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Clinical paper

Neurophysiology and neuroimaging accurately predict poor neurological outcome within 24 hours after cardiac arrest: The ProNeCA prospective multicentre prognostication study

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Abstract

Aims: To investigate the ability of 30-min electroencephalogram (EEG), short-latency somatosensory evoked potentials (SEPs) and brain computed tomography (CT) to predict poor neurological outcome (persistent vegetative state or death) at 6 months in comatose survivors of cardiac arrest within 24 h from the event.

Methods: Prospective multicentre prognostication study in seven hospitals. SEPs were graded according to the presence and amplitude of their cortical responses, EEG patterns were classified according to the American Clinical Neurophysiology Society terminology and brain oedema on brain CT was measured as grey/white matter (GM/WM) density ratio. Sensitivity for poor outcome prediction at 100% specificity was calculated for the three tests individually and in combination. None of the patients underwent withdrawal of life-sustaining treatments before the index event occurred.

Results: A total of 346/396 patients were included in the analysis. At 6 months, 223(64%) had poor neurological outcome; of these, 68 were alive in PVS. Bilaterally absent/absent-pathological amplitude cortical SEP patterns, a GM/WM ratio<1.21 on brain CT and isoelectric/burst-suppression EEG patterns predicted poor outcome with 100% specificity and sensitivities of 57.4%, 48.8% and 34.5%, respectively. At least one of these unfavourable

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patterns was present in 166/223 patients (74.4% sensitivity). Two unfavourable patterns were simultaneously present in 111/223 patients (49.7% sensitivity), and three patterns in 38/223 patients (17% sensitivity).

Conclusions: In comatose resuscitated patients, a multimodal approach based on results of SEPs, EEG and brain CT accurately predicts poor neurological outcome at 6 months within the first 24 h after cardiac arrest.

Keywords: Cardiac arrest, Anoxia-ischemia, Brain, Coma, Prognosis, Electroencephalogram, Somatosensory evoked potentials, Computed tomography

Introduction

Prognostication in comatose survivors of cardiac arrest (CA) is challenging. Although some indices such as short-latency somatosensory evoked potentials (SEPs) or pupillary reflexes are highly specific for predicting poor neurological outcome, their sensitivity does not attain 50%.[1–3] As a result, patients destined to a poor outcome are often not detected by these tests, and their prognosis remains indeterminate.[4] Moreover, in most prognostication studies, the predictors under investigation have been used as criteria for withdrawal of life-sustaining treatment (WLST), creating a self-fulfilling prophecy bias.[5,6]

In patients who are comatose after resuscitation from CA, the current guidelines for Post-Resuscitation Care[7] co-issued by the European Resuscitation Council (ERC) and the European Society of Intensive Care Medicine (ESICM) suggest a multimodal prognostication algorithm based on clinical assessment performed at 72 h or later after CA and on a combination of indices, including SEPs, electroencephalogram (EEG), serum biomarkers, and neuroimaging. These guidelines identified pupillary reflexes and SEPs as more robust predictors to be used first, whereas early myoclonus, EEG, biomarkers and neuroimaging are identified as less robust predictors, to be used only in combination and when results of more robust predictors are indeterminate. At the time the ERC-ESCIM guidelines were written the evidence supporting EEG was limited to relatively few studies in which the definitions of the EEG patterns associated with unfavourable outcome were inconsistent. However, in the last few years a series of studies[1,8–12] adopting the 2012 American Clinical Neurophysiology Society (ACNS) standardized terminology for EEG in the critical care setting,[13] has shown that specific EEG patterns predict poor neurological outcome after CA both early and accurately. In particular, in a preliminary retrospective study performed at our Institution,[14,15] we demonstrated that malignant EEG patterns, in combination with the presence of abnormal SEPs or oedema on brain computed tomography (CT) predicted poor neurological outcome at six months with high sensitivity and specificity as early as 24 h after CA. A special strength of this investigation was that WLST was not performed in the study population, limiting the risk of a self-fulfilling prophecy bias.[16] In order to validate these results and assess their reproducibility, we conducted the present investigation, based on a predefined subset of patients enrolled in the multicentre prospective ProNeCA study.

Materials and methods

Study design and patient selection

The ProNeCA (**Pro**gnostication of **Ne**urological outcome after **CA;** Clinicaltrials.gov:NCT03849911) is a prospective multicentre study conducted in 13 mixed medical-surgical intensive care units(ICUs) from eight university-affiliated and five non-university affiliated Italian hospitals and coordinated by the Careggi University Hospital in Florence, Italy.[17] The study included all consecutive adult (≥18years) patients who were admitted to participating ICUs in a coma (Glasgow Coma Scale ≤8) following resuscitation from CA between June 1, 2016 and June 1, 2018. Exclusion criteria were brain death, traumatic/surgical causes of CA, pre-existing neurological disability, and a life expectancy shorter than six months. The aim of the ProNeCA study was to assess the accuracy of EEG and SEPs (each recorded at 12–24 and 72 h after CA), and of brain CT (recorded within the first 24 h after CA) for predicting neurological outcome at six months. In 7/13 centres, including the coordinating centre, all prognostication tests were available, whereas in the remaining six centres only EEG and SEP data were collected. In this first report of the ProNeCA, we investigated early prediction of poor neurological outcome using EEG and SEPs recorded at 12–24 h after CA, and brain CT recorded within 24 h after CA in the seven centres where all prognostic modalities were available. In a subsequent study we will assess both the accuracy of EEG and SEPs for a later prediction of poor neurological outcome (72 h after CA) and the accuracy of EEG for early prediction of good neurological outcome (within 12 h after CA).

Index test recording and classification

All index tests were prescribed and interpreted by a single neurologist at each participating site.

EEG

A routine 30-min EEG was recorded according to the International 10–20 System by board-certified neurologists and EEG technicians and classified according to the ACNS terminology.[12,13] Eight EEG patterns were identified: continuous, nearly continuous, discontinuous, epileptiform discharges, low-voltage (<20 μV), burst-suppression, suppression (<10 μV) and isoelectric (<2 μV). Further details on the EEG classification are provided in the Electronic Supplementary Material (ESM Table 1).

SEPs

SEP cortical responses of the median nerve were recorded using standard procedures (for further details, see Appendix 1 and Ref.[18] The N20 and P25 waves were identified as the major negative peak with a latency of approximately 20 ms from the stimulus, and the major positive peak following N20, respectively. The SEP cortical response was defined as N (normal), P (pathological: N20/P25 amplitude lower than the limit of normality (5thpercentile) of each participating centre) and A (absent): no reproducible cortical components in presence of the P14 lemniscal wave.[1,11,19–21] Based on the combination of SEP grading on each hemisphere, we identified six SEP patterns: bilaterally normal (NN), bilaterally pathological (PP), bilaterally absent (AA), or a combination of the three above (NP, NA, AP). When both

SEP cortical and lemniscal waves were absent, patients were excluded from analysis, assuming that they were evolved towards brain death during the time interval from ICU admission to SEP evaluation.

Brain CT

Details on brain CT measurements are provided elsewhere.[18] Briefly, brain CT scans with slices from 2.5 to 4.8 mm of thickness were acquired. Circular (0.6 cm^2) regions of interest (ROIs) were identified in the corpus callosum (CC), and – at the basal ganglia level – in the caudate nucleus (CN), putamen (PU), and the posterior limb of the internal capsule(PLIC), bilaterally. The density of these ROIs was measured in Hounsfield Units (HU) and the severity of brain oedema was measured as the density ratio between the grey and the white matter: GM/WM ratio = (CN + PU)/(CC + PLIC) as previously described.[22] The results of the brain CTs were interpreted at the end of the study completion by investigators unaware of the patients' outcome.

Patient management

At each participating ICU, patients were managed according to local practices. The choice of the targeted temperature management (TTM) protocol, i.e., 34 °C vs. 36 °C, as well as the choice of sedatives, analgesics and neuromuscular blocking agents were at the discretion of the participating centre. However, use of TTM for a minimum of 24 h, avoiding fever (central body temperature below 37.5 °C) until 72 h after CA, and use of short-acting sedative agents such as propofol (range 1–2 mg/Kg/h) or midazolam (range 0.03–0.1 mg/Kg/h) were recommended. WLST was not performed in any of the participating centres and treatment was continued in all patients, except when brain death occurred. None of the study investigators was involved in patient management either during or after the patients' ICU stay.

Outcome assessment

Neurological outcome was classified using the Glasgow–Pittsburgh Cerebral Performance Categories (CPC). The CPC scale is as follows: 1 = no or minor neurological deficits; 2 = moderate neurological disability; 3 = severe neurological disability; 4 = persistent vegetative state and 5 = death. CPC was assigned by blinded assessors at hospital discharge using clinical examination, and at six months using telephone interviews.

The primary endpoint of this study was the accuracy of EEG, SEPs, and brain CT in predicting poor neurological outcome, defined as CPC 4 or 5 at 6 months. In order to make our results comparable with those of other studies using a different CPC threshold[23] we also calculated the accuracy of index tests for CPC 3–5 as a poor outcome.

Data reporting in this study is compliant with the Standards for Reporting of Diagnostic Accuracy Studies (STARD) Statement, 2015 version.[24] The STARD checklist for this study is included as an ESM.

Ethical approval

The study protocol was approved by the Regional Ethics Committee of Tuscany (Ref OSS.15.009). Written informed consent was obtained from the patient's authorized representative prior to the subject enrolment.

Statistical analysis

Continuous variables were reported as median and inter-quartile range (IQR), whereas categorical variables were reported as numbers and percentages. For the Glasgow Coma Scale the range was reported. Normality of baseline distribution was tested using the Shapiro–Wilk test. The Pearson's chi-square and the Mann–Whitney U tests were used for comparing categorical and continuous variables, respectively. For each of the instrumental outcome predictors a receiver operating characteristics (ROC) curve and the area under the curve(AUC), with its relevant 95% confidence intervals (CIs) were calculated. The sensitivity corresponding to a 100% specificity (false positive rate [FPR] = 0%) for each individual predictor was measured. The added value in terms of increased sensitivity of using a multimodal prediction strategy was assessed by calculating the cumulative proportion of patients who were correctly identified as having poor outcome when at least one among the three investigated indices reached the threshold for 100% specificity. We performed a tree-based analysis[25] to identify the best combination of different predictors in order to maximise sensitivity for outcome prediction, and calculated the sensitivity of the possible combinations of two criteria indicating poor outcome with 100% specificity. A p-value < 0.05 was considered statistically significant. The exact Clopper-Pearson method was used for calculation of 95% intervals around the point estimate. Statistical analysis was performed using Wizard 1.9 version (Evan Miller, USA) and IBM-SPSS Statistics for Windows 25.0 version (IBM Corp., Armonk, NY, USA).

Results

Among the 396 patients who were screened for inclusion, 362 fulfilled the inclusion criteria and had all the three tests performed. In six of them the tests could not be analysed, whereas ten patients were lost to follow-up, leaving 346 patients with measured primary outcome at 6 months (Fig.1). Of these, 232 (67%) survived to hospital discharge, of whom 96 (41%) had favourable outcome. At 6-month follow-up, 191 patients were alive, of whom 123 (64.3%) had favourable outcome. Among the 223 (64%) patients who had an unfavourable outcome at six months, 68 were in persistent vegetative state and 155 were dead. Table 1 shows the demographic and clinical characteristics of patient population. Older age, female gender, longer CA duration, and asystole as first recorded rhythm were associated with significantly higher rates of unfavourable outcome, while no significant association was observed with the use of TTM.

Single-parameter prediction of poor outcome

Based on ROC curve analysis, the optimal cut-off that maximised sensitivity for poor outcome prediction while maintaining 100% specificity was identified in SEPs, EEG, and brain CT, and index test results were dichotomised accordingly. SEP patterns were dichotomised as grade 2 (bilaterally absent or absent-pathological: AA, AP) vs. grade 1 (normal on at least one side or bilaterally pathological but present: NN, NP, NA, PP). EEG patterns were dichotomised as malignant (isoelectric and burst-suppression) vs. non-malignant (continuous, nearly continuous, discontinuous, epileptic discharges,

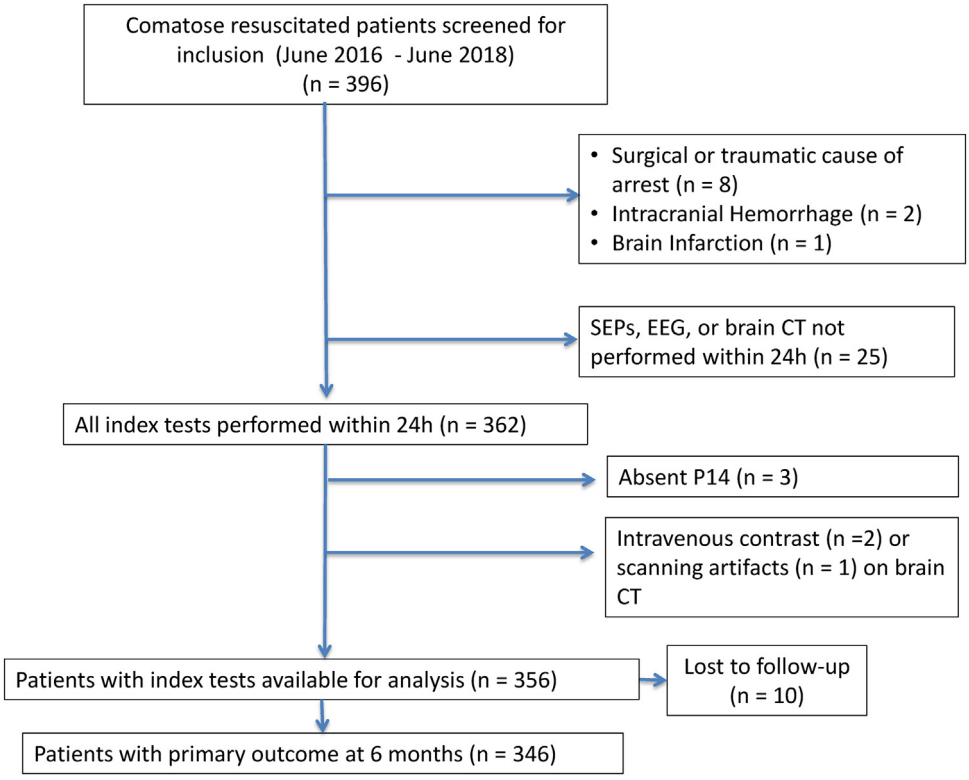

Fig. 1 – Flow chart of study inclusion.

low-voltage and suppression), whereas for brain CT a threshold of <1.21 of GM/WM ratio was identified. The corresponding sensitivities were 57.4%, 34.5%, and 48.8% respectively (Table 2), while their corresponding AUCs were 0.86 [95%CI 0.82–0.90], 0.87 [0.83–0.90] and 0.89 [0.84–0.94] respectively (Fig. 2a–c).

We recalculated the cut-off and the accuracies of the index tests using a CPC threshold of 3 (severe neurological disability) rather than 4 for poor neurological outcome). A 100% specificity was confirmed for all predictors, with slightly lower sensitivities. These were 49.6%, 42.2%, and 29.8% for Grade 2 SEPs, GM/WM ratio, and malignant EEG, respectively (see Ref.[26]

Multimodal prediction

At 100% specificity, the grade 2 (AA/AP) SEP pattern was the best single predictor in terms of sensitivity, occurring in 128/223 (57.4%) patients with poor outcome. Among the remaining 93 patients with poor outcome, 23 had a GM/WM ratio <1.21 on brain CT, raising the cumulative sensitivity to 70.4%. Finally, when a malignant EEG pattern was added, 15 additional patients with poor prognosis were identified and the sensitivity for poor outcome prediction raised to 74.4% [68.1–80], with 0% [0–3] false positive rate (tree-based analysis on Fig. 3; see also Table 2).

We assessed the sensitivities of a combination of multiple parameters predicting poor outcome with 100% specificity in the same patient. Among the 223 patients with poor neurological outcome at six months, three prognostic criteria were simultaneously present in 38 patients (17% sensitivity), whereas two criteria were present in 111 patients (49.7% sensitivity). More in detail, the association of grade 2 SEP and GM/WM ratio <1.21 occurred in 80 patients (35.8% sensitivity), the association of grade 2 SEP pattern and malignant EEG patterns occurred in 63 patients (28.2% sensitivity), whereas the association of malignant EEG patterns and GM/WM ratio <1.21 occurred in 44 patients (19.7% sensitivity).

Discussion

This is the first multicentre prospective study evaluating the accuracy of a combination of EEG, SEPs and brain CT for early neurological prognostication after CA. Its results confirmed those of our preliminary study[14] and showed that in the majority of comatose resuscitated adults poor neurological outcome can be accurately predicted within 24 h after CA, an early phase when results of clinical examination are unreliable, as demonstrated by previous literature[6,27] and also shown by the high proportion of initially absent pupillary reflex we observed in patients with good neurological outcome in our cohort.

We demonstrated the additive benefits of combining the most accurate predictors in a multimodal stepwise approach in order to maximise sensitivity while maintaining 100% specificity. When this approach was used, only 57/223 (25.6%) of patients destined to poor outcome at six months had an indeterminate prognosis at 24 h after the event. This 74.4% sensitivity was much higher than that observed in previous multimodal prognostic studies on post-CA patients (62% in Tsetsou et al.;[28] 50% in Hofmejer et al.[29]). In a very recent single-centre study[30] a stepwise prognostic model achieved a similar accuracy than in our study (77% sensitivity and 100% specificity). However, besides SEPs, EEG and imaging, that

Table 1 – Characteristics of the study population (n = 346).

Variables	Favourable outcome n = 123	Unfavourable outcome n = 223	*p* Value
Age, years	65 (48–67)	72 (55–71)	0.001
Gender, female	36 (29)	94 (42)	0.018
Out-of-hospital	91 (74)	182 (82)	0.09
Witnessed	105 (85)	177 (79)	0.17
CA duration (min)	15 (9-20)	20 (11-39)	0.001
Initial rhythm			0.001
VF/pVT	71 (58)	73 (33)	
PEA	29 (24)	58 (26)	
Asystole	10 (8)	61 (27)	
Unknown	13 (10)	31 (14)	
Pupillary reflex at neurophysiological evaluation		0.0001	
Absent	24 (20)	123 (55)	
Present	96 (78)	93 (42)	
Unknown	3 (2)	7 (3)	
GCS at ICU admission	3 (3–8)	3 (3–7)	0.03
TTM			0.43
No	68 (55)	139 (62)	
34 °C	49 (40)	74 (33)	
36 °C	6 (5)	10 (5)	
CPC at hospital discharge			
CPC 1	11 (3)	–	
CPC 2	23 (7)	–	
CPC 3	62 (18)	–	
CPC 4	–	136 (39)	
CPC 5	–	114 (33)	
CPC at 6 months			
CPC 1	43 (12)	–	
CPC 2	45 (13)	–	
CPC 3	35 (10)	–	
CPC 4	–	68 (20)	
CPC 5	–	155 (45)	

Data are presented as count (percentage) or median (interquartile range; range for GCS score).
Abbreviations: CPC, Cerebral Performance Category; GCS, Glasgow Coma Scale; ICU, intensive care unit; PEA, pulseless electrical activity; pVT, pulseless ventricular tachycardia; VF, ventricular Fibrillation; TTM, Targeted Temperature Management.

Table 2 – Accuracy of index tests (single and in combination) for prediction of poor outcome at 6 months.

Index test	TP	FP	TN	FN	Sensitivity % (95%CI)	False positive rate % (95%CI)
Single test prediction						
Grade 2 SEPs	128	0	123	95	57.4 (50.6– 63.9)	0 (0–3)
GM/WM ratio <1.21	109	0	123	114	48.8 (42.1– 55.6)	0 (0–3)
Malignant EEG	77	0	123	146	34.5 (28.3– 41.1)	0 (0–3)
Combination of two tests						
Grade 2 SEPs or GW/WM ratio <1.21	157	0	123	66	70.4 (63.9– 76.3)	0 (0–3)
Malignant EEG or GW/WM ratio <1.21	142	0	123	81	63.6 (56.3– 69.5)	0 (0–3)
Grade 2 SEPs or Malignant EEG	139	0	123	84	62.3 (55.6– 68.7)	0 (0–3)
Combination of three tests						
At least one test predicting poor outcome	166	0	123	57	74.4 (68.1– 80.0)	0 (0–3)

Grade 2 SEP pattern corresponds to a bilaterally absent N20 wave or an absent N20 wave on one side + a low-voltage N20 on the other side. A malignant EEG corresponds to an isoelectric or burst-suppression pattern as defined by the 2012 American Clinical Neurophysiology Society standardized terminology.[13]
Abbreviations: CI: Confidence Interval; EEG: Electroencephalogram; GW/WM: Gray Matter/White Matter; SEPs: Somatosensory Evoked Potentials.
FN, false negative; FP, false positive; TN, true negative; TP, true positive.

model also included clinical examination and serum biomarkers, which resulted in greater complexity and, as regards serum biomarkers, additional costs and presumably lower generalizability. Moreover, differently from our study, all the predictive models described in the studies above included two or more tests to be recorded later than 24 h.

Among the early predictors included in our model, EEG has been the most extensively studied in recent years. Previous studies[9,29,31]

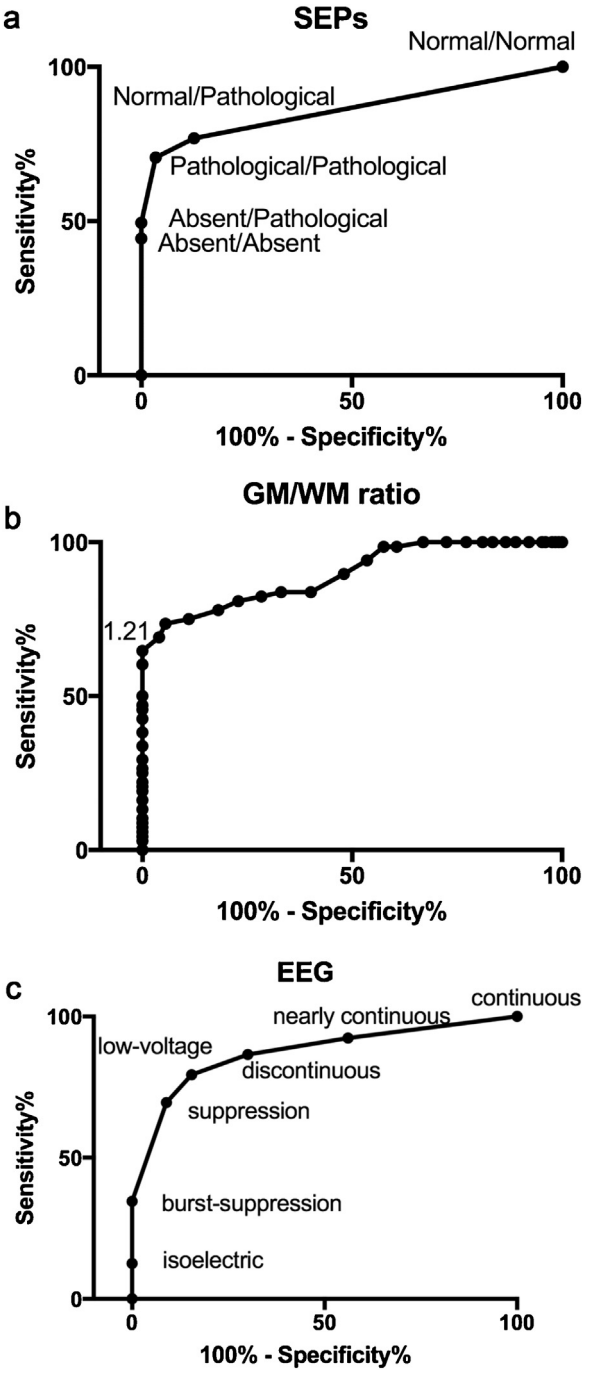

Fig. 2 – ROC curves for SEP cortical response (A), GM/WM ratio (B), and EEG patterns (C).

showed that a malignant EEG at 24 h after CA predicted poor outcome with 100% specificity and a sensitivity ranging from 28% to 48%, which is in line with the 34.5% sensitivity we observed in our population. However, these were single-centre studies in which continuous EEG was interpreted by experienced investigators. Conversely, our study was conducted in multiple centres using a routine 30-min EEG assessed by local staff members. When interpreting EEG results during the first 24 h from CA, clinicians should be aware of the potential interference from sedative agents used in the early post-resuscitation phase. In particular, propofol can induce burst-suppression in patients undergoing intravenous anaesthesia.[32] Although the presence of burst-suppression was not associated with any falsely positive prediction in our study, we cannot exclude that the use of propofol may have caused interference with EEG interpretation in other studies where the burst-suppression pattern was found to be less accurate for prediction of poor outcome.

This multicentre study confirmed our preliminary results[14] which showed that both the bilateral absence(AA) and the absence-pathological amplitude(AP) of the cortical SEP responses predicted poor neurological outcome with 0% FPR at 24 h after CA. This suggests that prognostication using SEPs may be considered earlier than currently recommended.[7] Indeed, neurological recovery despite a bilaterally absent N20 SEP wave during the first 24 h after CA has only exceptionally been described[2,3] and in some of these rare cases the absence of the N20 has been attributed to technical issues.[33] Moreover, in a sequential study from our group where SEPs were recorded during and after TTM in 60 comatose post-CA patients,[34] none of the subjects in whom the cortical SEP components were absent during TTM had neurological recovery or reappearance of the cortical waves after rewarming.

Our results concerning brain CT are particularly robust because – differently from other studies in literature – we performed CT systematically in all consecutive enrolled patients as part of a prospective design, rather than at discretion of the treating physician. These results confirmed that a 1.21 cut-off of the GM/WM ratio at the basal ganglia level on brain CT clearly discriminated between patients recovering and those not recovering consciousness (see Ref. [26]). However, brain CT did not show any granularity in discriminating patients with outcomes ranging from CPC 1 to CPC 3.[26] This last finding is in line with that of another large study,[35] and suggests that early signs of brain oedema after CA on brain CT are present only in the most severe cases of hypoxic-ischemic encephalopathy.

In our tree-based analysis we showed that a high sensitivity for poor outcome can be achieved when at least one malignant pattern is present on SEPs, brain CT or EEG. However, systematic reviews[2,3] have shown that no single index predicts outcome with absolute certainty. For this reason, in order to minimise the risk of a falsely pessimistic prediction, the 2015 ERC-ESICM guidelines recommend that a combination of multiple criteria should simultaneously be present when prognostication is made, especially as far as EEG and imaging are concerned.[6] This has obviously a cost in terms of sensitivity, since prognostic indices explore different anatomical and functional districts in the central nervous system and the subpopulations of patients with poor neurological outcome they identify do not completely overlap. Indeed, in our study, malignant EEG and signs of severe oedema on brain CT - a combination similar to that recommended by the ERC-ESICM guidelines - occurred simultaneously in only 19.7% of patients with poor outcome.

Our study has several strengths. Firstly, it has been conducted in multiple centres using accessible technologies, and tests were interpreted by the local medical staff participating in the study. This made our results generalizable. Secondly, because of the absence of WLST in our patient cohort, the self-fulfilling prophecy bias was minimised, which is very rarely achieved in prognostic studies.[36] Thirdly, the large size of our population ensured a good precision. For each predictor, the width of the 95%CIs for specificity was always less than 5%, a threshold adopted in the ERC-ESICM Guidelines as a prerequisite for a robust prediction.[6] Finally, our prediction model was accurate both when

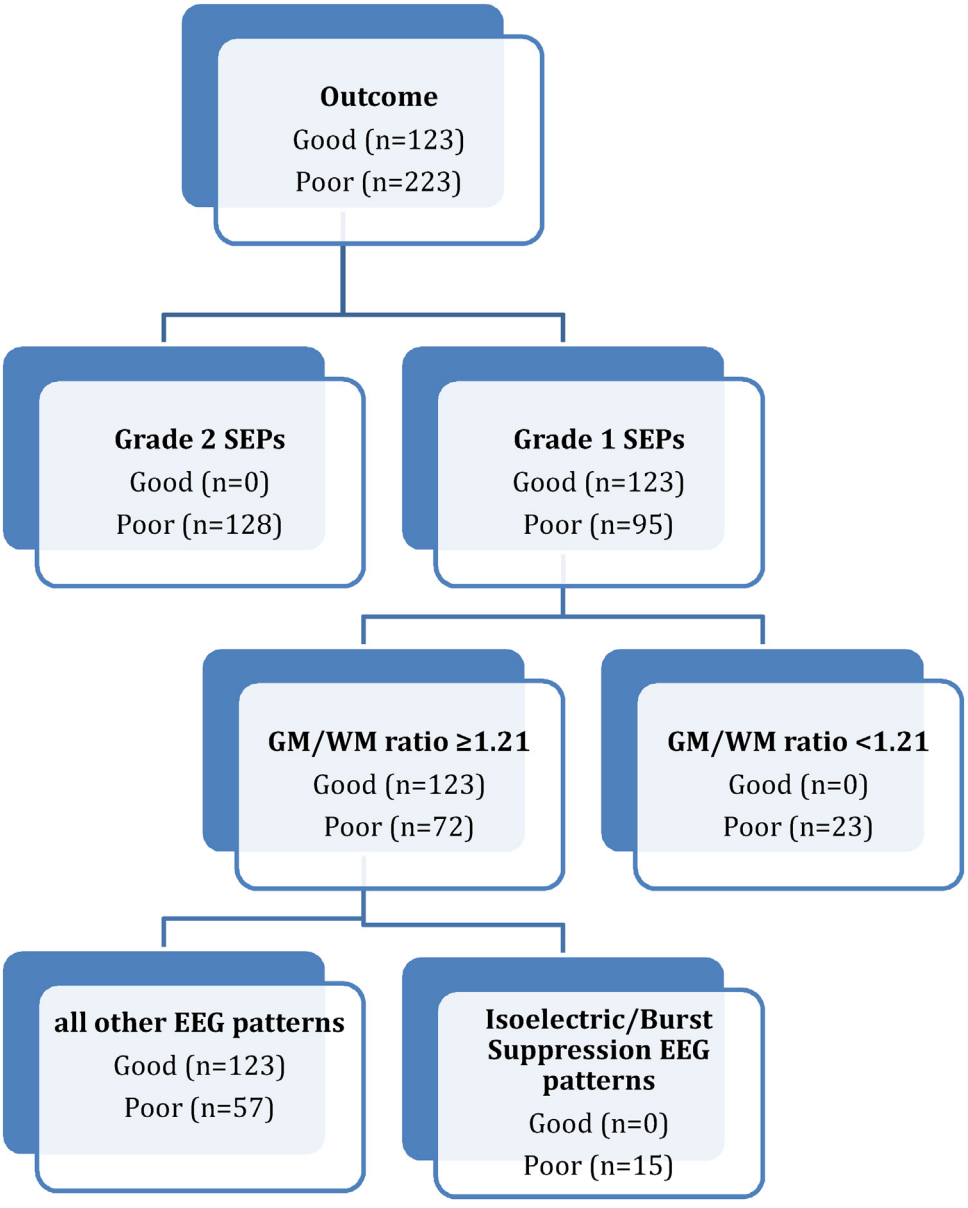

Fig. 3 – Classification-tree analysis for prediction of poor neurological outcome at 6 months. The tree identifies the best combination of index tests in order to maximise sensitivity.

the CPC 4–5 and when the CPC 3–5 thresholds were used to define poor outcome, even if sensitivity was lower with CPC 3–5.[15]

Some limitations of our study must be acknowledged. Firstly, the treating staff was not blinded to the results of prognostic tests. Therefore, we cannot exclude that this may have influenced treatment decisions in some way. However, the high rates of CPC 3 and 4 at six months we observed confirm that WLST was unlikely to occur in our cohort, and that the risk of self-fulfilling prophecy was minimised. Secondly, patient management was not standardised. The majority of patients included in our study did not undergo TTM, therefore, our results may not necessarily be generalizable to a TTM-treated population. However, the accuracy of these tests was 100% throughout our population, independently from temperature management. Thirdly, test results were interpreted by a single neurologist at each participating site; the lack of a second assessor prevented us from assessing the reproducibility of our index test readings. On the other hand, however, our study had a pragmatic design, aimed at reproducing the conditions in which prognostic tests are usually performed in everyday practice. Finally, the present study is limited to prognostication within 24 h after CA. We will investigate the validity of these predictors after TTM and suspension of sedation in a further study.

Conclusions

This is the first prospective multicentre study evaluating the reliability of a multimodal prognostic strategy based on standard EEG, SEPs

and brain CT performed within 24 h after CA. Its results showed that using this approach a poor neurological outcome can be predicted early, accurately, and with a very high sensitivity using tests available in most clinical settings. The robustness of these results is reinforced by the absence of a WLST as a standard of care in the population under investigation.

Conflict of interest statement

Claudio Sandroni is member of the Editorial Board of *Resuscitation,* co-author of the 2015 ERC-ESICM Guidelines on Post-Resuscitation Care and lead author of the 2013 ERC-ESICM Advisory Statement on Prognostication in comatose survivors of cardiac arrest.

The remaining authors have no conflict of interest to disclose.

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Appendix A.

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Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.07.032.

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