., 2009; Karakis et al., 2010; Rubin et al., 2013; Gururangan et al., 2018), quantitative EEG (QEEG) displays (Stewart et al., 2010; Swisher et al., 2015; Amorim et al., 2016; Haider et al., 2016). Importantly, TERSE does not lead to false seizure detections, which are common in other strategies, and thus does not introduce a risk of over treatment. These different approaches are not mutually exclusive. It is likely that combining TERSE with risk stratification prior to CEEG (Struck et al., 2017b), simplified EEG montages and QEEG displays will further decrease the burden of CEEG for ESz detection, while preserving sensitivity. The optimal combination should be investigated in future studies. Of note, the impact of TERSE was the lowest for patients in the highest risk group, which typically requires longer duration of monitoring. However, since low-risk patients represent >50% of those monitored, the overall gain of using TERSE in clinical practice will likely remain substantial. By significantly reducing the amount of time required to clear out low-risk CEEG, it can still allow neurophysiologists to focus on higher risk recordings. Also, we did not address the question of further monitoring required to assess ESz response to treatment. As opposed to ESz prediction, clinical findings and EEG patterns suggesting a higher risk of ESz recurrence upon treatment are largely unknown and, as a consequence, there is no strong recommendation on CEEG recording after ESz detection and treatment. These important points should be further studied. It is also likely that quantitative EEG (Stewart et al., 2010; Swisher et al., 2015; Amorim et al., 2016; Haider et al., 2016) might provide substantial help in this regard. Finally, as seizure burden seems to be an important element linking ESz with outcome, while increasing seizure burden associated with less favorable outcomes, it would be interesting to investigate if TERSE might be able to predict seizure burden, potentially helping further focus CEEG resources on patients more likely to benefit from intervention.

## 5. Conclusions

This retrospective study validates in an independent cohort the accuracy of a time-dependent ESz risk stratification model in critically ill patients. The model is based on simple clinical and EEG features and allows the detection of 95% of patients with ESz, while at the same time reducing by two-third the duration of required CEEG. Future studies should aim to improve risk stratification in the subgroup of patients with acute brain injury and absence of clinical seizures.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clinph.2020.05.031>.

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