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ORIGINAL ARTICLE

# Prognostic value of post-acute EEG in severe disorders of consciousness, using American Clinical Neurophysiology Society terminology

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**Summary**
*Objective.* — To evaluate whether electroencephalographic (EEG) features recorded during the post-acute stage in patients with severe disorders of consciousness (DoC) after acute brain injury (ABI), contribute to neurological outcome prediction of these patients at discharge from the intensive rehabilitation unit (IRU).
*Methods.* — We retrospectively evaluated all patients consecutively admitted to the IRU from August 2012 to December 2016. Inclusion criteria were: 1) age > 18years, 2) patients with unresponsive wakefulness syndrome (UWS) or in a minimally conscious state (MCS), and 3) EEG and a coma recovery scale-revised (CRS-R) score available within the first week after admission.

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Clinical evaluation was performed using the Italian version of the CRS-R score. EEGs were classified according to American Clinical Neurophysiology Society (ACNS) terminology. Clinical state at final discharge was evaluated using the CRS-R score.
*Results*. — In total, 102 patients were included in the analysis. After a mean of five months of IRU stay, among the 61 UWS subjects, 19 transitioned to MCS and 11 recovered to exit-MCS (E-MCS); twenty-three of the 41 subjects in MCS progressed to E-MCS. Using logistic regression, consciousness level (UWS/MCS-OR = 13.4), CRS-R score at admission (OR = 1.33) and use of activating drugs (OR = 4.7) were significant predictors of clinical improvement. Multivariable analysis showed that specific EEG patterns were independent predictors of improved consciousness at discharge in UWS patients.
*Discussion*. — EEG performed within the first week after IRU admission, classified according to ACNS-terminology in patients with UWS at admission, can provide useful prognostic contribution.


## Introduction

Acquired brain injuries (ABI) of different etiologies are common causes of morbidity and mortality [7,16,20,22,23,27,45—47]. Improvement in neurosurgical procedures and intensive care technology has decreased mortality rates [10]; however, it has increased the number of survivors developing severe disorder of consciousness (DoC) or severe/persistent disability [41]. In fact, after coma, patients often show unresponsive wakefulness syndrome (UWS) or a minimally conscious state (MCS) that can transition to an emergence from the MCS (exit-MCS, E-MCS) or to full recovery of consciousness only in some cases. Thus, both accurate classification of the patient's consciousness level and reliable neurological outcome prognosis are important goals during the entire observation period: not only at an early stage during the coma but also when patients have already been admitted to the Intensive Rehabilitation Unit (IRU). The evolution of the consciousness state has high inter-individual variability, depending on clinical data and investigation findings [17,21,25,30,32,37,55,56]. For this reason, late neurological outcome predictor evaluation is of great value, although only a few studies have examined this topic, using the Coma Recovery Scale-Revised (CRS-R) [41,42] or electroencephalogram (EEG) [4,9,29,34,35,44] as possible predictors of DoC improvement. However, these studies showed some limitations, mainly related to the use of only one parameter at a time. For this reason, in line with the paper by Kotchoubey and Pavlov [31], who highlighted the need for a comparison between the predictive values of auxiliary variables (i.e. the neurophysiological tests) and that of the clinical variables, we evaluated whether the use of both clinical features and EEG in a population with severe DoC after ABI could improve the neurological outcome prediction at discharge from the IRU. We also evaluated whether the American Clinical Neurophysiology Society (ACNS) EEG terminology [24] could be extended from Intensive Care Unit (ICU) to a post-acute context, and not only to patients affected by hypoxic-ischemic encephalopathy (HIE) but also by all of the etiologies of ABI, identifying specific EEG descriptors associated with different prognostic categories.

## Methods

### Participants and procedures

We retrospectively evaluated all patients admitted to the IRU from August 2012 to December 2016. The sample of patients screened in the present study partly overlapped that of a previous one [41]. Retrospective analysis of the database, in which patient data were entered, was approved by the local ethics committee via a waiver of the requirement to obtain informed consent for a minimal risk study. The inclusion criteria were:

- age > 18years;
- presence of one or more of the following etiologies of ABI: HIE, traumatic brain injury (TBI), intracerebral hemorrhage (ICH), subarachnoid hemorrhage or brain infarction;
- presence of UWS or MCS on admission;
- time post-onset < 3months;
- no previous neurodegenerative or psychiatric diseases;
- CRS-R evaluation performed within the first week after admission and at discharge from the IRU;
- EEG performed within the first week after admission.

Definitions of UWS and MCS were based on the CRS-R items, according to the Aspen criteria [50]. Within one week after admission, all patients were assessed using the Italian version of the CRS-R [18,36] by trained and experienced examiners (neurologists/speech therapists). CRS-R was usually performed in the morning, between 10am and 12 noon [14], with patient lying in the bed, but with head and trunk elevated in order to increase alertness and avoid sleepiness. The evaluation was performed in the absence of drug sedation: CRS-R was performed at least ten hours after the administration of drugs acting on the central nervous system, such as myorelaxant and sedative drugs (i.e. benzodiazepines and neuroleptics), in the absence of intercurrent medical conditions, such as fever or metabolic disorders, which could affect patient arousal, and in the absence of environmental interferences. Long-term antiepileptic treatment was not discontinued. The total CRS-R

score was recorded, and CRS-R evaluation was performed at least three times in a week in order to confirm patients' clinical diagnosis [54] and to determine the best CRS-R total score.

Standard 30-min EEG recordings were performed using a digital machine and an EEG prewired head-cap, with 19 electrodes (Fp1-Fp2-F7-F8-F3-F4-C3-C4-T3-T4-P3-P4-T5-T6-O1-O2-Fz-Cz-Pz) positioned according to the 10-20 International-Standard-System. Recordings were acquired with a sampling rate of 128 Hz. During review, digital filters (low-pass filter = 30 to 70 Hz; time constant = 0.1 or 0.3 sec; notch filter = 50 Hz) and sensitivity gain (2 to 10 $\mu$V/mm with a standard gain of 7 $\mu$V/mm) were adjusted according to interpretation needs. Electroencephalographic (EEG) recordings were performed in similar conditions to those reported above for CRS-R evaluation. Anonymized EEG recordings were classified, according to ACNS terminology [24] by two expert neurophysiologists, who were different from the physicians who conducted the clinical evaluation, and who were blinded to the initial and final CRS-R scores. The EEG descriptors taken into account were as follows: continuity, voltage, frequency, symmetry, reorganisation of an anterior-posterior gradient of the background activity, presence of reactivity and of spontaneous variability of the background activity, presence of epileptic discharges and of detectable EEG stage II sleep transient patterns. For further details of EEG description, see Hirsch et al. [24] and the Supplementary Materials.

During IRU stay, a personalized multidisciplinary rehabilitation program, planned according to patient needs (one-two hours/day, six days/week), and pharmacologic management [i.e. administration of ''awakening'' drugs/antiepileptic drugs (see supplementary materials)] were performed independently of both CRS-R and EEG findings.

According to the CRS-R score, performed at discharge, patients were classified as being UWS, MCS or E-MCS. Patients who showed UWS or MCS both at admission and at discharge from the IRU (UWS-UWS and MCS-MCS) were considered to be subjects with no improvement in their consciousness level. Patients transitioning from UWS to MCS (UWS-MCS) or to E-MCS (UWS-E-MCS) and from MCS to E-MCS (MCS-E-MCS) were considered to be subjects with an improvement in consciousness level. In an additional analysis, we considered all patients in E-MCS at discharge from IRU, independent of the clinical state at admission (UWS or MCS), to be clinically improved.

## Statistical analysis

The outcome measure was the clinical transition at the final discharge. The distribution of baseline characteristics was tested with Shapiro—Wilk test and non-parametric data were reported as medians and inter-quartile ranges (IQR). Categorical data were reported as frequencies (percentages). Univariate Pearson's $\chi^2$ test, Kruskal—Wallis test or Mann—Whitney U test were used for comparisons, as appropriate. The post-hoc analysis of the CRS-R results between groups was performed with the Mann—Whitney U test. Outcome predictor variables were further evaluated with multivariable logistic or linear regression models to predict clinical improvement. The regression model included sex, age, etiology, number of days post-onset, admission CRS-R score, the use of activating drugs and length of stay in IRU as covariates. The EEG results were added to these models as additional covariates. Clinical status, UWS and MCS were considered collectively and separated as different starting points. To test for the models' goodness-of-fit, we used the Hosmer—Lemeshow test for logistic regression models (UWS) and inspections of multi-collinearity, standardized residual plots and the variance inflation factor for linear regression models (MCS). Using a $2 \times 2$ table for each EEG descriptor we calculated sensitivity, specificity and the likelihood-ratio (LR) with 95% confidence intervals. Analyses were performed using Wizard for Mac and SPSS 24.0 software, running on Mac.

## Results

Among the 215 patients identified, 102 were included in the analysis (Fig. 1) and their demographic and clinical characteristics are reported in Table 1. As reported in Table 1, about 40% of patients classified as UWS at admission were affected by HIE and about 50% of the total sample of patients, independently from the clinical state (UWS or MCS) at admission to the IRU, were treated with antiepileptic drugs. During the IRU stay, 18 patients (7 in UWS and 11 in MCS at admission) were treated with activating drugs.

After a mean of five months in the IRU, among the 61 subjects in UWS at admission, 19 transitioned to MCS and 11 recovered to E-MCS, whereas 23 of 41 subjects in MCS at admission progressed to E-MCS. One of the 19 UWS patients who transitioned to MCS died one month after the clinical improvement because of septic shock.

In a univariate logistic regression, based on clinical features, in all cases (Table 2), the occurrence of improvement was related to the consciousness level at admission (MCS vs. UWS, odds ratio = 13.4, $P < 0.009$), to the CRS-R score (odds ratio = 1.33, $P < 0.003$), and to the use of activating drugs (odds ratio = 4.7, $P < 0.003$), whereas there were no differences in terms of age, sex, etiology, time post-onset, length of stay in IRU and use of antiepileptic drugs.

Given the initial clinical state and the extent of clinical improvement, we identified five groups of patients, as described in the outcome assessment. The univariate analysis showed that age, sex, ABI etiology, time post-onset, length of stay in IRU, and use of antiepileptic drugs were not predictors of clinical improvement (Table 3). The use of activating drugs, even if present in only 18 patients, showed a significantly different distribution in the five groups. Again, the CRS-R score at admission predicted an improvement in consciousness level: higher CRS-R scores were related to better neurological outcomes at discharge and nested in the occurrence of MCS. Therefore, we analysed EEG descriptors through both univariate and multivariable analysis, including the initial CRS-R score and the other clinical features as covariates, but distinctly in UWS and MCS. The separation of the results between UWS and MCS cases showed a clear difference in the results between these groups. According to both univariate and multivariable analysis, in UWS subjects (Table 4) a higher EEG frequency (alpha), the presence of reactivity and of spontaneous variability of the

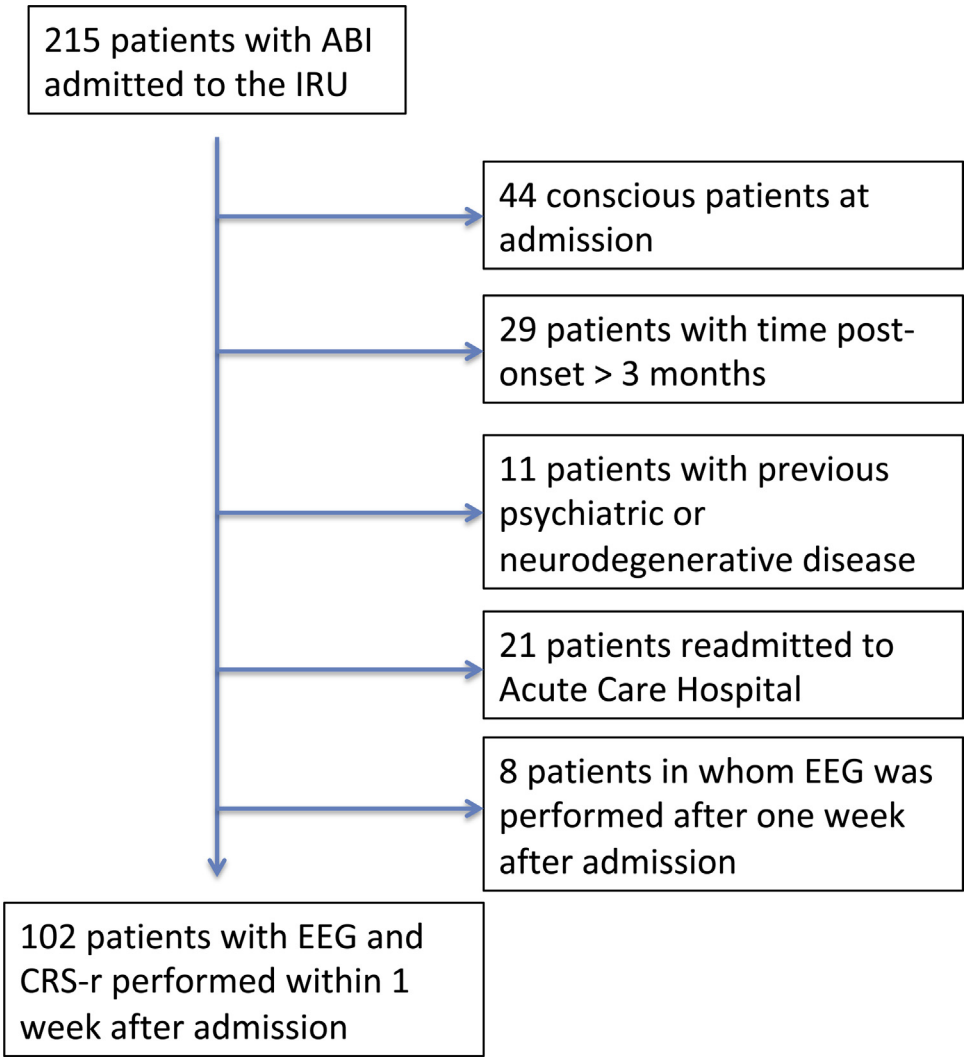


**Figure 1** Flow-chart. ABI: Acquired Brain Injuries; IRU: Intensive Rehabilitation Unit; CRS-R: Coma Recovery Scale-Revised.

**Table 1** Characteristics of the study sample at admission.

| | Total sample $n = 102$ | UWS $n = 61$ | MCS $n = 41$ | $P$ |
|---|---|---|---|---|
| Age at brain injury | | | | 0.93[a] |
| Median (IQR), years | 55.5(15.2) | 53.1(14.1) | 56.2(15.9) | |
| Sex, *n* (%) | | | | 0.76[b] |
| Women | 43 (42) | 20 (33) | 23 (56) | |
| Men | 59 (58) | 41 (67) | 18 (44) | |
| Etiology, *n* (%) | | | | 0.001[b] |
| Traumatic | 30 (29) | 18 (29) | 12 (29) | |
| Anoxic | 31 (30) | 26 (43) | 5 (13) | |
| Vascular/other | 41 (41) | 17 (28) | 24 (58) | |
| Time post-onset | | | | 0.62[a] |
| Median (IQR), days | 56 (20) | 58 (21) | 54 (19) | |
| AED *n* (%) | 51 (50%) | 31 (50%) | 20 (48%) | |

UWS: Unresponsive Wakefulness Syndrome; MCS: Minimally Conscious State; IQR: Inter Quartile Range; AED: Antiepileptic drugs.
[a] Mann–Whitney test.
[b] $Chi^2$ test.

**Table 2** Logistic regression results of improvement according to clinical characteristic.

| Variable | Odds ratio | Std error | z-score | *P* |
|---|---|---|---|---|
| Age at brain injury | 1.003 | 0.014 | 0.05 | 0.95 |
| Sex | 1.65 | 0.77 | 1.07 | 0.28 |
| Etiology | 1.12 | 0.32 | 1.07 | 0.28 |
| Time post-onset | 1.03 | 0.07 | 0.44 | 0.68 |
| CRS-R at admission | 1.33 | 0.13 | 2.93 | < 0.03 |
| Clinical State at admission UWS vs. MCS | 13.44 | 13.4 | 2.59 | < 0.01 |
| Length of IRU stay | 1.57 | 0.53 | 1.90 | 0.25 |
| Antiepileptic drugs | 0.52 | 0.25 | − 1.35 | 0.17 |
| Activating drugs | 4.7 | 3.41 | 2.14 | 0.003 |

CRS-R: Coma Recovery Scale-Revised; UWS: Unresponsive Wakefulness Syndrome; MCS: Minimally Conscious State; IRU: Intensive Rehabilitation Unit.

**Table 3** Characteristics of patients with or without improved consciousness at discharge.

| | Not | Improved | | Improved | | |
|---|---|---|---|---|---|---|
| Group | 1 | 2 | 3 | 4 | 5 | |
| Admission | UWS | MCS | UWS | MCS | UWS | *P*[a] |
| Discharge | UWS*n*=31 | MCS *n*=18 | MCS*n*=19 | E-MCS*n*=23 | E-MCS*n*=11 | |
| Age at brain injury | | | | | | 0.15 |
| Median Rank, years | 55.4 | 58.1 | 49.6 | 45.7 | 59.9 | |
| Sex, *n* | | | | | | 0.16 |
| Men | 15 | 9 | 6 | 9 | 4 | |
| Women | 16 | 9 | 13 | 14 | 7 | |
| Etiology, *n* | | | | | | 0.17 |
| Traumatic | 10 | 3 | 3 | 9 | 5 | |
| Anoxic | 14 | 4 | 10 | 3 | 2 | |
| Vascular/other | 7 | 11 | 6 | 11 | 4 | |
| Time post-onset | | | | | | 0.14 |
| Median Rank, days | 59.1 | 59.3 | 54.2 | 52.3 | 48.5 | |
| Length of IRU stay | | | | | | 0.15 |
| Median Rank, days | 122 | 120 | 115 | 109 | 100 | |
| CRS-R at admission | | | | | | 0.001 |
| Median (IQR) | 4 (2) | 12 (3) | 5 (2) | 16 (4) | 4 (2) | |
| Antiepileptic drugs | | | | | | 0.35 |
| (*n*%) | 16 (51) | 11 (61) | 11 (57) | 9 (39) | 4 (36) | |
| Activating drugs | | | | | | 0.02 |
| (*n*%) | 0 | 4 (22) | 5 (26) | 7 (30) | 2 (18) | |

UWS: Unresponsive Wakefulness Syndrome; MCS: Minimally Conscious State; E-MCS: emergence from the MCS. CRS-R: Coma Recovery Scale-Revised; IQR: Inter Quartile Range. *P* values was calculated with the Kruskal–Wallis text or $Chi^2$ as appropriated. Post-hoc analysis: CRS at admission: Mann–Whitney U test group 1 vs. 2, $P < 0.001$; group 1 vs. 3 n.s.; group 1 vs. 5, n.s.; group 3 vs. 5 n.s.; group 2 vs. 4, $P < 0.002$. Activating drugs $Chi^2$: group 1 vs. 2, $P < 0.006$; group 1 vs. 3, $P < 0.003$; group 1 vs. 5, n.s.; group 3 vs. 5 $P < 0.06$.; group 2 vs. 4, $P < 0.63$.

[a] Kruskal Wallis test.

background activity and the presence of detectable stage II sleep transient patterns were significant predictors of a better neurological outcome at discharge. On the other hand slower frequencies (delta), the absence of reactivity and of spontaneous variability of the background activity and the presence of epileptiform discharges were related to poorer neurological prognosis. The predictive value of the presence of an anterior/posterior gradient of the background activity, observed in the univariate analysis, could not be confirmed in the multivariable analysis. In MCS patients, no EEG descriptors showed a predictive value for clinical improvement (Table 5). To strengthen the utility of EEG in the UWS group, we calculated the pre-test/post-test probability (Table 6; Fig. 2). In our UWS population, the prior probability of clinical improvement was 49%. When EEG descriptors with a predictive value at multivariable analysis (Table 4) were considered, the posterior probability increased to values from 68% (absence of epileptic discharges) up to 96% (reactivity). In addition, we examined the utility of EEG for prognostication of evolution toward E-MCS at discharge from IRU, independently from the clinical state at admission. According to multivariable analysis,

**Table 4** EEG characteristics of patients with UWS at admission in relation to the evolution.

| Admission discharge | UWS UWS $n=31$ | Group UWS MCS $n=19$ | UWS E-MCS $n=11$ | Univariate Chi$^2$ $p=$ | Multivariate[a] $p=$ |
|---|---|---|---|---|---|
| EEG features | | | | | |
| Sporadic Epileptiform | | | | 0.12 | 0.04 |
| Discharges | | | | | |
| Absent | 23 | 6 | 11 | | |
| Present | 8 | 13 | 0 | | |
| Symmetry | | | | 0.72 | 0.94 |
| Yes | 22 | 13 | 7 | | |
| No | 9 | 6 | 4 | | |
| Background Frequency | | | | 0.001 | 0.002 |
| alpha | 0 | 0 | 5 | | |
| theta | 28 | 18 | 6 | | |
| delta | 3 | 1 | 0 | | |
| AP Gradient | | | | 0.02 | 0.54 |
| Present | 11 | 4 | 8 | | |
| Absent | 20 | 15 | 3 | | |
| Variability | | | | 0.001 | 0.04 |
| Present | 8 | 5 | 10 | | |
| Absent | 23 | 14 | 1 | | |
| Reactivity | | | | 0.01 | 0.02 |
| Present | 0 | 16 | 6 | | |
| Absent | 31 | 3 | 5 | | |
| Voltage | | | | 0.13 | 0.88 |
| Normal (> 20 microvolt) | 18 | 12 | 10 | | |
| Reduced | 13 | 7 | 1 | | |
| Stage II Sleep Transients | | | | 0.001 | 0.002 |
| Present | 0 | 0 | 4 | | |
| Absent | 31 | 19 | 7 | | |
| Continuity | | | | 0.36 | 0.29 |
| Present | 26 | 16 | 11 | | |
| Absent | 5 | 3 | 0 | | |

UWS: Unresponsive Wakefulness Syndrome; MCS: Minimally Conscious State; E-MCS: emergence from the MCS.
[a] Linear regression of EEG features versus improvement corrected for age, sex, etiology, time post-onset, activating drugs, and CRS-R at the admission.

background frequency, variability, reactivity and presence of stage II sleep transient were related to evolution toward E-MCS (Supplementary Materials Table 1). In Table 2 of the Supplementary Materials, we reported the pre-test/post-test probability of evolution toward E-MCS. In our UWS/MCS population, the prior probability of clinical improvement was 33%. When EEG descriptors with a predictive value at multivariable analysis (Supplementary Materials Table 1) were considered, the posterior probability increased to 80% only for the background frequency and for the presence of transient stage II sleep.

## Discussion

In our sample of patients with severe DoC, an EEG performed within the first week after IRU admission and classified according to the ACNS terminology [24], contributed prognostic information with regards to neurological outcome.

Prognosticating neurological outcome at the post-acute stage after severe ABI is a topic of great interest because it could improve the communication process with relatives [13,26,28] and facilitate individualised multidisciplinary rehabilitation management. However, it is only recently that a few authors [13,23—29] have tried to investigate clinical and paraclinical data as possible predictors of late neurological outcome.

In particular, a few previous studies showed that higher CRS-R scores at admission to the IRU were associated with higher consciousness level at discharge [37,41]. However, initial consciousness state of patients (UWS or MCS) was taken into account in only in one of these reports, [37], whereas in the other study [41] neither the extent of the improvement not the initial consciousness state was reported. Moreover, in this last study, the initial CRS-R score only partially predicted patient neurological outcomes. Given these limitations, we decided to evaluate both the CRS-R score and the EEG at admission as possible prognostic predictors. We chose EEG because, to date, it is one of the investigations that is most often performed in patients with DoC, both as a diagnostic tool to reach an accurate classification of the consciousness level [15,19,43] and as a prognostic tool [4,9,29,34,35,44]. However, standard EEG descriptors have been used as predictor tools in only one

**Table 5** EEG characteristics of patients with MCS at admission in relation to the evolution.

| Admission Discharge | MCS MCS $n=18$ | MCS E-MCS $n=23$ | Univariate Chi$^2$ $P$ | Multivariate[a] $P$ |
|---|---|---|---|---|
| EEG features | | | | |
| Sporadic Epileptiform Discharges | | | 0.10 | 0.15 |
| Absent | 13 | 21 | | |
| Present | 5 | 2 | | |
| Symmetry | | | 0.56 | 0.44 |
| Yes | 8 | 14 | | |
| No | 18 | 9 | | |
| Background Frequency | | | 0.30 | 0.27 |
| alpha | 3 | 7 | | |
| theta | 15 | 16 | | |
| delta | 0 | 0 | | |
| AP Gradient | | | 0.22 | 0.52 |
| Present | 14 | 21 | | |
| Absent | 4 | 2 | | |
| Variability | | | 0.90 | 0.57 |
| Present | 13 | 16 | | |
| Absent | 5 | 7 | | |
| Reactivity | | | 0.30 | 0.56 |
| Present | 9 | 16 | | |
| Absent | 9 | 7 | | |
| Voltage | | | 0.43 | 0.91 |
| Normal (>20 microvolt) | 15 | 21 | | |
| Reduced | 3 | 2 | | |
| Stage II Sleep Transients | | | 0.57 | 0.15 |
| Present | 2 | 4 | | |
| Absent | 16 | 23 | | |
| Continuity | | | 0.86 | 0.19 |
| Present | 18 | 23 | | |
| Absent | 0 | 0 | | |

MCS: Minimally Conscious State; E-MCS: emergence from the MCS.
[a] Linear regression of EEG features versus improvement corrected for age, sex, etiology, time post-onset, activating drugs and CRS-R at the admission.

previous study [4]; EEG descriptors are easily and objectively assessed by visual examination and can overcome ambiguity in the interpretation of EEG prognostic categories [52,57]. However, in the study of Bagnato et al. [4], authors did not evaluate some EEG descriptors that have been previously investigated for diagnostic purposes [15,19,43]. Moreover, they [4] did not take into account the CRS-R score as a possible neurological outcome predictor, but rather only as a tool for assessing consciousness level.

Given these limitations, and according to recent suggestions that the predictive value of the auxiliary variables (i.e., neurophysiological tests) should be compared with the values of clinical features [31], we compared the predictive value of EEG to that of the clinical variables. We observed, as expected, that clinical improvement was strongly related to the level of consciousness at admission. As such, we performed a subgroup analysis in patients with UWS and MCS at admission. Moreover, we decided to use single EEG descriptors according to ACNS EEG terminology [24], because they allow better standardization of the EEG pattern description between different operators [8,23,48,49,51]. Through the use of this EEG classification, we were able to confirm the results of Bagnato et al. [4] with respect to the prognostic power of the frequency and reactivity of the background activity, with higher background frequencies and the presence of reactivity being associated with improved consciousness in UWS patients at admission. Conversely, EEG voltage was not correlated with clinical evolution in any of the patient groups of our sample. The predictive value of reactivity shown here was expected according to existing literature: even though previous studies have assessed several types of stimuli (i.e. passive [9] or forced eye-opening [4,5], pain [29,35], warm water [34] or even stimuli without a clear description [44]), and despite the fact that the criteria for its definition were substantially different across studies, results from the literature in this respect are very homogeneous.

In our sample, the presence of detectable stage II sleep transient patterns was associated with improved consciousness level in UWS patients. This EEG feature was mainly used as a diagnostic tool [11,12,33,39,43], with sleep pattern abnormalities as a robust indicator of the severity of DoC, regardless of the etiology. Only a few authors [2,53] have reported the utility of this EEG feature in the prediction of clinical improvement of DoC. In our sample, we observed the occurrence of sleep spindles only in a low percentage of patients, probably because to the length of our EEG recording. In fact, standard EEG recordings of 30 min

**Table 6** Sensitivity, Specificity, likelihood ratio and Posterior probability for clinical improvement of the different EEG Descriptors. Prior probability: 49%.

| EEG Descriptor | Sensitivity % | Specificity % | LR+ (95%CI) | Posterior Probability (95%CI) | LR- (95%CI) | Posterior Probability (95%CI) |
|---|---|---|---|---|---|---|
| Sporadic Epileptiform Discharges | 56.7% | 74.2% | 2.20 (1.12—4.31) | 68% (52—81) | 0.58 (0.37—0.92) | 36% (26—46) |
| Symmetry | 66.7% | 29.8% | 1.15 (0.67—2.32) | 48% (39—56) | 0.94 (0.54—1.43) | 53% (37—70) |
| Background frequency | 16.7% | 98.4% | 10 (0.60—18) | 90% (36—99) | 0.85 (0.72—1.00) | 45% (41—49) |
| AP gradient | 40.0% | 64.5% | 1.13 (0.59—2.15) | 52% (36—68) | 0.93 (0.63—1.38) | 47% (38—57) |
| Variability | 39.0% | 65.0% | 1.13 (0.57—2.25) | 65% (48—79) | 0.93 (0.63—1.38) | 61% (51—70) |
| Reactivity | 73.3% | 96.9% | 23 (3.3—16) | 96% (76—99) | 0.28 (0.15—0.50) | 21% (13—32) |
| Voltage | 73.3% | 41.9% | 1.26 (0.87—1.83) | 55% (46—64) | 0.64 (0.31—1-31) | 38% (23—56) |
| Stage II sleep transient | 13% | 100% | 8.4 (0.46—15.2) | 89% (30—99) | 0.88 (0.76—1.02) | 46% (42—49) |
| Continuity | 90% | 16% | 1.07 (0.88—1.30) | 51% (46—56) | 0.62 (0.16—2.37) | 37% (13—70) |

LR: likelihood ratio; CI: confidence interval, bold type indicates a significant increase of probability.

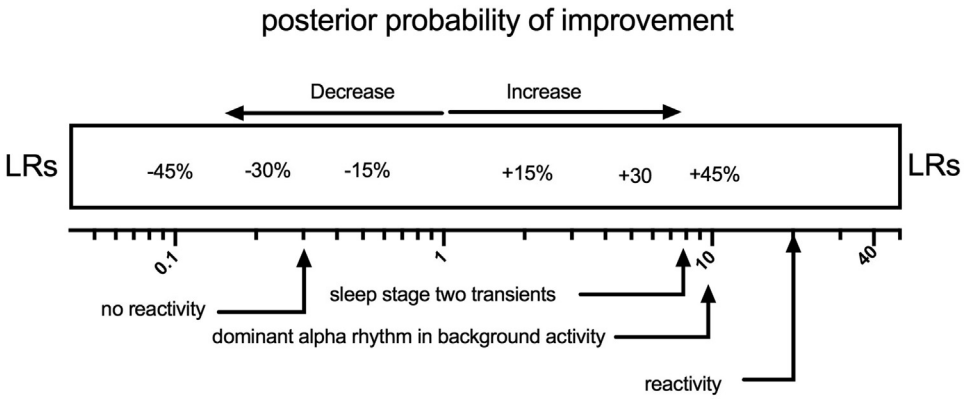


**Figure 2** Graphical box of increases and decreases of posterior probabilities, in relation to likelihood ratios, in significant EEG features. LRs = likelihood ratios.

seem to have no effect on specificity but an effect on sensitivity, compared to a protracted EEG recording, where the chance to observe sleep patterns could be greater. Finally, using the ACNS EEG terminology [24], we identified another EEG descriptor that has not previously been taken into account: spontaneous variability of the background activity that, when present, was a favourable neurological outcome predictor in patients with UWS at admission.

Our analysis also showed some EEG features more frequently related to absence of improvement in the consciousness level: lower frequencies (delta), absence of reactivity and of spontaneous variability of the background activity, and presence of epileptic discharges. In fact, the prognostic significance of the presence of epileptic discharges is conflicting. Bagnato et al. [3] observed that the occurrence of structural epilepsy did not affect the recovery of consciousness; on the other hand Pascarella et al. [38] reported that the presence of epileptiform activity could hamper the recovery of consciousness. Concerning the presence of reorganisation of an anterior-posterior gradient of the background activity, multivariable analysis did not confirm the favourable prognostic power observed in the univariate analysis. Finally, besides the voltage, not even the continuity of the background activity showed a significant

prognostic power in our sample. This result was probably due to the fact that these EEG features are mainly found at an early stage of ABI and mainly in subjects affected by HIE of a severe degree. These latter subjects, in particular, were usually not admitted to the IRU, because they often died before intensive care unit (ICU) discharge or were admitted to long-term care wards.

The clinical utility of EEG descriptors in improving prognostic information is strengthened by the comparison of pre-test/post-test probability. As reported in Table 6, all of the EEG descriptors statically significant at the multivariable analysis (Table 4) showed a significant value of LR+ and a post-test probability greater than the local population probability of clinical improvement, in UWS patients.

Concerning MCS patients, in our sample, we observed no EEG prognostic findings. This result could be due to the fact that among this group, we observed less heterogeneous EEG findings, which could be related to their clinical state. Another explanation could be that patients with MCS- and MCS+ were analysed together [6] because of our limited sample. Therefore, in our opinion, it would be worth further investigating the prognostic value of the EEG, taking these subgroups of MCS patients separately.

In summary, we showed that EEG is a useful neurological prognostic tool in DoC patients after ABI, not only in an early stage (during the coma), but also in the post-acute stage. The use of ACNS terminology for EEG classification allowed us to evaluate the prognostic power of all the EEG descriptors already analysed in previous studies, where, however, they were mainly evaluated individually. In addition, the use of this EEG terminology improved the identification of other EEG descriptors with prognostic value that had not yet been distinguished.

### Limitations

Our study had some limitations. First of all, being retrospective, clinical and instrumental information were collected from medical charts and may have been incomplete. Concerning clinical evaluation, we are aware that clinical status can fluctuate within the same day and between days [40]. For this reason, clinical evaluation and EEG recording were both performed in the time-period during the morning [14]. Moreover, we defined clinical diagnosis taking into the account the best CRS-R total score obtained in at least three evaluations [54].

Moreover, EEG reactivity was not tested in a systematic way, even though at least three kinds of stimulations were performed (noxious and acoustic stimuli, and passive eye-opening) in our protocol, and EEG recording duration was quite short for the evaluation of a reliable occurrence of detectable sleep patterns. In addition, even though our sample consisted of about 100 patients, it was not large enough in terms of accounting for the extent of improvement in consciousness level and for the initial state of consciousness to generalize our results; thus, our findings need to be confirmed in a wider sample. Moreover, we acknowledge that the total CRS-R score and the diagnostic category defined with this score implied a ''nested'' effect, but we tried to take into account this circular effect in our statistical analysis. Finally, we evaluated the improved consciousness at discharge from the IRU (approximately five months after ABI). This time of observation could be considered too short because a delayed recovery is possible, especially for patients affected by TBI.

## Conclusion

Prognosticating neurological outcome is an important tool both in the early stages [1] and later stages after ABI, with different goals. On the one hand, an early neurological prognosis is needed to improve patient management in ICU and to better identify the appropriate rehabilitation care unit after hospital discharge, according to the real recovery expectations [48,49]. On the other hand, long-term neurological prognosis in patients already admitted to the IRU is important for several reasons. First of all, it can improve the communication process with relatives and patients' caregivers. In addition, the knowledge of long-term neurological outcomes can improve individualized multidisciplinary rehabilitation management, identifying the most appropriate rehabilitation strategies according to realistic recovery expectations. Moreover, an EEG can add useful information in patients whose CRS-R score may not be reliable because of the presence of confounding factors, such as critical illness myopathy-neuropathy or aphasia, which, affecting the motor function or the auditory, oromotor/verbal functions and communication scale, respectively, could lead to a CRS-R score appearing lower. Thus, in our opinion, it is always worth performing an EEG evaluation at an early stage (within one week of admission to the IRU) for patients with severe DoC. This is because the EEG is a simple, inexpensive and risk-free test that can be performed at the patient's bedside. It can often add useful information, not only about potential causes of transitory alteration of the consciousness state (i.e. presence of epileptic discharges/non convulsive epileptic status or septic/dysmetabolic alterations) but also because it can add useful prognostic information, besides those provided by the neuro-behavioural observation, even though limited to UWS patients. However, our findings are only preliminary, because of being limited to a retrospective sample, and they need to be reconfirmed in future prospective studies.

## Disclosure of interest

The authors declare that they have no competing interest.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neucli.2019.07.001.

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