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Clinical paper

# Topography of MR lesions correlates with standardized EEG pattern in early comatose survivors after cardiac arrest

*Rike Barth*[a,1], *Frederic Zubler*[a,*,1], *Anja Weck*[b,c], *Matthias Haenggi*[b], *Kaspar Schindler*[a], *Roland Wiest*[d], *Franca Wagner*[d]

[a] *Sleep-Wake-Epilepsy Center, Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Switzerland*

[b] *Department of Intensive Care Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland*

[c] *Department of Intensive Care Medicine, Central Hospital Region Biel/Bienne, Biel/Bienne, Switzerland*

[d] *Department of Diagnostic and Interventional Neuroradiology, Support Center for Advanced Neuroimaging (SCAN), Inselspital, Bern University Hospital, University of Bern, Switzerland*

## Abstract

**Aim:** Multimodal prognostication in comatose patients after cardiac arrest (CA) is complicated by the fact that different modalities are usually not independent. Here we set out to systematically correlate early EEG and MRI findings.

**Methods:** 89 adult patients from a prospective register who underwent at least one EEG and one MRI in the acute phase after CA were included. The EEGs were characterized using pre-existent standardized categories (highly malignant, malignant, benign). For MRIs, the apparent diffusion coefficient (ADC) was computed in pre-defined regions. We then introduced a novel classification based on the topography of ADC reduction (MR-lesion pattern (MLP) 1: no lesion; MLP 2: purely cortical lesions; MLP 3: involvement of the basal ganglia; MLP 4 involvement of other deep grey matter regions).

**Results:** EEG background reactivity and EEG background continuity were strongly associated with a lower MLP value ($p < 0.001$ and $p = 0.003$ respectively). The EEG categories highly malignant, malignant and benign were strongly correlated with the MLP values (rho = 0.46, $p < 0.001$).

**Conclusion:** The MRI lesions are highly correlated with the EEG pattern. Our results suggest that performing MRI in comatose patients after CA with either highly malignant or with a benign EEG pattern is unlikely to yield additional useful information for prognostication, and should therefore be performed in priority in patients with intermediate EEG patterns ("malignant pattern").

**Keywords:** EEG, MRI, Prognostication, Hypoxic ischemic encephalopathy, Cardiac arrest, Coma

## Introduction

Early accurate prognostication in comatose patients after cardiac arrest (CA) remains a major challenge for neurologists and intensivists[1–3]. According to current guidelines, prognostication after CA should be based on a multi-modal approach combining clinical and paraclinical examinations, and should not rely on a single test.[1–6] Previous studies have shown that the specificity for favorable or unfavorable outcomes increases with the number of predictors considered.[7–10] It has also been proposed to stratify electrophysiological tests according to their false positive rate toward unfavorable outcome.[3] However, there is no generally defined consensus on the best way to combine the information obtained by different modalities. This problem is aggravated by the fact that these modalities are unlikely to be independent since most of them assess the function and/or structure of the central nervous system.[1]

* Corresponding author at: Sleep-Wake-Epilepsy Center, Department of Neurology, Inselspital, University Hospital and University of Bern, Freiburgstrasse 10, 3010 Bern, Switzerland.

E-mail address: frederic.zubler@gmail.com (F. Zubler).

[1] These authors contributed equally to the study.

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Positive correlation between prognostic modalities has been demonstrated by others and have included clinical examination and electroencephalography (EEG),[11] EEG and somatosensory evoked potentials (SSEP),[11,12] EEG and neuron-specific enolase (NSE),[13] as well as magnetic resonance imaging (MRI) and NSE.[14] One previous study was explicitly designed to compare MR and EEG findings in comatose patients after CA.[15] Surprisingly, the authors reported that "malignant" EEG patterns were more frequent in patients with less severe MR findings. However, the definition of malignant EEG pattern used for this study was primarily based on the presence of epileptiform activity. This definition constitutes a severe limitation, since epileptiform activity is not invariably associated with an unfavorable outcome,[14,16–18] and is usually not categorized as one of the most severe EEG patterns.[8,19] While the combination of EEG and MRI has been used for prognostication,[10] a systematic correlation of both methods incorporating widely used EEG-categories is missing. However, such a study would be crucial to improve neurological prognostication guidelines, and to allocate resources for MRI in the early phase for those patients for whom it is likely to provide more information than EEG alone.

EEG was one of the first, and has become the most widely available paraclinical tool for prognostication in patients with hypoxic-ischemic encephalopathy.[2,8,18–22] The recent introduction of a standardized terminology[24] has improved the inter-rater reliability and allowed for study comparisons.[25,26] In addition, EEG is not invasive and can be easily applied to intensive care patients with a relatively low cost-of-use.

The use of MRI for prognostication is more recent, but has rapidly gained interest during the last decade.[27–29] MRI allows the detection of cytotoxic edema, which occurs within hours after cardiac arrest. Restricted diffusion by cytotoxic edema can be quantified by the Apparent Diffusion Coefficient (ADC) value of each voxel. One of the main advantages of MRI is the ability to assess the anatomical distribution of diffusion restrictions. However, there is no standardized protocol for quantifying ADC reduction.[3] The major limitations of MRI in clinical practice are availability, costs, and the resources needed for performing the examination in comatose patients.

In this study, we set out to correlate the presence and topography of DWI/ADC lesions with standardized EEG patterns in comatose patients in the early phase after CA. We hypothesized that classical EEG markers of poor outcome would be associated with higher overall probability of MR lesions, especially in the subcortical grey matter.

## Methods

### *Patients and treatment*

Patients from the prospective monocentric register from the Intensive Care Department of the University Hospital of Bern were retrospectively analyzed. Patients with age >18, admitted between January 2016 and March 2019, who underwent an MR scan of the brain and at least one EEG during coma were included. Of note, both examinations are routinely performed in our center as standard of care for clinical assessment, unless the patients awake or spontaneously progress to brain death before second or third day. Exceptions consist of technical contra-indications for MRI (e.g. extracorporeal membrane oxygenation) or advanced directive from the patient/family. Exclusion criteria were: CA of non-cardiac origin, previous structural brain lesions such as stroke, neurodegenerative disorders or tumor. The study protocol was approved by the Ethics Committee of the Canton of Bern (KEK Nr. 116/15).

On arrival at the ICU, standard of care consisted of targeted temperature management (TTM) with controlled normothermia at 36 °C, which was implemented with feed-back devices (Alsius/Arctic Sun). Starting from October 2018, few patients were treated with hypothermia (33 °C; 5 patients) or "absence of fever" (<37.5 °C, 1 patient) after inclusion in another study. Decision to withdraw life supporting treatment was taken at least 48 h after CA and 24 h after rewarming and in absence of sedation in presence of at least two of the following criteria: i) absent brainstem reflexes, ii) absent motor response or only extension to pain stimulus, iii) bilateral absence of N20 in somatosensory evoked potentials, iv) unreactive EEG background, v) generalized bi-hemispherical cortical MRI diffusion restriction and a serum neuron-specific enolase level measured twice above 33 ug/l. The outcome was prospectively assessed with the Cerebral Performance Category (CPC), whereby the best value between CPC at discharge and CPC at 3 months was considered. A CPC value of 1 or 2 was considered a favorable outcome, and a CPC of 3, 4, or 5 was considered an unfavorable outcome.

### *Magnetic resonance imaging (MRI)*

Image acquisition was performed with 3T Siemens MR scanners (either Magnetom Vida, Magnetom Verio or Magnetom Skyra_fit; Erlangen/ Germany). The image analysis was performed retrospectively by a board-certified neuroradiologist (FW) blinded to the patients' clinical data and EEG findings. For details about the MR sequences see Supplementary Appendix.

We quantified the MRI findings based on the DWI /ADC restrictions. An axial T2w and a coronal T2w-FLAIR were used to detect old hyperintense abnormal signal alterations, to exclude chronic infarction, or as a reference to exclude T2-"shine through" effect. ADC values were measured in pre-defined regions of interest (ROIs) located in the cerebral cortex, the cerebellar cortex, the hippocampi, the basal ganglia, both thalami and the brain stem. The cerebral cortex contained eight ROIs (one in each frontal, parietal, temporal, and occipital lobe). ROIs sizes were 4 $mm^2$ for the cerebral and cerebellar cortex and the hippocampi, 10 $mm^2$ for the basal ganglia, thalami and the brain stem. ROIs that revealed restricted diffusion and corresponding decreased ADC values $<650 \times 10^{-6}$ $mm^2/s$ were considered as pathologically restricted as previously suggested.[31]

We then defined four different patterns called *MR-lesion patterns (MLPs)* based on DWI/ADC restriction in the different ROIs. *MLP 1* was defined as an absence of any gray matter lesion; *MLP 2* as purely cortical grey matter lesions; *MLP 3* as the presence of basal ganglia lesions without involvement of other subcortical grey matter (with or without cortical lesions); and *MLP 4* as lesions of the thalami and/or hippocampi and/or brain stem (with or without cortical or basal ganglia lesion). Representative examples are displayed in Fig. 1. This classification system was decided prior analysis.

### *Electroencephalogram (EEG)*

EEG recordings were acquired over 20–30 min with a NicoletOne recording system (VIASYS Healthcare, Inc., Madison, WI, U.S.A.) using 19 electrodes placed according to the 10–20 international system, with additional ground and reference electrodes. During the recordings, auditory (calling of patient's name, hand clapping) and

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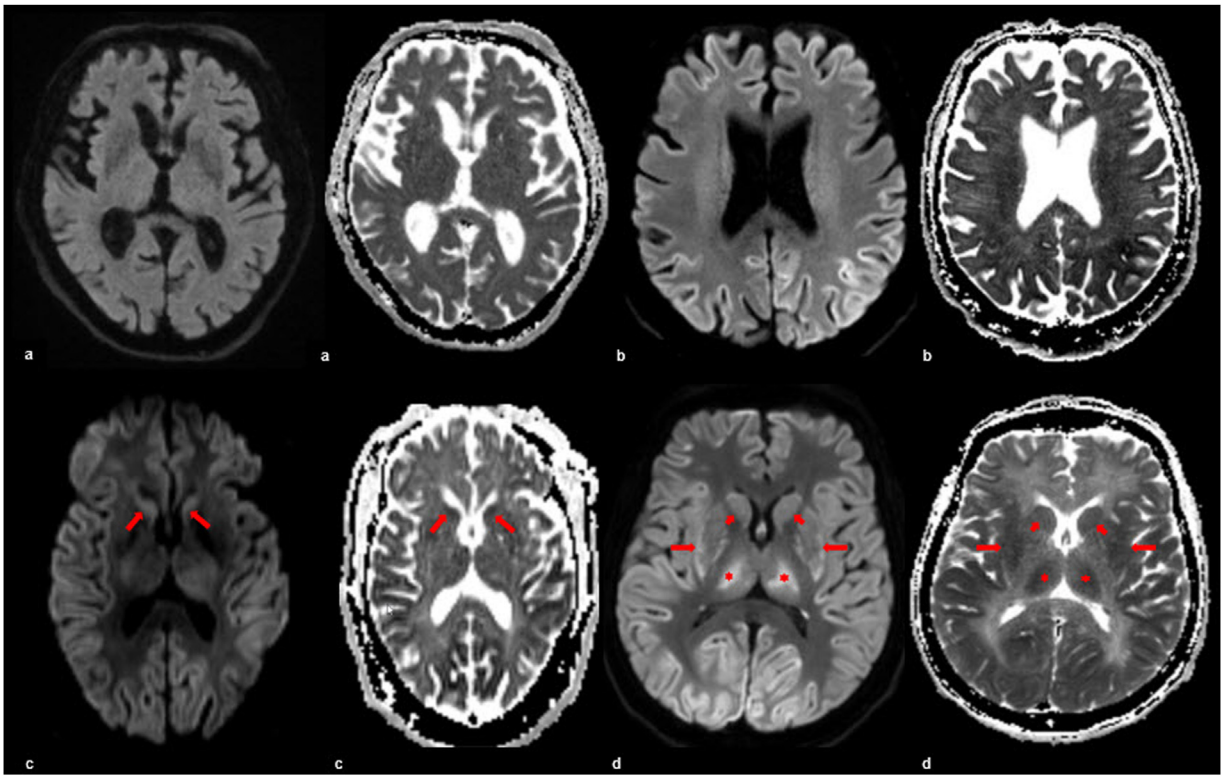


**Fig. 1 – Representative examples for the four MRI lesion pattern (MLPs); for each subject the diffusion weighted imaging (DWI, left) and apparent diffusion coefficient (ADC, right) are presented. (a) MLP 1: normal brain MR scan of a 82-year-old male with absence of gray matter lesion. (b) MLP 2: MR scan of a 77-year-old male with symmetric involvement of the frontal and parietal cortex in absence of subcortical lesions. (c) MLP 3: MR scan of a 74-year-old male with involvement of the basal ganglia (arrows) and of the cortex (fronto-temporo-parieto-occipital bi-hemispherical symmetric). (d) MLP 4: MR scan of a 75-year-old female with involvement of the thalami (stars), the basal ganglia (arrows) and the fronto-temporo-parieto-occipital cortex bi-hemispherical symmetric.**

somatosensory (finger nail pinching, sternum rubbing) stimuli were applied at least 3 times, with a minimum of 10 s intervals. For patients who underwent several EEGs, we considered the recording temporally closest to the MR scan.

EEG traces were retrospectively analyzed de novo by two board-certified electroencephalographers (RB and FZ) blinded to the clinical outcome and the MR results. EEGs were interpreted according to the standardized criteria of the American Clinical Neurophysiology Society.[24] In particular, the presence of the following EEG markers routinely used for prognostication were assessed: *EEG background reactivity* was defined as an increase or decrease of frequency and/or amplitude clearly attributable to the stimuli. Stimulus-induced periodic patterns or rhythmic spike waves were not considered reactivity. *EEG background continuity* was defined as the absence of suppression (amplitude 10 μV or less) or attenuation (amplitude between 10 and 20 μV) in absence of stimulus. *Epileptiform activity* was defined as the presence of either spiky or sharp periodic discharges, rhythmic spike-waves, sporadic epileptiform discharges or electrographic seizures. In addition, each EEG was classified into one of the mutually exclusive categories defined by Westhall et al.,[19] namely *highly malignant pattern* (suppressed background or burst-suppression, with or without superimposed periodic pattern), *malignant pattern* (presence of at least one of the following: abundant periodic discharges or rhythmic spike-waves, electroencephalographic seizure, discontinuous or low-amplitude background, reversed anterior-posterior amplitude gradient, absence of reactivity) or *benign pattern* (absence of malignant feature).

### *Statistical analysis*

The EEG markers (reactivity, continuity, epileptiform activity) were considered as categorical binary (not ordinal) variables. The classifications into one of the three EEG categories (highly malignant, malignant, benign) and the MRI-pattern (MLP 1–4) were treated as categorical ordinal variables. Differences in the MLP values depending on the presence or absence of each EEG binary markers were assessed with a Mann–Whitney-U-test with ties correction. The correlation between the MLP value and the EEG category was assessed with Kendall's tau B. Differences between outcome groups for patients demographics and raw EEG or MRI findings were described using Fisher exact tests (proportions) or Mann–Whitney U test (numerical values). Statistical analysis was performed in Matlab R2017a (Mathworks) using the Statistics and Machine Learning Toolbox.

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## Results

### Patients

89 patients (25 females) were included (Fig. 2). The mean age (±SD) was 65 years (±12; range 36−85). 25 patients (28%) had a favorable outcome and 64 (72%) an unfavorable outcome, of which 59 patients (66%) died. Cause of death was withdrawal of life-sustaining treatment (WLST) due to poor neurological prognostic for 50 patients, WLST due to advance directive or family wishes for 7 patients; the cause of death remains unknown in 2 patients who were transferred to another hospital. Patients demographics are presented in Table 1.

### MRI

The mean delay from CA to MRI was 47.7 h (±16; range 20−103). DWI/ADC restrictions were observed in 64 (72%) patients. The lesion distribution was usually bi-hemispherical symmetric. The cortex, in particular the parieto-occipital lobes, was the most affected anatomical region (55 patients), followed by the basal ganglia (47 patients) and the remaining subcortical grey matter (26 patients). The MR lesions and the resulting MLP categories are presented in Table 1.

### EEG

The mean delay from CA to EEG was 50.8 h (±22, range 12−110). The EEG background was reactive in 46 (53%) patients; the EEG was continuous in 47 (53%) patients and showed epileptiform activity in 27 (30%) patients. The following distribution of EEG categories was found: 16 (18%) benign patterns, 45 (51%) malignant patterns, and 28 (31%) highly malignant patterns. EEG findings are presented in Table 1.

### MRI-EEG correlation

#### EEG binary markers

Distribution of MRI-lesion patterns as function of binary EEG markers is shown in Fig. 3. EEG background reactivity was strongly associated with lower MLP values ($p < 0.001$). In particular, an absence of visible hypoxic lesion (MLP 1) was found in 63% of patients with reactive EEG and only in 12% of patients with non-reactive EEG. EEG background continuity was also significantly associated with lower MLP values ($p = 0.003$); 53% patients with continuous background had no diffuse MRI lesions, whereas this was only the case for 21% of patients with discontinuous background. By contrast, patients with epileptiform activity had slightly lower MLP values – however this association was not statistically significant ($p = 0.204$).

#### EEG category

Distribution of MRI-patterns in relation to the classification into one of the three EEG categories[19] is presented in Fig. 4. Higher MLP values were found in patients with more severe EEG patterns; the correlation was statistically significant (rho = 0.46, $p < 0.001$). Importantly, the majority (14/16) of patients with a benign EEG pattern had no MR lesion (MLP 1), and the remaining two patients had purely cortical grey matter lesions (MLP 2). By contrast, three quarters of patients with highly malignant EEG pattern had sub-cortical grey matter lesions (MLP 3 and MLP 4).

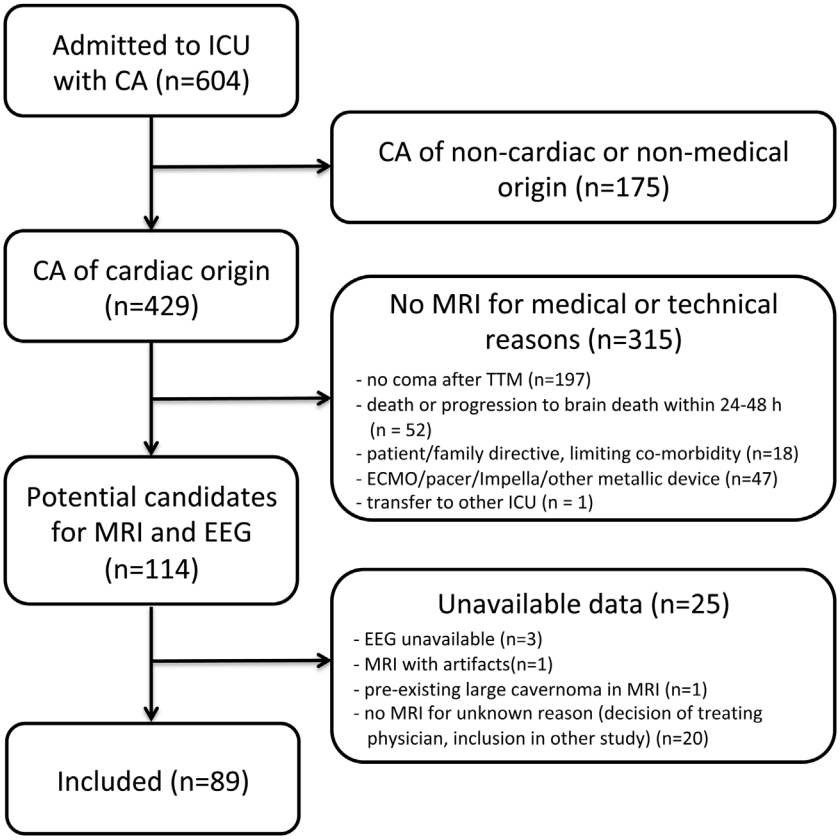


**Fig. 2 – Flow chart of patient inclusion.**

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**Table 1 – Patients demographics and detailed MRI and EEG findings. For real-valued variable, the median and interquartile range are given. NSE: Neuron-specific enolase, MLP: MRI-Lesion pattern. *1*: available for 70/89 patients; *2*: median of patients with propofol; the sedation was usually interrupted before or at start of the EEG.**

| Demographics | Favorable outcome (N = 25) | Unfavorable outcome (N = 64) | p |
|---|---|---|---|
| Females | 8 (32%) | 17 (27%) | 0.61 |
| Age (years) | 58 [51–71] | 65.5 [55–73] | 0.21 |
| NSE[1] (ng/ml) | 32.9 [23.3–71.1] | 67.4 [39.7–172.8] | 0.006 |
| Latency CA-MRI (h) | 48.00 [41.50–54.83] | 45.15 [36.00–62.73] | 0.52 |
| Latency CA-EEG (h) | 48 [42.5–54.8] | 45.2 [36.0–62.7] | 0.57 |
| Latency EEG-MRI (h) | 2.00 [2.00–4.00] | 3.00 [2.00–12.75] | 0.32 |
| Patients sedated w/ propofol | 12 (48%) | 33 (52%) | 0.76 |
| Propofol[2] (mg/kg) | 1.38 [0.75–3.06] | 1.92 [0.91–2.48] | 0.95 |
| | | | |
| MRI lesion location | | | |
| Cortical (combined) | 2 (8%) | 53 (83%) | <0.001 |
| Cortical frontal | 1 (4%) | 42 (66%) | <0.001 |
| Cortical temporal | 0 (0%) | 27 (42%) | <0.001 |
| Cortical parietal | 1 (4%) | 51 (80%) | <0.001 |
| Cortical occipital | 0 (0%) | 49 (77%) | <0.001 |
| Cortical cerebellum | 2 (8%) | 26 (41%) | 0.002 |
| Basal ganglia | 1 (4%) | 46 (72%) | <0.001 |
| Hippocampi | 1 (4%) | 20 (31%) | 0.005 |
| Thalami | 0 (0%) | 20 (31%) | <0.001 |
| Brainstem | 0 (0%) | 7 (11%) | 0.18 |
| | | | |
| MRI lesion patterns | | | |
| MLP 1 | 23 (92%) | 11 (17%) | <0.001 |
| MLP 2 | 1 (4%) | 7 (11%) | 0.43 |
| MLP 3 | 0 (0%) | 21 (33%) | <0.001 |
| MLP 4 | 1 (4%) | 25 (39%) | <0.001 |
| | | | |
| EEG binary markers | | | |
| EEG reactive background | 24 (96%) | 22 (34%) | <0.001 |
| EEG continuous background | 23 (92%) | 24 (38%) | <0.001 |
| EEG epileptiform activity | 4 (15%) | 23 (36%) | 0.08 |
| | | | |
| EEG patterns | | | |
| EEG benign pattern | 13 (52%) | 3 (5%) | <0.001 |
| EEG malignant pattern | 12 (48%) | 33 (52%) | 0.82 |
| EEG highly malignant pattern | 0 (0%) | 28 (44%) | <0.001 |

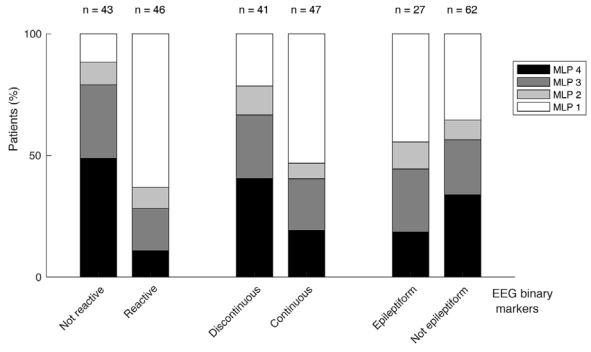


**Fig. 3 – Distribution of the MRI lesion patterns (MLPs) in presence/absence of EEG markers for unfavorable outcome. The absence of EEG background reactivity and a discontinuous EEG background were both significantly associated with higher MLP values ($p < 0.001$ and $p = 0.003$ respectively). By contrast, the presence of epileptiform activity on the EEG was not associated with higher MLP values ($p = 0.20$).**

## Discussion

In this study, we correlated EEG and MRI findings from comatose patients in the early phase after CA. To characterize EEGs, we used markers and standardized categories previously validated for prognostication. For MRI, in absence of a widely accepted classification, we introduced a new grading system based on the topography of pathological DWI/ADC values in the cortical and subcortical grey matter structure (Fig. 1).

Our study revealed that two markers for favorable outcome, EEG background reactivity[23,32–35] and EEG background continuity[36,37] were significantly associated with lower MLP grading. Our results are in accordance with those of Rossetti et al.,[13] who found these two EEG markers to be associated with lower neuron-specific enolase (NSE) values. The authors suggested that early EEG abnormalities correlate with post-anoxic brain damage, instead of being a mere sign of global dysfunction. Our study confirms this hypothesis by demonstrating that more severe EEG patterns are indeed associated with higher probability of visible lesions in the MRI, especially in the subcortical

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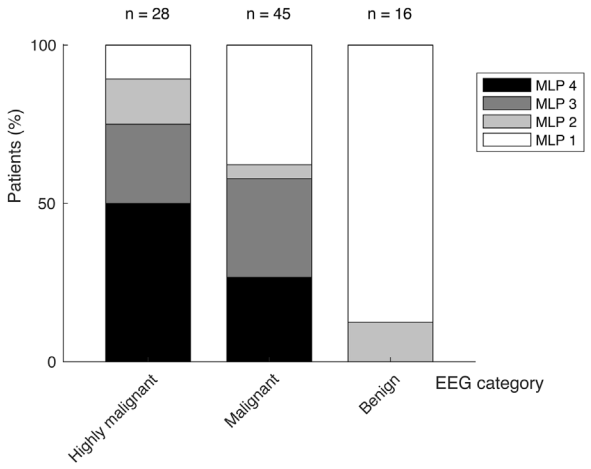


**Fig. 4 – Distribution of the MRI lesion patterns (MLPs) as a function of standardized EEG categories.[19] EEG categories typically associated with poor outcome had significantly higher MLP values (rho = 0.46, $p < 0.001$).**

grey matter. Our finding that the association with lower MLP values was the most pronounced for reactivity is highly relevant in regard to the recent discussion about the value of EEG reactivity for prognostication.[18,35,38]

By contrast, the presence of epileptiform activity was not associated with different distributions of MLPs. More precisely, epileptiform activity showed a trend toward lower MLP values. Interestingly, in the work of Rossetti et al.,[13] epileptiform EEG activity showed a trend toward lower NSE values. As already mentioned by the authors of this study, one can postulate that this finding is explained by the extensive structural brain damages impeding the generation of detectable epileptiform activity. This also corroborates the conclusions of the study from Mettenburg et al.,[15] who reported that EEG patterns defined by the presence of epileptiform activity were associated with less severe brain injury in the MRI.

Finally, we found a strong correlation between a previously described standardized EEG pattern classification[19,39] and our newly proposed classification (MLP 1–4).

Our results are important for several reasons. First, they offer the first direct confirmation that classical EEG features, in particular the standardized classification proposed by Westhall et al.,[19] reflects the presence and topography of structural brain lesions. Second, they offer an a-posteriori validation of our decision to use MR categories based on an anatomical distribution of lesions (see also below). Finally, our results might help clinicians deciding in individual cases whether the organizational and financial burden of performing an MRI for a comatose patient is likely to bring *additional* information for prognostication.

### *Towards a stratified prognostication strategy*

In the presence of a benign EEG pattern, the MRI is likely to show an absence of diffusion restriction or, in fewer cases, only superficial grey matter involvement. For this subgroup of patients, performing an MRI is thus unlikely to provide new information. Also for patients with a highly malignant EEG pattern, the MRI will probably not change the course of therapy. First, because these patients are likely to have grey matter lesions. Second - and more importantly – because this EEG pattern is almost invariably associated with an unfavorable outcome when performed at least 72 h after CA.[19,39]

By contrast, in presence of a malignant EEG pattern, which represents a sort of "intermediate" category, the information resulting from the MRI might contribute to prognostication. This was the case in our collective (although the retrospective nature of our analysis sets a very high risk for self-fulfilling prophecy): 11/17 (64%) patients with malignant pattern and absence of lesion (MLP 1) had a favorable outcome, whereas this was only the case in 1/26 (4%) patients with malignant EEG pattern and subcortical cortical lesion (MLP 3–4). Only two patients had purely cortical lesions (MLP 2), they both had an unfavorable outcome.

It has recently been shown in a multi-centric trial that all patients with a benign EEG pattern had preserved N20-potentials in the SSEP.[12] Taken together, these results support the role of EEG as first paraclinical test in a stratified approach to prognostication.

### *MRI categories*

Currently, there is no consensus about the way to characterize patterns in diffusion restriction for outcome prognostication after CA. Among different approaches, the whole-brain averaged ADC value,[15,27] the percentage of brain volume below a certain threshold,[10] or the topography of regions with reduced ADC[30] have been used. Since automated methods with voxel-wise ADC measurements are not yet widely available for clinical use,[30] we decided to use an anatomical based classification. We introduced a new classification comprising four categories based on the topography of grey matter lesions. Our classification was motivated by previous neuroradiological studies in which deep grey matter structure seemed to be less often affected by hypoxia than cortical structures (and thus might indicate a more severe pattern).[10,15,29,40] Other visual classification paradigms might have been possible, for instance based on the extension of cortical involvement.[30] The results might have been similar, since in our subjects an extended cortical involvement usually corresponded to high MLP values. For instance, 12/13 patients with diffusion restriction in all four cortical lobes also had subcortical lesions.

### *Limitations and future studies*

Our study has several limitations. First, because of the retrospective nature of the analysis, only patients for which an MRI was ordered by the treating physician were involved. As consequence, patients who regained consciousness or evolved toward brain death during the first 36–48 h were not included (since the former group is larger, this led to an overrepresentation of unfavorable outcome in the included patients). However, this population is likely to reflect the real-world category of patients for which an MRI is considered. In addition, even though both MRI and EEG are part of standard of care in patients who remain comatose after TTM, ca. 20% of patients who would have been included did not have an MRI or and EEG (Fig. 2). A systematic bias cannot be excluded – even though such a bias is more likely to affect a study on prognostication than a study on MRI and EEG correlation.

Second, since EEG and MRI findings were taken into account for withdrawal of life-sustaining treatment (WLST), we could only correlate the results of these examinations with each other, and not compare their predictive values for prognostication. A larger study in which neither EEG nor MRI are incorporated into a decision on WLST is needed to confirm our findings, and define prognostic algorithms.

The variable delay between CA and the examinations constitutes a further limitation. EEG patterns can evolve in the early phase; for

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instance burst-suppression or a suppressed background in the first 20–30 h after CA are not inevitably associated with unfavorable outcomes.[18,33,41] The timing is also crucial for MRI,[28] even though the optimal timing for detecting ADC lesion is still disputed.[31] Finally, we excluded patients with non-cardiac origin of CA. Importantly, our results might not be valid for MRIs performed after more than five days and/or for patients with other origin of CA.

## Conclusion

Early prognostication after cardiac arrest remains a challenging task. Even though clinicians have several diagnostic and prognostic tools at their disposal, the optimal combination remains unclear. Our results suggest that MRI is the most likely to offer additional information compared to EEG alone in the presence of an intermediate EEG pattern (so-called "malignant" pattern). Further characterization of the information gained by each modality depending on the results of previous tests is essential to develop a general and stratified prognostic algorithm.

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## Conflict of interest

None of the authors reports a conflict of interest.

## CRediT authorship contribution statement

**Rike Barth:** Formal analysis, Writing - review & editing. **Frederic Zubler:** Conceptualization, Formal analysis, Writing - original draft. **Anja Weck:** Resources. **Matthias Haenggi:** Resources, Formal analysis, Writing - review & editing. **Kaspar Schindler:** Resources, Writing - review & editing. **Roland Wiest:** Resources. **Franca Wagner:** Conceptualization, Formal analysis, Writing - original draft.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2020.01.014.

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