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EEG recording latency in critically ill patients: Impact on outcome. An analysis of a randomized controlled trial (CERTA)

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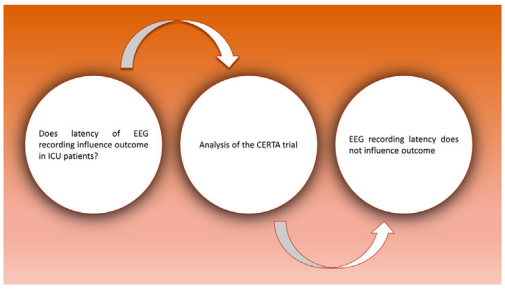
HIGHLIGHTS

- We explored if latency to EEG recordings in critically ill adults has an impact on outcome.
- No correlation was found between EEG delay and mortality or functional outcome.
- Continuous EEG increases seizure/status epilepticus detection but did not correlate with outcome.

GRAPHICAL ABSTRACT



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ABSTRACT

Objective: To assess, in adults with acute consciousness impairment, the impact of latency between hospital admission and EEG recording start, and their outcome.
Methods: We reviewed data of the CERTA trial (NCT03129438) and explored correlations between EEG recording latency and mortality, Cerebral Performance Categories (CPC), and modified Rankin Scale (mRS) at 6 months, considering other variables, using uni- and multivariable analyses.
Results: In univariable analysis of 364 adults, median latency between admission and EEG recordings was comparable between surviving (61.1 h; IQR: 24.3–137.7) and deceased patients (57.5 h; IQR: 22.3–141.1); p = 0.727. This did not change after adjusting for potential confounders, such as lower Glasgow Coma Score on enrolment (p < 0.001) and seizure or status epilepticus detection (p < 0.001). There was neither any correlation between EEG latency and mRS (rho 0.087, p 0.236), nor with CPC (rho = 0.027, p = 0.603).
Conclusion: This analysis shows no correlation between delays of EEG recordings and mortality or functional outcomes at 6 months in critically ill adults.
Significance: These findings might suggest that in critically ill adults mortality correlates with underlying brain injury rather than EEG delay.

Abbreviations: ACNS, American Clinical Neurophysiology Society; cEEG, continuous electroencephalogram; CERTA, Continuous EEG Randomized Trial in Adults; CPC, Cerebral Performance Category; EEG, electroencephalogram; FOUR, Full Outline Of Unresponsiveness; GCS, Glasgow Coma Scale; GPDs, generalized periodic discharges; GRDA, generalized rhythmic delta activity; IQR, interquartile range; LPDs, lateralized periodic discharges; LRDA, lateralized rhythmic delta activity; mRS, modified Rankin Score; rEEG, routine electroencephalogram; SE, status epilepticus.

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1. Introduction

Consciousness impairment represents a frequent cause of admission in Intensive Care Units. In this setting, electroencephalography (EEG) is essential to evaluate brain function, mostly to uncover nonconvulsive seizure activity, and to assist in neurological prognostication (Claassen et al., 2004; Cronberg et al., 2020; Friedman et al., 2009; Sutter et al., 2013); its use, particularly in continuous EEG (cEEG), is steadily increasing (Hill et al., 2019; Ney et al., 2013). Several international guidelines recommend cEEG recordings (Claassen et al., 2013; Herman et al., 2015); nevertheless, it is more time- and resource-consuming than routine EEG (rEEG, typically lasting 20 min (Hill et al., 2019; Urbano et al., 2021)) and many centers outside North America still could not implement it in large scale, lacking resources for a 24 h, 7 days a week continuous EEG surveillance (Hilkman et al., 2018; Rossetti et al., 2018).

A recent multicenter randomized controlled trial (Continuous EEG Randomized Trial in Adults (CERTA); NCT03129438) assessed the relationship of cEEG versus repeated rEEG to clinical outcome in critically ill adults with acutely impaired consciousness (Rossetti et al., 2020); there was no difference between groups regarding mortality and functional status at 6 months. Nevertheless, it has been demonstrated that cEEG recorded up to 48–72 h increases detection of seizures or status epilepticus (SE) compared to rEEG (Claassen et al., 2004; Rossetti et al., 2020), allowing an estimation of the seizure burden (De Marchis et al., 2016; Payne et al., 2014), and a reliable prediction of the risk of their occurrence (Rodriguez Ruiz et al., 2017; Struck et al., 2020). Furthermore, specific EEG features assessed following the American Clinical Neurophysiology Society (ACNS) recommendations (Hirsch et al., 2021; Hirsch et al., 2013), such as sporadic epileptiform discharges, and elements of the ictal-interictal continuum (lateralized rhythmic delta activity (LRDA), generalized periodic discharges (GPDs), lateralized periodic discharges (LPDs)), are significantly associated with clinical outcome (Muller et al., 2020). Again, this relationship seems particularly strong in patients undergoing cEEG, which thus appears more efficient than rEEG regarding prognostic information (Beuchat et al., 2021; Vassallo et al., 2021).

It is still unclear, however, whether the delay between hospital admission and EEG recording start may play an impact on clinical outcome (Gaspard et al., 2021): it may be postulated that earlier recognition of seizures/SE may be more favorable in terms of prognosis. To our knowledge, this relevant issue has received little attention to date. Hence, we evaluated whether latency between admission or trial randomization and EEG have a relationship with outcome. Additionally, we investigated if the time of the day (i.e. working hours versus off- hours) of seizures or SE detection was related to mortality.

2. Methods

2.1. Study population, clinical variables, and outcome

We reviewed prospectively acquired data of the CERTA study, a multicenter randomized clinical trial conducted in four large Swiss hospitals; its methodological background (Rossetti et al., 2018) and its protocol (Rossetti et al., 2020), have been published elsewhere. This study was approved by the ethic committee of each participating center (leader: Commission cantonale d'éthique de la recherche sur l'être humain 2017-00268). Recruited patients (or their proxy or guardians) gave their written informed consent, details have been published elsewhere (Guinchard et al., 2021).

Briefly, 364 adults with acute consciousness impairment (defined as Glasgow Coma Scale (GCS) $\leq$ 11 or Full Outline Of Unresponsiveness score (FOUR) $\leq$ 12) were randomized to one cEEG (30–48 h) or two rEEGs (20–30 min each, repeated within the same timeframe) (Rossetti et al., 2018) when EEG was requested by treating physicians. Patients in palliative care, with recent seizures (within 36 h) or SE (within 96 h before randomization), were not enrolled. EEG interpretation, performed according to the ACNS recommendations (Hirsch et al., 2013), had to be communicated to the treating teams at least 3 times a day during working days, and 2 times a day during holidays and week-ends, without routine overnight coverage (Rossetti et al., 2018). Mortality and functional status (modified Rankin Score, mRS; or Cerebral Performance Categories, CPC) were prospectively collected at 6 months, blinded for the EEG intervention (Rossetti et al., 2018).

For the present study, we retrieved information about latency between hospital admission, study randomization (which per protocol had to occur quickly after treating clinicians set the indication to EEG recording (Rossetti et al., 2020)) and recording initiation. Both timings were considered, as in some situations EEG indications may be delayed from hospital admission, such as e.g. in patients with sepsis developing at the hospital or brain tumors suffering from complications (Rossetti et al., 2021). We considered mortality as the primary outcome, and mRS and CPC at 6 months as secondary outcomes. We assessed several demographical and clinical variables: demographics, GCS, mRS before admission, randomization to cEEG, latency between admission and EEG start, latency between randomization and EEG start, history of previous seizures, main reason for admission (anoxic-ischemic encephalopathy, intracranial hemorrhage, brain trauma, and other, such as ischemic stroke, infections, neoplasia). We also considered occurrence of sporadic epileptiform discharges, elements of the ictal-interictal continuum (GPDs, LPDs, LRDA), generalized rhythmic delta activity (GRDA), and detection of seizures or SE during EEG intervention. Data included the latency of EEG recording start from admission and study randomization of the whole cohort and of the subgroup of patients with seizure detection, and if seizures /SE occurred during working hours (i.e. weekdays from 8 am to 6 pm, during which a nearly continuous surveillance was performed) or not.

2.2. Statistics

Comparisons were assessed using Mann-Whitney U, 2-sided Fisher or chi-square tests, as appropriate. Spearman's rank coefficients were applied to evaluate correlations between EEG delay, EEG duration, and mRS and CPC at 6 months. Tests with p-value $\leq$ 0.05 were considered statistically significant. A multivariate logistic regression was applied to identify independent variables related to mortality, focusing on EEG recording delay, adjusted for statistically significant variables in univariate analyses; goodness of fit was assessed through a Hosmer-Lemeshow test. We also analyzed the relationship between mortality and seizures/SE detection during office or off-hours. Calculations were made using Stata, version 17 (College Station, TX).

3. Results

We analyzed 364 critically ill adults with consciousness impairment, of whom 182 underwent cEEG and 182 rEEG (Rossetti et al., 2020). There were 123 (33.8%) women, with a mean age of 63.8 years (standard deviation [SD] ± 15.0); 177 (48.6%) patients died. Table 1 illustrates the distribution of demographical, clinical and electroencephalographic variables, stratified according to survivorship. The main clinical diagnoses were anoxic-ischemic encephalopathy (68 deaths, 38.4%), intracranial hemorrhage (38 deaths, 21.5%) and brain trauma (15 deaths, 8.5%).

Table 1
Mortality at 6 months stratified for variables of interest. Values represent numbers (and percentages), or medians (and interquartile ranges). Bold numbers are significant.

	Survival (187; 51.4%)	**Mortality** (177; 48.6%)	**p-value**	**test**
Female Gender	61 (32.6%)	62(35%)	0.627	Pearson chi2
mRS before admission	1 (IQR: 0–2)	1 (IQR: 0–2)	0.093	Mann-Whitney U-test
GCS on randomization	3 (IQR: 3–7)	3 (IQR: 3–5)	**<0.001**	Mann-Whitney U-test
Randomization to cEEG	93 (49.7%)	89 (50.3%)	0.916	Pearson chi2
Latency between hospital admission and EEG start [h]	61.1 (IQR: 24.3–137.7)	57.45 (IQR: 22.3–141.1)	0.727	Mann-Whitney U-test
Latency between randomization and EEG start [h]	1.4 (IQR: 1–2.5)	1.5 (IQR: 0.9–2.4)	0.777	Mann-Whitney U-test
History of previous epileptic seizures*	19 (10.2%)	15 (8.5%)	0.581	Pearson chi2
Anoxic-ischemic encephalopathy	44 (23.5%)	68 (38.4%)	**0.002**	Pearson chi2
Intracranial hemorrhage	47 (25.1%)	38 (21.5%)	0.409	Pearson chi2
Brain trauma	33 (17.6%)	15 (8.5%)	**0.010**	Pearson chi2
Other diagnoses**	95 (50.8%)	77 (43.5%)	0.163	Pearson chi2
Detection of seizures or SE	7 (3.7%)	30 (16.9%)	**<0.001**	Pearson Chi2
Latency between admission and first seizure or SE detection [h]	66.6 (IQR: 38.6–97.4)	42.9 (IQR: 17.1–76.6)	0.415	Mann-Whitney U-test
Sporadic epileptiform discharges	72 (38.5%)	74 (41.8%)	0.520	Pearson Chi2
Ictal-interictal continuum (GPDs, LPDs, LRDA)	37 (19.8%)	48 (27.1%)	0.098	Pearson Chi2
GRDA	63 (33.7%)	19 (10.7%)	**<0.001**	Pearson Chi2

cEEG = continuous electroencephalography, CHUV = Centre Hospitalier Universitaire Vaudois, GCS = Glasgow Coma Scale, GPDs = generalized periodic discharges, GRDA = generalized rhythmic delta activity, [h] = hours, LPDs = lateralized periodic discharges, LRDA = lateralized rhythmic delta activity, mRS = modified Rankin Scale, SE = status epilepticus.

* before 36 h (seizures), 96 h (Status epilepticus) preceding randomization.

** ischemic stroke, other systemic conditions (infection, inflammation, and neoplasia), and unknown.

Patients who died had lower Glasgow Coma Scale (GCS) on admission, higher prevalence of anoxic-ischemic encephalopathy and seizures/SE detection. More precisely, brain trauma, intracranial hemorrhage, and other diagnoses -with the exception of anoxic-ischemic encephalopathy- were not associated with mortality. Only presence of seizures/SE on EEG was associated with mortality, but not GPDs, LPDs, LRDA, sporadic epileptiform discharges or GRDA occurrence.

There was no significant difference across groups regarding latencies to EEG recordings. The delay between study randomization to recording start fully complies with the study protocol (within 4 h of randomization) (Rossetti et al., 2020). In order to assess the impact of the different variables of interest on mortality, we conducted a multivariable logistic regression, exploring EEG delay from admission adjusted for statistically significant variables in univariable analyses (Table 2). Delay to EEG recording remained not correlated to mortality, while lower GCS, and seizures/SE detection were independently related to it (with an excellent goodness of fit: p = 0.404, Hosmer-Lemeshow). Of note, presence of brain trauma and GRDA was not associated with higher risk of mortality.

Correlations between EEG latency and randomization arm (cEEG or rEEG), mRS or CPC at 6 months (Table 3) were also not significant.

In addition, we analyzed the subgroup of patients with seizures or SE detected in the two EEG intervention arms: median delay between admission and EEG recording seemed somewhat shorter in patients who died (20.3 h; IQR: 17–71.8), than the ones who survived (60.3 h; IQR: 38.5–97.3). Nevertheless, this difference was not statistically significant (p = 0.215, U-test). Correlations between EEG latency and mRS (rho −0.721, p = 0.068, Spearman) or CPC (rho −0.198, p = 0.240, Spearman) at 6 months were also not significant. In these patients, there were 33 seizures /SE detections during office hours (26 deaths, 78%), and 4 during off-hours (4 deaths, 100%); the difference was not statistically significant (p = 0.570, Fisher). Furthermore, out of 182 patients who underwent rEEG, 8 were detected with seizures or SE, of whom 7 during the first rEEG and 1 during the second one.

Table 2
Multivariable logistic regression for mortality, exploring EEG delay from hospital admission. Bold values are significant.

	OR	**p-value**	**95% CI**
Latency between admission and EEG start	1	0.323	0.99–1
GCS score	0.82	**<0.001**	0.73–0.92
Anoxic-inschemic encephalopathy	1.16	0.57	0.69–1.95
Brain trauma	0.45	**0.037**	0.21–0.95
Detection of seizure or SE	5.34	**<0.001**	2.16–13.23
GRDA	0.3	**<0.001**	0.16–0.54

EEG = electroencephalography, GCS = Glasgow Coma Scale, SE = status epilepticus, GRDA = generalized rhythmic delta activity.

Table 3
Spearman's correlations between EEG delay from hospital admission, interventional EEG length and functional outcome.

	Rho	**p-value**
EEG duration [min]	0.05	0.345
Delta mRS at 6 months	0.087	0.236
CPC at 6 months	0.027	0.603

EEG = electroencephalography, [min] = minutes, mRS = modified Rankin Score, CPC = cerebral performance category.

4. Discussion

In this analysis of critically ill adults with acutely reduced consciousness, we did not identify any significant impact of latency between admission (or randomization, a surrogate of the timing for EEG request) and EEG recording start, whether on mortality or functional outcomes. Additionally, time of seizures /SE detection did not seem to play a major role in terms of clinical outcome.

EEG is essential to diagnose mostly nonconvulsive seizures /SE, which occur in a substantial proportion of patients with consciousness impairment (Sutter, 2016). However, these results seem to suggest that its delay does not influence clinical patient management (e.g., introduction, change or interruption of anti-seizure medications or sedation, performance of brain imaging) to the point that it may exert a measurable impact on patients' mortality or functional outcome. Rather, mortality independently correlates with known factors related to underlying brain injury (Brenner, 2002) such as depth of consciousness impairment, underlying etiology, seizures/SE detection, or lack of GRDA occurrence (which was recently shown in this dataset to correlate with better prognosis) (Beuchat et al., 2021). In these patients' setting, the biological background seems actually more determinant for prognosis than seizures/SE, which in turn may reflect, at least in part, a marker

of severity of brain injury that is not always modifiable with antiseizure drugs (Bauer and Trinka, 2010). All patients with seizures/SE indeed received treatment according to current standards (Rossetti et al., 2020); while the study was not designed to answer to the question, it seems highly unlikely that antiseizure treatment may have triggered directly a worse prognosis. The lack of a clear relationship between mortality and the time of the day when seizures or SE were detected (office hour versus off-hours, when seizure management can be delayed) seems to further support the assumption that seizures/SE rather represent a hallmark of underlying severity.

The previous findings should be put into the context of seizures/SE occurrence. Although in the rEEG arm the majority of seizures and SE were detected during the first recording, suggesting that these events appeared early, the sensitivity of rEEG to seizures/SE detection has been repetitively demonstrated to be clearly lower than cEEG (Claassen et al., 2004; Limotai et al., 2019; Rossetti et al., 2020; Singh et al., 2019). In addition, cEEG offers additional prognostic information compared to rEEG (Beuchat et al., 2021; Vassallo et al., 2021). Recording latencies in the subgroup of patients with seizures/SE who subsequently died was non-significantly shorter; this may suggest that these participants had a profile that tended to trigger earlier EEG recordings, but they died despite receiving somewhat earlier treatment. Again, in our opinion this should not suggest that earlier seizure detection and treatment in causally related to worse prognosis, but that these conditions may reflect more severe underlying conditions.

One of the study strengths is that functional outcome and mortality were assessed at 6 months, thus representing a robust outcome. Also, all data, including EEG features, were carefully and prospectively acquired during the CERTA study using standardized, pre-defined measures (internal validity), and generalization to other clinical cohorts seems applicable, as the rate of seizures/SE detection in the cEEG arm is very similar to previous estimations (Alvarez et al., 2017; Limotai et al., 2019). These results should, however, be interpreted in light of some limitations. The relatively limited sample size might reduce statistical power, especially regarding EEG findings in the rEEG group; indeed the main goal of the CERTA study was to assess an outcome difference across EEG intervention groups, while this analysis was performed post-hoc. Seizures/SE treatment by the clinical staff occurred according to local practice (Rossetti et al., 2020), which was uniform across centers but not standardized, reflecting the pragmatic nature of the trial. There was no 24/7 surveillance of patients undergoing cEEG nor rEEG, therefore no control group to compare the present results is available. Finally, we do not have data on risk of long-term seizures/SE development (Gaspard et al., 2021), which represents a relevant clinical outcome.

5. Conclusion

This post-hoc analysis of a randomized trial shows no correlation between delays of EEG recordings and mortality or functional outcomes at 6 months in critical ill adults needing EEG for their clinical situation. Furthermore, in this clinical setting, timing of occurrence of seizures/SE does not seem to have an impact on prognosis. This might suggest that several EEG features represent, at least at times, markers of the underlying brain damage rather than modifiable risk factors.

CRediT authorship contribution statement

Andrea O.Rossetti: Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing.

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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.

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