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The probability of seizures during EEG monitoring in critically ill adults

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HIGHLIGHTS

- Seizures occurred in 27% of 625 acutely ill patients. Most were detected within the first 30 min.
- The 72 h risk for seizures decays to <5% over 16 h in patients with epileptiform EEG abnormalities.
- The 72 h risk for seizures decays to <5% over 2 h in patients without epileptiform EEG abnormalities.
- Less than 5% of patients have a seizure without preceding epileptiform abnormalities.

ABSTRACT

Objective: To characterize the risk for seizures over time in relation to EEG findings in hospitalized adults undergoing continuous EEG monitoring (cEEG).
Methods: Retrospective analysis of cEEG data and medical records from 625 consecutive adult inpatients monitored at a tertiary medical center. Using survival analysis methods, we estimated the time-dependent probability that a seizure will occur within the next 72-h, if no seizure has occurred yet, as a function of EEG abnormalities detected so far.
Results: Seizures occurred in 27% (168/625). The first seizure occurred early (<30 min of monitoring) in 58% (98/168). In 527 patients without early seizures, 159 (30%) had early epileptiform abnormalities, versus 368 (70%) without. Seizures were eventually detected in 25% of patients with early epileptiform discharges, versus 8% without early discharges. The 72-h risk of seizures declined below 5% if no epileptiform abnormalities were present in the first two hours, whereas 16 h of monitoring were required when epileptiform discharges were present. 20% (74/388) of patients without early epileptiform abnormalities later developed them; 23% (17/74) of these ultimately had seizures. Only 4% (12/294) experienced a seizure without preceding epileptiform abnormalities.
Conclusions: Seizure risk in acute neurological illness decays rapidly, at a rate dependent on abnormalities detected early during monitoring. This study demonstrates that substantial risk stratification is possible based on early EEG abnormalities.
Significance: These findings have implications for patient-specific determination of the required duration of cEEG monitoring in hospitalized patients.

1. Introduction

High rates of seizures have been observed in hospitalized patients with a broad range of acute medical and neurological conditions (Claassen et al., 2004; Jordan, 1992). Early detection is critical to timely intervention to minimize both direct and secondary neurological and medical complications (Young and Jordan, 1998; Jordan, 1999; Vespa et al., 2003, 2010). Continuous EEG monitoring (cEEG) is the gold standard for identification of seizures

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in hospitalized patients, as seizures in this population are frequently nonconvulsive (Claassen et al., 2004; Jordan, 1992).

In the largest previous investigation of electrographic seizures in acutely ill adults, seizures were detected in 19% of 570 patients (Claassen et al., 2004). 56% with seizures had their first event within 1 h of initiating monitoring, and this percentage increased to 82, 88, and 93% within 12, 24 and 48 h (Claassen et al., 2004). However, the temporal relationship between the appearance of epileptiform abnormalities and electrographic seizures was not assessed. We recently investigated cEEG findings in relation to seizure risk in 242 adults, and found that risk for seizures in patients lacking epileptiform discharges (e.g. spikes, sharp waves, or periodic epileptiform discharges) decreased rapidly, vanishing by 4 h (upper 95% CI 3%) (Shafi et al., 2012). However, our study did not analyze the evolution of seizure risk in patients with epileptiform abnormalities.

Here we extend our prior work to include 625 patients, and present a novel analysis of the temporal evolution of seizure risk in relation to cEEG findings. This analysis accounts for transitions between seizure risk states, and provides a population-level time-dependent probability that a seizure will occur within the next 72 h, depending on the severity of cEEG abnormalities detected so far, across a wide variety of neurologic disease etiologies. This analysis provides a principled basis for determining the necessary duration of cEEG monitoring, particularly when resources are limited or cost-prohibitive.

2. Methods

2.1. Study population and clinical data

Reports, primary EEG data, and medical records were reviewed for all patients who underwent cEEG at Massachusetts General Hospital between August 1st, 2010 and June 2nd, 2012, with local IRB approval. Patients admitted electively for diagnosis or surgical planning were excluded. All other patients aged >18 monitored for at $\geqslant$18 consecutive hours were included. For patients monitored more than once during a hospitalization (during non-consecutive intervals), only the first cEEG monitoring period was analyzed. All cEEGs were ordered by treating physicians (rather than as part of a protocol), and all cEEGs included were performed for the purpose of seizure surveillance in acutely ill patients. Monitoring was terminated at the discretion of the epilepsy fellow and attending neurophysiologist as part of standard care, with the most common reason for discontinuation being absence of seizure activity.

2.2. EEG recordings

cEEG data was recorded using international 10–20 scalp electrode conventions. Based on direct page-by-page review of the entire primary EEG data, we determined the timing of the first electrographic seizure and/or epileptiform abnormality (periodic epileptiform discharges (PEDs), spikes, or sharp waves). Spikes, periodic patterns, and electrographic seizures were defined according to standard criteria (Chong and Hirsch, 2005; Hirsch et al., 2013). cEEG data were classified as containing: (1) electrographic seizures, (2) PEDs, (3) spikes or sharp waves, and (4) no epileptiform abnormalities.

Based on chart review, two of the study neurologists (MMS, MBW) retrospectively determined the neurologic status of patients at the time cEEG monitoring was initiated (awake, lethargic or stuporous, and comatose). Coma was defined as the absence of eye opening or verbal response to voice or pain in conjunction with the inability to follow commands.

2.3. Statistical analysis

Data were analyzed using custom software developed in Matlab (Matlab Statistics Toolbox, Natus, MA). Odds ratios were calculated to compare risk factors for seizures; statistically significant factors were identified using Fisher's exact test. In patients without seizures during the initial 30 min, univariate analyses were conducted to identify associations with subsequent seizures. Cumulative distribution functions (CDFs) for the timing of first seizures were estimated using the Kaplan–Meier method (Collett, 2003; Rausand and Høyland, 2003). An important motivation for using Kaplan–Meier curves is that they properly handle censored data, specifically right-censored data, which occurs when a patient withdraws from a study, i.e. is lost from the sample (e.g. because cEEG monitoring is discontinued) before the final outcome (electrographic seizures in the present context) is observed. This feature of the Kaplan–Meier method is critical to our retrospective analysis, because it allowed us to make principled estimates of the time-dependent risk for seizures using data from a wide range of patients who were monitored for variable lengths of time. The probability of seizures within the next 72 h for the entire population and for subgroups with and without epileptiform abnormalities was estimated based on the CDFs (see Supplemental Material) (Collett, 2003; Rausand and Høyland, 2003). The effect of coma on the time-dependent probability of seizures was assessed using a Cox proportional hazard (PH) model with the presence or absence of coma as the covariate. This effect was assessed for three separate scenarios and patient groupings: first, for the entire patient cohort, before commencement of cEEG monitoring; second, for the group of patients observed to have epileptiform abnormalities (spikes, sharp waves, or periodic discharges) but no seizures within the first 30 min of monitoring; and third, for patients without epileptiform abnormalities or seizures within the first 30 min of monitoring. In these analyses coma was considered to have a statistically significant effect on the probability of subsequent seizures if the Cox PH regression coefficient, β, for coma had a p-value less than 0.05. In each case the appropriateness of the Cox PH model was assessed using the test of Harrel and Lee (Kleinbaum and Klein, 2012), i.e. by testing for correlations of the Schoenfeld residuals of the Cox PH model with the order of failure (seizure) times, and judging the Cox PH model to be appropriate if the p-value for these correlations is larger than 0.05. Of note, Cox PH regression analysis is also appropriate for estimating time-dependent risks from right-censored data (see above).

3. Results

3.1. Study cohort

A total of 625 adult (18–99 years, mean 63 ± 17; 300 (48%) female, admitted non-electively and who underwent >18 h of cEEG monitoring were identified. The distribution of admission diagnoses is given in Table 1.

3.2. Predictors of seizures before monitoring

Seizures were recorded in 27% (168/625) of patients (Table 1, Fig. 1). Clinical variables significantly associated with seizures included subdural hematoma (67%) and hypoxic ischemic encephalopathy (59%); diagnoses with fewer seizures included SAH (14%), ICH (16%), and TBI (16%). After excluding patients with seizures within <30 min of recording, only HIE remained significantly associated with seizures (31%).

Coma present at the commencement of cEEG monitoring was associated with a higher incidence of subsequent seizures: 37%

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(63/172) of comatose patient eventually had seizures vs 23% (105/453) without coma, and Cox regression analysis confirmed that this association was clinically and statistically significant (HR 1.72, $p < 0.001$). However, coma was no longer a statistically significant predictor of seizures after excluding the 98 patients with seizures during the first 30 min of cEEG monitoring and dividing the remaining 527 patients into subgroups with and without epileptiform discharges, though a trend persisted (HR 1.65, $p = 0.14$ for cases with early epileptiform discharges; HR 1.10, $p = 0.9$ for cases without). Graphical illustrations of these effects of coma on seizure risk over time are shown in Supplemental Fig. 1.

Table 1
Clinical and EEG variables associated with seizures at any time during monitoring (left), and with in patients with no seizures detected within the first 30 min. The data in each column indicate the percent of patients with seizures (number of subjects with seizures/total number of subjects). Epi, epileptiform discharges; PEDs, periodic epileptiform discharges; AMS, altered mental status; SAH, subarachnoid hemorrhage; ICH, intracranial hemorrhage; TBI, traumatic brain injury; CVA, ischemic stroke ("cerebrovascular accident"); HIE, hypoxic ischemic encephalopathy (postanoxic coma); TME, toxic-metabolic encephalopathy; BT, brain tumor; CNSI, CNS infection; NSG, Neurosurgery; SDH, sudural hematoma; Epi, epileptiform abnormality (spikes/sharp waves or PEDs; does not include electrographic seizures).

Etiology	Overall seizures	No Szs after 30 min Seizures
AMS	29 (29/101)	14 (12/84)
SAH	14 (7/49)	7 (3/45)
ICH	16 (11/68)	7 (5/70)
TBI	16 (11/68)	5 (3/60)
CVA	27 (16/59)	14 (7/50)
HIE	59 (26/44)	31 (8/26)
TME	17 (7/42)	5 (2/37)
BT	32 (12/38)	19 (6/32)
CNSI	26 (6/23)	15 (3/20)
NSG	23 (8/35)	18 (6/33)
Epilepsy	39 (11/28)	23 (5/22)
SDH	67 (6/9)	25 (1/4)
Other	32 (16/50)	10 (3/29)
Spikes	–	25 (25/99)
PEDs	–	27 (16/60)
Any Epi.	–	26 (41/159)
No Epi.	–	8 (29/368)

The probability of seizures was strongly influenced by findings detected within the first 30 min (Table 1). Among the 527 patients without early seizures, any epileptiform discharges within the first 30 min was associated with subsequent seizures (41/159 patients (26%) with epileptiform discharges subsequently had seizures). In contrast, the absence of epileptiform discharges within the first 30 min predicted absence of subsequent seizures (29/368 patients (8%) had subsequent seizures).

Further statistical details regarding the relationship of clinical factors to risk for subsequent seizures are included in Supplemental Table 1.

3.3. Time to first epileptiform abnormality and seizures

The summary statistics for cEEG findings are presented in Fig. 1, and the time to detect epileptiform abnormalities is shown for all 625 patients in Fig. 2. Seizures were ultimately detected in 27% (168/625), 58% (98/168) of which had the first seizure within the first 30 min. Early seizures (within <30 min) occurred most frequently in patients with hypoxic-ischemic encephalopathy and subdural hematoma (Table 1). Epileptiform abnormalities were detected in advance or in the absence of subsequent seizures in 37% (233/625) of studies; 68% of this subgroup (159/233) had only epileptiform discharges, without seizures, in the first 30 min. In the 527 patients without early seizures, 13% (70/527) later had seizures, 59% (41/70) of which demonstrated epileptiform discharges within the first 30 min. 59% (368/625) of subjects lacked epileptiform abnormalities within the first 30 min, and only 8% (29/368) of these later had seizures. Of these 8%, more than half (59%, 17/29) first developed herald epileptiform discharges. Of the 47% (294/625) without any epileptiform discharges ever, seizures occurred in 4% (12/294).

3.4. Subtypes of early epileptiform abnormalities and transitions

Supplemental Table 1 categorizes patients by cEEG abnormality, from least to most severe: normal/slow background < spikes/sharp waves < periodic epileptiform discharges (PEDs) < electrographic

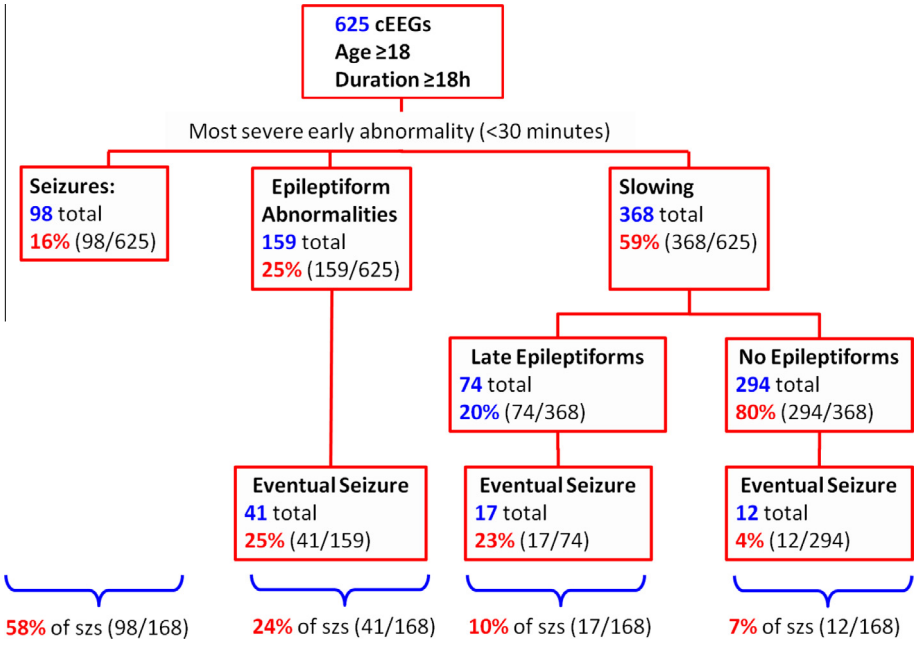

Fig. 1. Seizure detection statistics. Numbers and percentages of patients in whom the most severe abnormality detected so far after 30 min of cEEG monitoring is slowing or no abnormality, epileptiform discharges (spikes/sharps or PEDs), or electrographic seizures (second row of boxes); and numbers within each category who eventually develop seizures.

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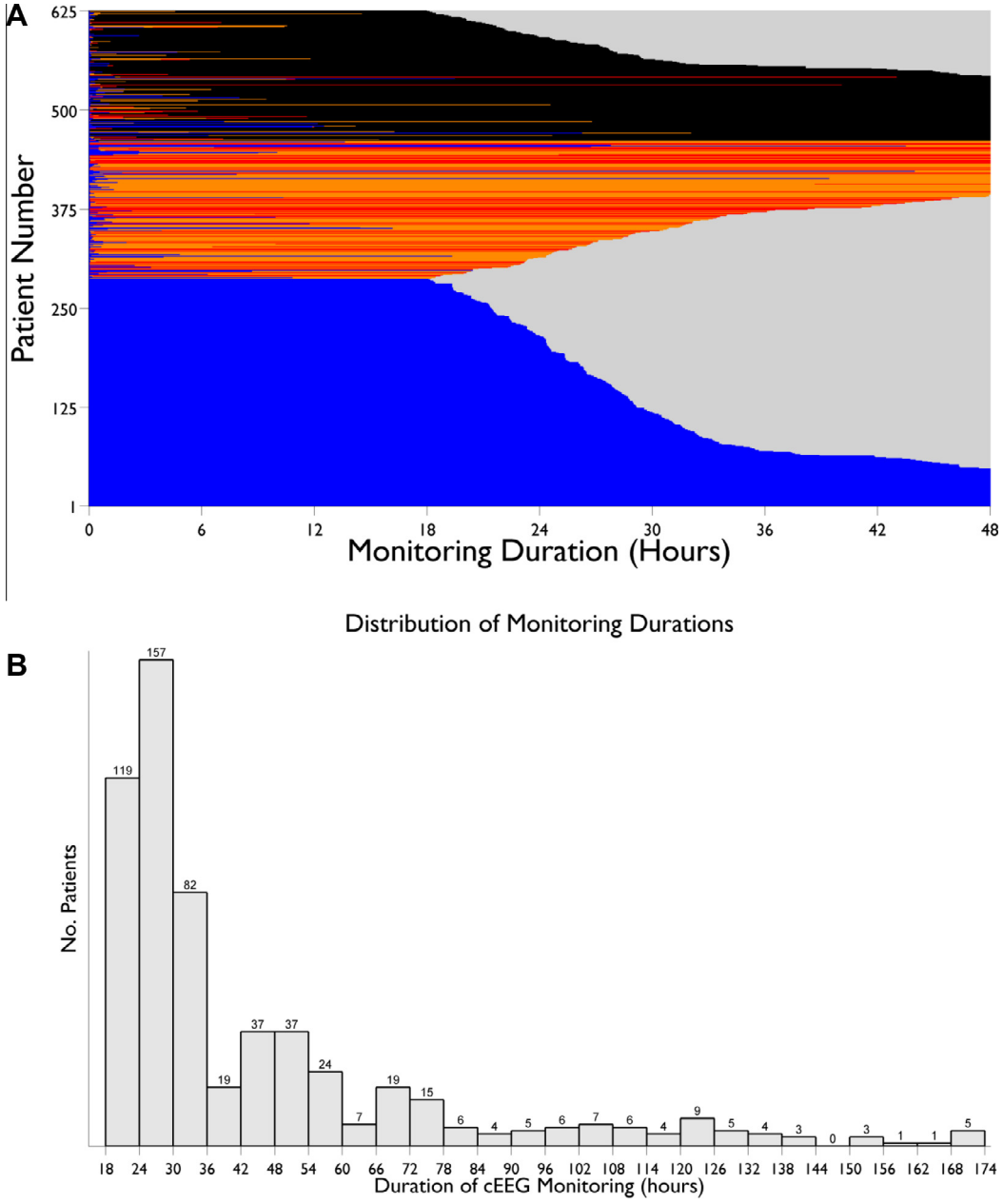

Fig. 2. Time to event plots and monitoring durations. (A) The time elapsed since beginning cEEG monitoring until detection of epileptiform abnormalities, seizures, or the end of monitoring for all 625 patients, up until 48 h; data beyond 48 h is not shown. Event lines for subjects with no epileptiform abnormalities detected so far are colored blue. The development of epileptiform discharges is indicated by line color: a change to orange indicates the appearance of spikes or sharp waves; to red, the appearance of lateralized or generalized periodic epileptiform discharges (PEDs); to black, the detection of electrographic seizures. Termination of a line into the light gray zone indicates the time that cEEG monitoring was discontinued. In the analysis, patients whose monitoring ended without having a seizure are 'right censored' at the time cEEG monitoring is discontinued, meaning that it is unknown whether or not they went on to have subsequent seizures. Note that line color encodes the category of the most severe abnormality detected so far, but does not necessarily imply that the abnormality is continuously present, i.e. lines are not permitted to change back to a "less severe" color. (B) Distribution of cEEG monitoring durations. By design, no study briefer than 18 h in duration was included. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

seizures. Among all 625 patients, within the first 30 min 368 (59%) had no abnormality or only slowing; 99 (16%) had spikes or sharp waves; 60 (10%) had PEDs; 98 (17%) had electrographic seizures.

Most abnormalities were detected early. However, moderate flux to higher risk categories continued throughout monitoring (Fig. 2, Supplementary Table 2). Of 368 patients without early epileptiform pathology, 67 (18%) later developed spikes or sharp waves, 17 (5%) developed PEDs, and 29 (8%) developed seizures. In the 99 patients with early spikes or sharp waves, PEDs were later detected in 12 (12%), and seizures in 25 (25%). Among the 60 patients with early PEDs, 16 (27%) subsequently had electrographic seizures. Thus, overall transition rates to more severe categories were 31% (113/368) from normal/slowing; 37% (37/99) from spikes/sharp waves; and 27% (16/60) from PEDs.

3.5. Seizure and epileptiform discharge accumulation curves

Seizure timing data (Fig. 1) were used to estimate cumulative distribution curves (CDFs), the expected proportion with seizures over time (Fig. 3; see Supplemental Material). Within the entire cohort, seizures initially rapidly, then after 30 min rose more slowly. The observed percentage of recordings showing seizures

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after 80 h was 27%; the final estimate (accounting for censoring due to early cEEG discontinuation) was 32% after 80 h of monitoring (Fig. 3a).

Next we subdivided patients into those with and without early epileptiform discharges, excluding patients who had experienced seizures by 30 min (Fig. 3b). Seizure percentages reached 2.7% by 4 h, increased to 3.7% by 20 h, and remained at 3.7% thereafter. In patients with early epileptiform discharges, 25% (41/159) eventually had seizures, the last seizure occurring after 79.7 h of monitoring, whereas the estimated final seizure burden corrected for censoring was 31%. Because fewer studies have very long durations (e.g. 44 h) due to censoring, late seizures have a larger impact on the estimated CDFs. Finally, we estimated the cumulative percentage of patients who initially lacked but subsequently developed epileptiform discharges (Fig. 3c). The percentage of transitions (slowing/normal → epileptiform discharges) rose to 12% by 4 h, then more slowly to 17% by 24 h, and 24% by 48 h.

3.6. Percentage of seizures with and without preceding epileptiform abnormalities

Though at lower risk, our data show that patients without early epileptiform discharges may still occasionally have seizures (Supplemental Fig. 2a, Supplemental Table 2). Delayed seizures may occur without preceding epileptiform abnormalities (slowing/normal background → seizures) or after first developing epileptiform discharges (slowing/normal background → epileptiform abnormalities → seizures). To assess the relative contributions of each pattern, we estimated hazard rate functions (instantaneous transition probabilities) (see Supplementary Material, and Supplementary Fig. 2b), and found that ~40% of subjects who develop seizures are expected to first have epileptiform discharges; ~60% will transition directly to seizures.

3.7. Future seizure probability curves

To investigate the dependence of seizure risk on EEG features, we estimated the probability that a seizure will occur within the next 72 h as a function of monitoring duration and EEG features. Separate curves were estimated for the entire cohort (Fig. 4a) and for subpopulations with and without epileptiform abnormalities (Fig. 4b; see Supplemental Material). At the beginning of monitoring the 72-h future seizure probability for entire cohort is 27%. This probability decays rapidly, dropping to 10% by 1.8 h (109 min), and thereafter more slowly, reaching 5% by 8.7 h (520 min).

Critically, segregating patients based on EEG findings enables rapid differentiation of those at high vs. low risk of seizures within the next 72 h. Initially, all patients are in the "no epileptiform discharges" category, hence the 72-h probability of seizures is that of the entire population, 27%. Over time, if the EEG remains without epileptiform abnormalities, the risk of subsequent seizures declines rapidly to 10% then 5% by 15 and 110 min (Fig. 4b). For patients with epileptiform abnormalities, the 72-h seizure risk is high immediately after the first discharge, approximately 36%. This risk decays more gradually with further uneventful monitoring, to 10% by 7 h, and 5% by 16 h (Fig. 4b). These curves demonstrate how early EEG findings determine an individual's risk of seizures, enabling monitoring tailored to a specific acutely ill patient, rather than relying solely on etiology-specific population statistics.

4. Discussion

In this retrospective study of 625 hospitalized patients who underwent continuous EEG monitoring, we found that the presence or absence of epileptiform abnormalities very early in the course of monitoring accurately stratified the risk of seizures within the subsequent 72 h. Seizures occurred in 27% (168/625), of which 58% (98/168) were detected within the first 30 min of monitoring. In patients with epileptiform discharges but no seizures during the first 30 min, 25% (41/159) subsequently had a seizure, versus only 8% (29/368) without early epileptiform discharges. Accounting for early study termination by data censoring methods, the estimated risk for seizures within the following 72 h of monitoring decays with markedly different rates depending on early EEG features. In patients with epileptiform discharges, the probability of a seizure within 72 h falls below 10% and 5% at 7 and 16 h, respectively, after the appearance of epileptiform discharges. In patients without epileptiform abnormalities, the 72-h seizure probability falls below 10% at just 15 min, then to 5% at just under 2 h. Thus, EEG findings can help delineate the need for extended cEEG monitoring, with patients lacking early epileptiform discharges being at low risk for seizures.

The overall seizure frequency in our cohort of 27% was within the 8–34% range reported in prior cEEG studies of critically ill neurological patients (Privitera et al., 1994; DeLorenzo et al., 1998; Jordan, 1999; Vespa et al., 1999; Towne et al., 2000; Claassen et al., 2004, 2007; Jette et al., 2006; Carrera et al., 2008; Abend et al., 2011) although higher than the 19% in the largest similar study (Claassen et al., 2004). Compared with prior studies, percentages of seizures ultimately detected were similar for subarachnoid hemorrhage (14% in our study vs. 4–19% in previous reports), (Sundaram and Chow, 1986; Hasan et al., 1993; Butzkueven et al., 2000; Claassen et al., 2004) intracerebral hemorrhage (16% vs. 13–28), (Jordan, 1993; Vespa et al., 1999; Claassen et al., 2004; Vespa, 2005). TBI (16% vs. 4–28), (Annegers et al., 1980; Temkin et al., 1990; Jordan, 1993; Lee et al., 1995; Vespa et al., 1999; Claassen et al., 2004; Vespa, 2005) ischemic stroke (27 vs. 6–26), (Jordan, 1993; Vespa et al., 1999; Claassen et al., 2004; Vespa, 2005) toxic-metabolic encephalopathy (17% vs. 18–60), (Jordan, 1993; Claassen et al., 2004) brain tumor (32% vs. 23–54), (Jordan, 1993; Claassen et al., 2004) CNS infection (26 vs. 29–33), (Jordan, 1993; Claassen et al., 2004; Carrera et al., 2008) post-neurosurgical status (23% vs. 4–34), (Matthew et al., 1980; Foy et al., 1981; Kvam et al., 1983; Baker et al., 1995) and altered mental status not-otherwise-specified (29% vs. 18–37) (Privitera et al., 1994; Claassen et al., 2004). We found higher frequencies of seizures in patients with hypoxic ischemic encephalopathy (HIE) (59% vs. 20–35) (Krumholz et al., 1988; Wijdicks et al., 1995; Claassen et al., 2004; Wright and Geocadin, 2006). Variability in seizure frequencies between studies may be due to differences in composition and sample sizes of study populations, cEEG ordering patterns, and criteria used to distinguish electrographic seizures from other related pathological patterns.

As reported previously by others (Claassen et al., 2004) coma was associated with a higher incidence of seizures in our cohort. However, this association was not statistically significant after excluding patients whose seizures occurred within the first 30 min of cEEG monitoring and after taking into account the presence or absence of epileptiform abnormalities within the first 30 min of cEEG observation. This suggests that when the goal of cEEG monitoring is to dynamically estimate the risk of future seizures over time, the presence or absence of spikes, sharp waves, or periodic epileptiform discharges may suffice, at least when monitoring for 24–72 h, as is currently the conventional clinical practice. An accurate determination of risk dynamics beyond 72 h would require routine extended monitoring longer than is currently done in clinical practice, or in any study to date.

Seizure frequencies within our retrospective cohort may be higher than base rate seizure frequencies within each neurologic condition included in our cohort, as cEEG monitoring was ordered by physicians on the basis of suspicion for seizures rather than in a

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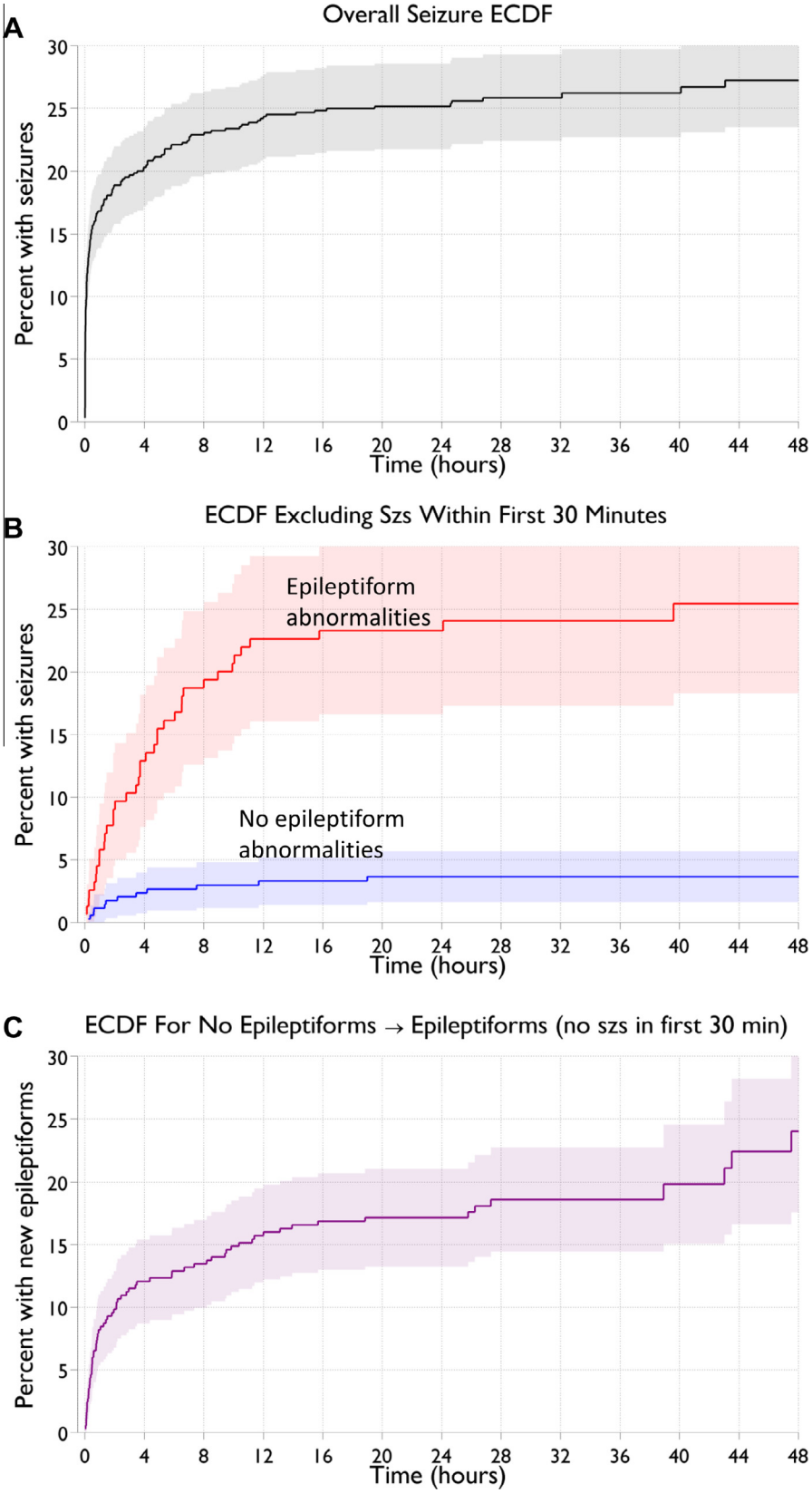

Fig. 3. Estimated cumulative distribution curves (ECDFs). Curves showing the estimated proportion of subjects at risk for developing seizures over the first 48 h of monitoring, counting from the beginning of cEEG monitoring (A), and from $t = 30$ min after dividing patients into those with and without epileptiform abnormalities (but no seizures) within the first 30 min of cEEG monitoring (B). The ECDF for developing spikes/sharps or PEDs in subjects without epileptiform discharges in the first 30 min is also shown (C). ECDFs are estimated from the data in Fig. 2 while statistically correcting for early discontinuation of some studies (data censoring).

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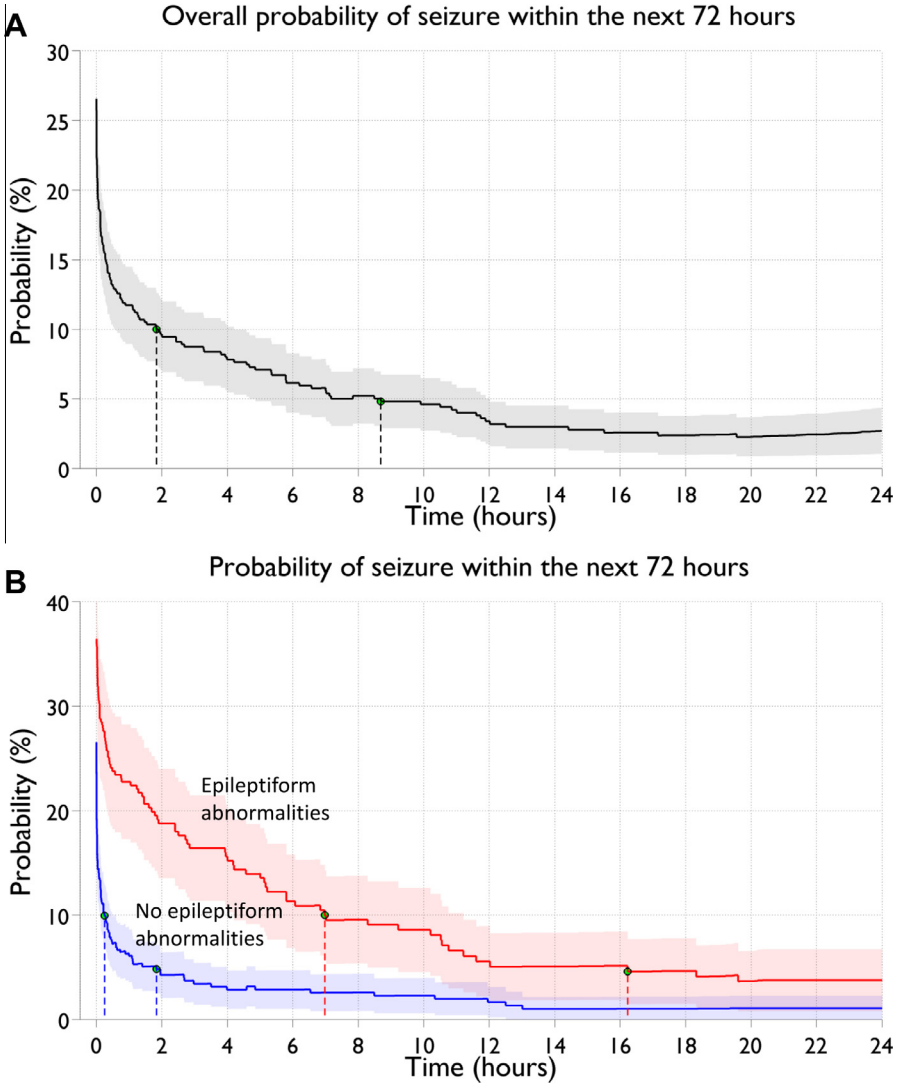

Fig. 4. Future seizure probability curves. (A) Estimated probability that a seizure will occur within the next 72 h if none have occurred so far is shown for the entire cohort, counting from $t = 0$, and (B) for subgroups with (red curve) and without (blue curve) epileptiform abnormalities after the initial 30 min of observation. Times at which the estimated 72-h seizure probability decays to 10% and 5% are marked. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

systematic prospective fashion. Such a 'selection bias' may have contributed to the high values for seizure frequency in our SDH and HIE subgroups (67% and 59%, respectively), and for the relatively high rates in those with 'nonstructural' etiologies including altered mental status (29%), and toxic metabolic encephalopathy (17%). However, these high rates, coupled with the growing recognition that nonconvulsive seizures are common and underdiagnosed in critically ill patients, suggest that the thresholds for initiating cEEG monitoring may still be too high, leading to missed opportunities for intervention (Jordan, 1993; Kaplan, 1999; Murthy, 2003; Hirsch, 2004; Vespa, 2005).

However, while the number of patients being monitored may be too low, the duration of cEEG monitoring needed to determine that a patient is at low risk for seizures remains a critical issue, particularly in institutions where cEEG monitoring remains a limited resource (Jordan, 1993; Claassen et al., 2004). The authors of the largest previous comparable study suggested that 24–48 h is sufficient to detect the majority of seizures (95% by 24 h in patients without coma; 87% by 48 h in patients with coma); however, the conclusions of that study were limited in three key ways. First, there was no analysis of the relationship between the timing of detection of EEG abnormalities and subsequent seizures (Claassen et al., 2004). While our data also suggest that prolonged monitoring may be indicated in patients with epileptiform discharges, in patients where no epileptiform abnormalities emerge within the first two hours, we find that the 72-h risk for seizures is already <5%; consequently, prolonged monitoring may not be necessary in these patients.

A second critical difference between the present study and that of Claassen et al. is the approach to data analysis (Supplemental Fig. 3). In the study by Claassen et al., the recommended duration of monitoring was based on the 110 out of 570 subjects eventually found to have seizures, by evaluating the percentage of seizures of these 110 subjects which would have been detected as a function of monitoring duration. Subjecting our data to the same "percent-of-eventual-seizures detected" analysis yields comparable results: Monitoring time required to detect >95% of patients with seizures required >48 h within the subgroup found to have early epileptiform discharges, and >72 h in subjects without early epileptiform abnormalities. This seemingly "paradoxical" finding (longer monitoring is required to detect seizures in subjects with less severe abnormalities) reflects the fact that the "percent-of-eventual-seizures detected" analysis neglects the denominator containing subjects who *did not* go on to have seizures, and thus

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provides an approximation to the probability of seizure detection vs. time *in subjects who we know a priori will eventually have seizures*. By contrast, here we have estimated the probability of *future* seizure detection in subjects for whom we do not already know the future outcome, conditional on pathological EEG features observed so far. Ultimately, when the motivation for ordering cEEG is to answer the question, "Is my patient having seizures or at risk for seizures in the near future?", the analysis techniques presented in this study appear more appropriate.

Finally, in Claassen et al.'s study, as in the present study, the duration of monitoring varied considerably (monitoring duration reported as median = 48 h for subjects without seizures and median = 108 h in subjects with seizures Claassen et al.; vs. overall median 31.29, range 18–562, SD 58 h in the present study). Accordingly, the issue of data censoring (study ending before a seizure occurs) must be carefully taken into account in estimating seizure probability versus time. Though the "percent-of-eventual-seizures detected" approach was not claimed by Claassen et al. to represent the probability of seizure occurrence versus time, the results are frequently interpreted in this way. This interpretation is statistically problematic and may lead to paradoxical conclusions, such as: If no subjects in the cohort were monitored longer than 7 days, then the "percent-of-eventual-seizures detected" approach suggests that the "probability" of seizure detection by day 7 must be 100%, an untenable conclusion.

Our results do not provide comprehensive guidance about how long individual patients must be monitored, and thus should be applied with care. Even in the low-risk subgroup of our cohort which lacked initial epileptiform abnormalities, the transition dynamics estimated from our data suggest that seizures may still occur beyond 24 or 48 h, albeit at a low rate, either directly (without first developing epileptiform abnormalities) or indirectly via transitioning first to a higher risk state (i.e. with epileptiform abnormalities). Of note, a large number of data points are available at 24, 48 and 72 h (506, 211 and 124 studies, respectively); after this point, the number of data points is relatively low. Consequently, predictions made by survival analysis methods are likely to be accurate within 72 h. By the same token, our data does not support reliable estimates of seizure risk more than 72 h after the initiation of monitoring, as the population of studies from which to draw inferences becomes smaller.

An important limitation which our analysis shares with the aforementioned study by Claassen et al. (2004) is the wide variety of neurological diagnoses included within our patient cohort. Consequently, while our results provide general guidelines for the duration of monitoring, these must be tailored to the degree of suspicion and risks of missing seizures in individual patients. As a corollary, while prolonged monitoring of lower-risk patients generally involves diminishing returns, prolonged monitoring may be warranted in specific circumstances. For example, up to 31% of patients with status epilepticus prove refractory to initial treatment, >50% of patients with refractory status epilepticus have breakthrough seizures during treatment with pharmacologically induced coma, and >50% have recurrent seizures after pharmacological coma is lifted (Claassen et al., 2001; Mayer et al., 2002). In all cases, patient-specific cost/benefit considerations informed by clinical judgment should continue to determine the duration of cEEG monitoring in individual patients. Furthermore, some etiologies may have a natural history with unique seizure risk dynamics different than that of the general population (e.g. a lower initial seizure risk but higher risk of delayed seizures in patients admitted with an acute subarachnoid hemorrhage). Further work is needed to clearly define disease-specific risk dynamics.

Our study represents the first detailed analysis of the temporal dynamics of risk for seizures during cEEG monitoring of critically ill neurological patients. Nevertheless, our study is limited by its retrospective design, limited and non-uniform duration of monitoring, and limited numbers within specific clinical and electrographic subgroups. Thus, while our results suggest that early cEEG findings allow rapid discrimination between patients at high vs. low risk for subsequent seizures, prospective disease-specific studies are needed to confirm and extend these findings, and to clarify how they can be further tailored to specific clinical scenarios.

Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clinph.2014.05.037.

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