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# Continuous Versus Routine Standardized Electroencephalogram for Outcome Prediction in Critically Ill Adults: Analysis From a Randomized Trial

**OBJECTIVES:** To investigate electroencephalogram (EEG) features' relation with mortality or functional outcome after disorder of consciousness, stratifying patients between continuous EEG and routine EEG.

**DESIGN:** Retrospective analysis of data from a randomized controlled trial.

**SETTING:** Multiple adult ICUs.

**PATIENTS:** Data from 364 adults with acute disorder of consciousness, randomized to continuous EEG (30–48 hr;  $n = 182$ ) or repeated 20-minute routine electroencephalogram ( $n = 182$ ).

**INTERVENTIONS:** None.

**MEASUREMENTS AND MAIN RESULTS:** Correlations between electrographic features and mortality and modified Rankin scale at 6 months (good 0–2) were assessed. Background continuity, higher frequency, and reactivity correlated with survival and good modified Rankin scale. Rhythmic and periodic patterns carried dual prognostic information: lateralized periodic discharges were associated with mortality and bad modified Rankin scale. Generalized rhythmic delta activity correlated with survival, good modified Rankin scale, and lower occurrence of status epilepticus. Presence of sleep-spindles and continuous EEG background was associated with good outcome in the continuous EEG subgroup. In the routine EEG group, a model combining background frequency, continuity, reactivity, sleep-spindles, and lateralized periodic discharges was associated with mortality at 70.91% (95% CI, 59.62–80.10%) positive predictive value and 63.93% (95% CI, 58.67–68.89%) negative predictive value. In the continuous EEG group, a model combining background continuity, reactivity, generalized rhythmic delta activity, and lateralized periodic discharges was associated with mortality at 84.62% (95% CI, 75.02–90.97) positive predictive value and 74.77% (95% CI, 68.50–80.16) negative predictive value.

**CONCLUSIONS:** Standardized EEG interpretation provides reliable prognostic information. Continuous EEG provides more information than routine EEG.

Disorders of consciousness (DoCs) represent a frequent cause of admission in ICUs; early neurologic prognostication is essential for management. In this context, electroencephalogram (EEG) contains relevant prognostic information (1). The American Clinical Neurophysiology Society (ACNS) provided a standardized ICU-EEG description, which allows a generalizable taxonomy and communication (2). Clinical significance and prognostic implication of some EEG patterns encountered in ICU remain in part unclear.

Continuous EEG Randomized Trial in Adults (CERTA) is a multicenter randomized controlled trial (RCT) that showed no difference in mortality in

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patients with DoC, randomized to continuous EEG (cEEG), or repeated routine EEG (rEEG) (3). Within this study population, we aimed to investigate if specific EEG features were related to mortality or functional outcome, stratifying for the interventional EEG arm.

## MATERIALS AND METHODS

### Study Design

Retrospective analysis of prospectively collected data from an RCT.

### Study Population and Clinical Variables

In the trial, approved by the ethic commission (Project-ID Commission cantonale d'éthique de la recherche sur l'être humain 2017-00268), adult patients with acute DoC (Glasgow Coma Scale  $\leq 11$  or full outline of unresponsiveness scores  $\leq 12$ ) of any etiology were randomized to one cEEG (30–48 hr) or two 20–30-minute rEEGs over 48 hours without repetition within the same day. Subjects in palliative care, with recent seizures or status epilepticus (SE), were excluded (3). Etiologies were categorized as: 1) ischemic stroke, 2) intracerebral hemorrhage (ICH), 3) brain trauma (traumatic brain injury [TBI]), 4) toxic-metabolic, 5) other systemic conditions (infection, inflammation, and neoplasia), 6) cardiac arrest (CA), and 7) unknown. Withdrawal of life-sustaining treatment was made after multimodal assessment (including EEG), reaching an interdisciplinary consensus and with close involvement of the family.

### Outcome

Mortality and the modified Rankin scale (mRS, good 0–2) at 6 months were prospectively assessed, blinded to the intervention arm.

### EEG variables

Video-EEGs were recorded using 21–23 electrodes following the international 10–20 system and prospectively interpreted by ACNS-certified readers according to the 2012 ACNS terminology (2). To account for potential variations between the two rEEGs recordings or during cEEG, we considered: 1) sleep-spindles, preserved reactivity, and rhythmic or periodic patterns (RPPs) if reported at any time; 2) the fastest

background frequency; 3) the worst background continuity; and 4) occurrence of electrographic seizures and/or SE, which were predefined (3), at any time.

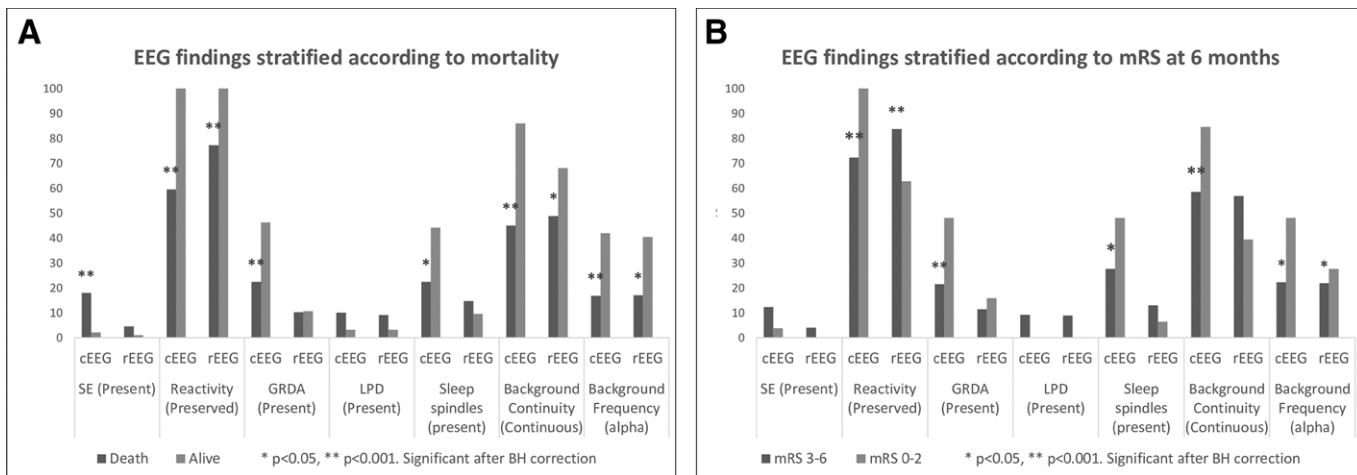
### Statistics

Correlations were evaluated using Wilcoxon, Fisher exact, and Student *t* tests, as appropriate. The Benjamini-Hochberg procedure was applied to control for false discovery rates (*q* value of 0.05). Backward stepwise logistic regression (variable removal = 0.10) was used to model EEG predictors of outcome. Model performances were assessed with the area under the receiver operating characteristics curve (AUC) and goodness of fit through the Hosmer-Lemeshow test. Moderation analyses were performed to determine if the effects of EEG variables on mortality and functional outcome were moderated by EEG duration. Conditional effects at the different values of the moderator (0 for cEEG and 1 for rEEG) were computed when the tests of highest order unconditional interactions produced *p* values below 0.1 (4). Gender and age were used as covariates. Data analysis was performed using R version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS software (version 27; SPSS, Inc., Chicago, IL).

## RESULTS

The trial included 364 patients; 182 each were randomized to cEEG and rEEG. Patients' characteristics have been previously described (3) and are summarized in **Supplemental Table 1** (<http://links.lww.com/CCM/G756>). Prevalence of cEEG did not differ across patients who died or reached mRS 3–6 at 6 months (3). Older age, SE, lateralized periodic discharges (LPDs), unreactive, slower, and non-cEEG background correlated with mortality and higher mRS, whereas continuous, alpha, reactive EEG background, and generalized rhythmic delta activity (GRDA) correlated with survival and mRS 0–2 (see **Supplemental Table 2**, <http://links.lww.com/CCM/G757>, for values). EEG outcome predictors stratified according to randomization are summarized in **Figure 1**.

Moderation analysis, regarding EEG features, is presented in **Table 1**. After correction for age and gender, sleep-spindles and EEG continuity presented a better correlation with outcome in patients undergoing cEEG.



**Figure 1.** EEG findings stratified according to mortality (A) and Modified Rankin Scale (mRS) at 6 mo (B) in the continuous EEG (cEEG) and routine EEG (rEEG) groups. *x*-axis shows outcome. *y*-axis shows patient's percentage. Patients with good outcome, defined as survival or mRS 0–2, are represented in *light gray*. Patients with poor outcome, defined as death or mRS 3–5, are represented in *dark gray*. Comparisons between outcome groups were performed using Fisher exact with BH correction for multiple comparisons. GRDA = generalized rhythmic delta activity, LPD = lateralized periodic discharge, SE = status epilepticus.

**TABLE 1.**  
**Moderation (Controlled by Age and Gender) of Electroencephalogram Findings on Outcome Prediction With Randomization Arm as Moderator**

EEG Findings	Effect of EEG Parameters; <i>p</i> , OR (95% CI)	Moderation Effect; <i>p</i> , OR (95% CI)	Conditional Effect; <i>p</i> , OR (95% CI)	
			Continuous EEG	Routine EEG
<b>Mortality at 6 mo</b>				
Seizure (present) <sup>a</sup>	0.4, 1.8 (0.5–7.1)	0.73, 0.6 (0.0–9.4)	-	-
SE (present) <sup>b</sup>	<b>0.008, 6.4 (1.6–25.2)</b>	0.63, 0.5 (0.03–7.9)	-	-
Sleep-spindles (present) <sup>c</sup>	0.39, 0.8 (0.4–1.4)	<b>0.009, 4.7 (1.5–15.3)</b>	<b>0.002, 0.4 (0.2–0.7)</b>	0.32, 1.6 (0.6–4.3)
Continuous background <sup>d</sup>	<b>&lt; 0.0001, 0.2 (0.1–0.4)</b>	<b>0.03, 3.0 (1.1–8.1)</b>	<b>&lt;0.001, 0.1 (0.06–0.3)</b>	<b>0.003, 0.4 (0.2–0.7)</b>
Discontinuous background	0.37, 1.3 (0.7–2.2)	0.37, 0.6 (0.2–1.8)	-	-
Burst suppression <sup>b</sup>	<b>0.006, 5.1 (1.9–38.7)</b>	<b>0.11, 0.2 (0.04–1.4)</b>	<b>0.003, 10.7 (2.3–50.1)</b>	0.08, 2.4 (0.89–6.54)
Suppressed background <sup>b,e</sup>	-	-	-	-
Alpha <sup>d</sup>	<b>&lt; 0.0001, 0.3 (0.2–0.5)</b>	0.76, 1.7 (0.4–3.2)	-	-
Theta <sup>b</sup>	<b>0.004, 2.0 (1.2–3.1)</b>	0.84, 0.9 (0.4–2.3)	-	-
Delta <sup>b</sup>	0.25, 2.7 (0.5–15.4)	0.70, 2.0 (0.06–61.7)	-	-
GRDA (present) <sup>d</sup>	<b>&lt; 0.0001, 0.3 (0.2–0.5)</b>	0.19, 2.7 (0.8–8.9)	-	-
LPD (present) <sup>b</sup>	0.09, 2.3 (0.9; 6.1)	0.16, 0.8 (0.1–5.3)	-	-
LRDA (present) <sup>a</sup>	0.78, 0.9 (0.4–2.1)	0.11, 5.5 (0.9–32.1)	0.12, 0.4 (0.1–1.3)	0.26, 2.1 (0.59–1.99)
GPD (present) <sup>a</sup>	0.68, 1.2 (0.6–2.4)	0.26, 0.5 (0.1–1.8)	-	-
<b>Modified Rankin Scale at 6 mo</b>				
Seizure (present) <sup>b,f</sup>	0.99, 0.001 (inf–inf)	0.99, inf (0–inf)	-	-
SE (present) <sup>b,g</sup>	0.10, 0.0005 (0–inf)	0.99, inf (0–inf)	-	-
Sleep-spindles (present) <sup>c</sup>	<b>0.26, 1.5 (0.8–2.7)</b>	<b>0.06, 2.9 (0.8–10.6)</b>	<b>0.01, 1.4 (1.2–4.1)</b>	0.58, 1.3 (0.48–3.6)

(Continued)

**TABLE 1. (Continued)****Moderation (Controlled by Age and Gender) of EEG Findings on Outcome Prediction With Randomization Arm as Moderator**

EEG Findings	Effect of EEG Parameters; <i>p</i> , OR (95% CI)	Moderation Effect; <i>p</i> , OR (95% CI)	Conditional Effect; <i>p</i> , OR (95% CI)	
			Continuous EEG	Routine EEG
Continuous background <sup>d</sup>	<b>0.002, 2.4 (1.4–4.1)</b>	<b>0.04, 3.0 (1.0–8.8)</b>	<b>0.001, 4.1 (1.8–9.7)</b>	0.97, 1.4 (0.7–2.7)
Discontinuous background	0.78, 1.1 (0.6–2.0)	0.48, 0.7 (0.2–2.2)	-	-
Burst suppression <sup>b</sup>	<b>0.04, 0.3 (0.1–0.9)</b>	0.15, 0.2 (0.02–1.8)	-	-
Suppressed background <sup>b,e</sup>	-	-	-	-
Alpha <sup>d</sup>	<b>&lt; 0.0001, 3.1 (1.9–5.2)</b>	0.70, 1.2 (0.5–3.3)	-	-
Theta <sup>b</sup>	<b>0.0005, 0.4 (0.3–0.7)</b>	0.54, 0.8 (0.3–1.9)	-	-
Delta <sup>a</sup>	0.85, 1.2 (0.2–6.9)	0.70, 2.0 (0.06–68.4)	-	-
GRDA (present) <sup>d</sup>	<b>0.0003, 2.8 (1.6–4.9)</b>	0.86, 1.1 (0.4–3.4)	-	-
LPD (present) <sup>a,f</sup>	-	-	-	-
LRDA (present) <sup>a</sup>	0.11, 0.4 (0.1–1.2)	0.71, 0.7 (0.08–5.6)	-	-
GPD (present) <sup>a</sup>	0.52, 0.8 (0.3–1.8)	0.41, 0.5 (0.09–2.7)	-	-

EEG = electroencephalogram, GPD = generalized periodic discharge, GRDA = generalized rhythmic delta activity, LPD = lateralized periodic discharge, LRDA = lateralized rhythmic delta activity, OR = odds ratio, SE = status epilepticus.

<sup>a</sup>Bad outcome predictors (death or Modified Rankin Scale [mRS]  $\geq 3$ ).

<sup>b</sup>Significant in univariate analysis of the whole population (continuous EEG [cEEG] and routine EEG [rEEG] combined) (Supplemental Table 2, <http://links.lww.com/CCM/G757>).

<sup>c</sup>Good outcome predictors (survival or mRS 0–2).

<sup>d</sup>Significant in univariate analysis of the whole population (cEEG and rEEG combined) (Supplemental Table 2, <http://links.lww.com/CCM/G757>).

<sup>e</sup>Reactivity and suppressed background were not analyzed due to complete separation of the data (no survivors with absent reactivity or suppressed EEG). LPDs were not considered for modified Rankin scale due to complete separation of the data (no patients with LPDs and good functional outcome).

<sup>f</sup>Only three patients with seizures and modified Rankin scale 0–2 at 6 mo without any patient with rEEG randomization, good functional outcome, and seizures.

<sup>g</sup>Only two patients with SE and modified Rankin scale 0.2 at 6 mo without any patient with rEEG randomization, SE, and good functional outcome.

Boldface values indicate significant results.

EEG global prognostication performances were then investigated. In the rEEG subgroup, backward elimination resulted in a model of combined variables of reactivity, sleep-spindles, LPDs, background frequency, and continuity (66.1% global accuracy, AUC 0.737, and excellent goodness of fit:  $p = 0.75$ ). Sensitivity to mortality was 46.99% (95% CI, 35.93–58.26), specificity 82.98% (95% CI, 73.84–89.95), positive predictive value 70.91% (95% CI, 59.62–80.10), and negative predictive value 63.93% (95% CI, 58.67–68.89). In the cEEG subgroup, the model resulted in background continuity, reactivity, GRDA, and LPDs (78.4% global accuracy, 0.766 AUC, and excellent goodness of fit:  $p = 0.822$ ). Sensitivity was 66.27% (95% CI, 55.05–76.28),

specificity 89.25% (95% CI, 81.11–94.72), positive predictive value 84.62% (95% CI, 75.02–90.97), and negative predictive value 74.77% (95% CI, 68.50–80.16). Prognostic performances of EEG features are presented in **Supplemental Table 3** (<http://links.lww.com/CCM/G758>).

Due to the RPPs' dual prognostic significance, we concentrated on patients with and without GRDA or LPD. In the pooled population, GRDA was negatively associated with mortality, poor functional outcome, and SE. GRDA was encountered more frequently in cEEG and younger patients, and after TBI and less frequently after CA. LPDs, conversely, were described more frequently in older patients and after ICH, and



were positively associated with mortality, poor functional outcome, seizure, and SE occurrence (see **Supplemental Table 4**, <http://links.lww.com/CCM/G759>, for values).

## DISCUSSION

Although in the CERTA trial EEG duration did not affect mortality (3), specific EEG variables showed a significantly stronger association with outcome in patients receiving cEEG. cEEG detects nonconvulsive SE and RPPs more efficiently than rEEG (1, 3, 5), but no studies addressed the influence of recording duration on prognostication. These results suggest that cEEG prognosticates more accurately than rEEG. However, even if the association between some EEG findings and outcome is moderated by EEG duration, the global prognostication ability of cEEG and rEEG remains similar (rEEG AUC = 0.74 vs cEEG AUC = 0.77). As such, rEEG recording with conversion into cEEG in unclear clinical situations could represent a reasonable option.

The prognostic role of EEG background confirms previous reports, mostly after CA or TBI (1, 6), but our data add information in other causes of DoC. This is in line with a recent study from our group (investigating the same cohort) who found that EEG could predict survival in all etiology groups (7).

RPPs provided dual prognostic information. LPDs were associated with poor outcome and ictal activity, as described earlier (8–10). GRDA correlated with good outcome and lower SE occurrence. The lack of GRDA association to seizures is known (10), but the correlation between GRDA and good outcome has not been reported. GRDA is described in numerous conditions, and favorable outcome in encephalopathy patients was reported (11, 12). The mechanism underlying GRDA and other RPPs is different. LPDs correlate with structural lesions, seizure, and worse outcome (9, 10). Periodic patterns could also mirror an active process involved in increased metabolic activity (13). These have not been reported with GRDA. They seem to be associated with more diffuse brain dysfunction that can be amenable to recovery (11, 12). GRDA good prognostic performances (89% specificity toward survival) and the preservation of the association in multivariate analyses mitigate, in our view, the possibility that this finding represents a confounder, rather than a true explanatory variable.

This study has limitations. EEGs were recorded during the acute illness, and we cannot exclude pre-morbid EEG abnormalities. There is no consensus of how mRS should be dichotomized. We choose a cutoff at greater than or equal to 3 as it was the most frequently used in the literature. As clinicians had access to EEGs reports, some self-fulfilling prophecy cannot be excluded; however, GRDA is not widely recognized as a good outcome predictor. Due to the design of the CERTA trial (3), patients with recent seizures or SE were excluded, limiting generalizability to this category of patients. One must also consider the limited sample size and the high mortality.

In conclusion, EEG features correlate with outcome in adults with DoC. This suggests that EEG could be integrated into multimodal prognostic approaches. Future prospective trials are needed to formally determine the prognostication value of EEG in DoC from any origin. As cEEG provides additional information, it should be specifically considered in unclear prognostic situations.

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