HHS Public Access

Author manuscript

Resuscitation. Author manuscript; available in PMC 2018 January 01.

Published in final edited form as:

Resuscitation. 2017 January ; 110: 120–125. doi:10.1016/j.resuscitation.2016.10.024.

Combination of initial neurologic examination, quantitative brain imaging and electroencephalography to predict outcome after cardiac arrest

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Abstract

Background—Prognosticating outcome following cardiac arrest is challenging and requires a multimodal approach. We tested the hypothesis that the combination of initial neurologic examination, quantitative analysis of head computed tomography (CT) and continuous EEG (cEEG) improve outcome prediction after cardiac arrest.

Methods—Review of consecutive patients receiving head CT within 24hrs and cEEG monitoring between April 2010 and May 2013. Initial neurologic examination (Full Outline of UnResponsiveness_Brainstem reflexes (FOUR_B) score and initial Pittsburgh Post-Cardiac Arrest Category (PCAC)), gray matter to white matter attenuation ratio (GWR) on head CT and cEEG patterns were evaluated. The primary outcome was in-hospital mortality.

Results—Of 240 subjects, 70 (29%) survived and 22 (9%) had a good neurologic outcome at hospital discharge. Combined determination of GW ratio and malignant cEEG had an incremental predictive value (AUC: 0.776 for mortality and 0.792 for poor neurologic outcome), with 0% false positive rate when compared with either test alone (AUC of GW ratio: 0.683 for mortality and 0.726 for poor outcome, AUC of malignant cEEG: 0.650 for mortality and 0.647 for poor outcome). Addition of FOUR_B or PCAC to this model improved prediction of mortality (p=0.014 for FOUR_B and 0.001 for PCAC) but not of poor outcome (p=0.786 for FOUR_B and 0.099 for PCAC).

Conclusions—Combining GWR with cEEG was superior to any individual test for predicting mortality and neurologic outcome. Addition of clinical variables further improved prognostication

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Conflict of Interest

The authors have no conflict of interest to report.

for mortality but not neurologic outcome. These preliminary data support a multi-modal prognostic workup in this population.

Keywords

cardiac arrest; prognostication; examination; imaging; electroencephalography

Introduction

Coma after successful resuscitation from cardiac arrest (CA) is the most common cause of ICU admission, and the main cause of in-hospital mortality is withdrawal of life sustaining treatment for perceived poor neurological prognosis (WLST).[1–4] Targeted temperature management (TTM) is considered standard treatment after CA and can influence sedative drug metabolism and may interfere with accurate prognostication.[5–8] Moreover, WLST is strongly associated with persistent coma. Therefore, strategies for accurate prediction of neurological outcome after CA are critically needed.

Several prognostic tools such as neurologic examination, somatosensory evoked potential (SSEP), serum biomarkers, electroencephalography (EEG), brain computed tomography (CT) and diffusion weighted magnetic resonance imaging (DW-MRI) have been evaluated as predictors of neurological outcome.[9–19] The combination of multiple modalities is recommended because no single test short of physical examination meeting brain death criteria can predict neurologic outcome correctly.[20–22] We previously reported that combining the initial neurologic examination with continuous EEG (cEEG) was superior to any individual test for predicting outcome after CA.[23] Using a multimodal approach can minimize the risk of erroneous prognostication of poor outcome.

We hypothesized that the combination of initial neurologic examination, quantitative analysis of brain CT and cEEG can improve outcome prediction after CA. We performed a retrospective analysis of data to test whether the combination of initial brain stem reflex examination evaluated using Full Outline of UnResponsiveness Brainstem (FOUR_B) score or Pittsburgh Cardiac Arrest Category (PCAC), quantitative analysis of head CT calculated by gray matter to white matter attenuation ratio (GWR) and cEEG was superior to either test alone for predicting outcome after CA.

Methods

Study design and setting

We conducted a retrospective analysis of prospectively collected data from a single urban teaching hospital between April 2010 and May 2013. This study was approved by the University of Pittsburgh Institutional Review Board. We included patients who received both head CT scan within 24 hrs and cEEG monitoring. All patients receive serial clinical examinations as part of clinical care. Exclusion criteria were as follows: age < 18 yrs, traumatic cardiac arrest, history of cerebrovascular accident, intravenous contrast in brain CT and large artifacts in brain CT.

The patients were managed according to our previously published post-cardiac arrest care protocols.[13,23,24] Briefly, TTM at 33°C was induced with rapid infusion of 30 cc/kg of 4°C saline and thermostatically controlled surface cooling devices (Gaymar Industries, Orchard Park, NY; Arctic Sun, Bard Medical Division, Louisville CO) and maintained for 24 hrs. Intravascular cooling is rarely employed after cardiac arrest in our cohort. Propofol was infused to suppress shivering, or midazolam was infused in cases of hypotension. Neuromuscular paralysis was used often during induction period and rarely used during maintenance and rewarming period.

Methods of measurement

Initial neurologic examination was routinely assessed using FOUR score and PCAC within the first 6 hours of resuscitation and without sedation and paralysis by one of the post-cardiac arrest service physicians. The FOUR score is composed of Motor, Brainstem, Respiratory and Eye responses. Each domain has a 0–4 score and a higher score indicates greater function. As previously reported, we used the FOUR_B score to stratify patients into three groups; FOUR_B = 0–1, FOUR_B = 2 and FOUR_B = 4.[23] We also quantified severity of post-arrest illness using the validated Pittsburgh Cardiac Arrest Category system, where: I) awake, II) coma (not following commands but intact brainstem responses) + mild cardiopulmonary dysfunction (SOFA cardiac + respiratory score <4), III) coma + moderate-severe cardiopulmonary dysfunction (SOFA cardiac + respiratory score ≥4), and IV) coma without brainstem reflexes.[3, 25]

Our hospital implemented 22-channel digital cEEG recordings for the first 48 h after resuscitation from CA as standard monitoring for all comatose post-cardiac arrest patients in August 2009.[13] cEEGs were interpreted during patient care by board certified neurologists, and malignant patterns were defined as follows: non-convulsive status epilepticus (NCSE), convulsive status epilepticus (CSE), myoclonic status epilepticus (MSE) and generalized periodic epileptiform discharges (GPEDs). The definition of each malignant pattern has been described previously.[13] Myoclonic status epilepticus was characterized as the presence of myoclonic jerks or facial movements associated with GPEDs or with the bursts in a burst suppression pattern. The presence of reactivity and continuous background was not always provided in the clinical interpretation and was not included in the report of the EEG for this study. Patients with malignant EEG patterns are treated with a bolus of lorazepam followed by levetiracetam and valproic acid. Phenytoin is employed next, followed by either a continuous infusion of midazolam or phenobarbital for refractory cases.

Baseline brain CT scanning in patients presenting comatose after resuscitation is a part of standard care in our hospital. CT scans were obtained on a GE Light Speed VCT scanner (GE Healthcare, Little Chalfont, UK) with 5 mm slices at the time of emergency department admission. GWR was calculated by an investigator blinded to clinical information as previously reported.[17] Briefly, Hounsfield Units (HU) were recorded at the basal ganglia level; caudate nucleus, putamen, genu of corpus callosum, and posterior limb of internal capsule and also recorded at the cerebrum level; the medial cortex and medial white matter at the level of the centrum semiovale and high convexity area. Average gray matter to white matter ratio (aGWR) was calculated as the mean of the Basal Ganglia GWR and Cerebrum

GWR. Patients were divided into three groups according to their aGWR; severe edema (aGWR < 1.1), mild edema (aGWR 1.1 – 1.2) and no edema (aGWR ≥ 1.2).

Outcome measures

The primary outcome of this study was in-hospital mortality. Functional outcome was assessed at the time of hospital discharge by one of the Post-Cardiac Arrest Service attending physicians using Cerebral Performance Category (CPC). The five categories of the CPC are: CPC 1, conscious and alert with good cerebral performance; CPC 2, conscious and alert with moderate cerebral performance; CPC 3, conscious with severe cerebral disability; CPC 4, comatose or in persistent vegetative state; and CPC 5, brain dead, circulation preserved. We defined a good outcome as a CPC score of 1 or 2.[26]

Statistical analysis

The data were summarized using means and standard deviations (SD). For patient characteristics and comparisons between groups, we used a parametric and nonparametric analysis of variance for continuous variables and Fisher's exact test or chi-square test for categorical variables. We determined predictive performance using receiving operating characteristic curves set up with logistic regression models to assess and compare for equality of the area of under the curve (AUC) using the Delong test. First, we determined the AUC of each test using the ROC curves: FOUR_B, PCAC, GWR and cEEG. And then, to test the superiority of the combination of cEEG and GWR than that of either test alone, the AUC of combination of GWR and cEEG were calculated and compared with that of each test. Finally, we added FOUR_B or PCAC into this model and compared with combination of GWR and cEEG. Statistical analyses were performed using SPSS 20.0 (Chicago, IL) and MedCalc 15.2.2 (MedCalc Software, Mariakerke, Belgium). P values ≤ 0.05 were considered statistically significant. The Youden Index was used to determine the optimal cut off point for mortality and poor neurologic outcome.[27]

Results

Patient demographics

Of the 671 patients seen during the study period, 93 were awake on presentation (PCAC I). In the remaining 578 comatose patients, 314 were excluded due to: lack of CT imaging, CT imaging of poor quality, or imaging completed >24 hrs after arrest. An additional 5 had intracranial hemorrhage and 1 was confounded by IV contrast. An additional 14 subjects did not have cEEG monitoring. Three subjects rapidly awoke and one subject was hypothermic (29°C) on arrival. Thus, 240 subjects met both inclusion and exclusion criteria. Mean age was 56 (SD 17) years and 147 (61%) subjects were male. Ventricular fibrillation was initial rhythm for 66 (27%) subjects. Seventy subjects (29%) survived at hospital discharge and 22 (9%) subjects experienced good neurological outcome. Ninety-three subjects had FOUR_B scores of 0–1, 62 had FOUR-B scores of 2, 76 had FOUR_B scores of 4 and 9 had missing initial FOUR_B score. The distribution of post-arrest illness severity was as follows: PCAC II 25% (n=61), PCAC III 14% (n=33), and PCAC IV 57% (n=137). Malignant cEEG patterns were observed in 75 subjects (31%). [Table 1] Average GWR ranged from 0.899 to

1.534. Thirty-seven subjects exhibited severe brain edema (GWR < 1.1) and 38 subjects had mild brain edema (GWR 1.1 – 1.2).

Association between initial FOUR_B and GW ratio

Average GWR was well correlated with initial FOUR_B Score ($p < 0.001$) [Table 2]. In subjects with GW ratio < 1.2, 43 (57%) had initial FOUR_B score of 0 or 1. Moreover, in subjects with GW ratio < 1.1, 26 (70%) had initial FOUR_B score of 0 or 1. Among subjects with GW ratio > 1.2, 50 (30%) had FOUR_B score of 0 or 1, 49 (30%) had FOUR_B score of 2 and 61 (37%) had FOUR_B score of 4. Even though the majority of subjects with GWR < 1.1 had FOUR_B score of 0 or 1, 6 (16%) subjects had both pupillary light reflex and corneal reflex.

Association between malignant cEEG patterns and GWR

Average GWR was not associated with malignant cEEG patterns ($p=0.687$) [Table 3]. In subjects with GW ratio < 1.1, only 2 (5%) had malignant cEEG. Both subjects exhibited myoclonic status epilepticus (MSE). Otherwise, in subjects with GW ratio between 1.1 and 1.2, 18 (47%) subjects had malignant cEEG.

Prognostic value of single modality

Table 4 shows the areas under the ROC curves, sensitivity, specificity, PPV and NPV of each single test. The cutoff value of GW ratio was 1.066 to maintain 0% of FPR for predicting mortality. The cutoff value of GW ratio was 1.077 to maintain 0% of FPR for predicting poor neurologic outcome. [Supplemental Figure 1]

Prognostic value of combined modality

Table 5 shows the areas under the ROC curves for single test. The AUC of combination of GWR and malignant cEEG at 48 hrs to predict mortality is 0.776 (95% C.I. 0.718–0.827) which is superior to either GW ratio alone or malignant cEEG at 48hrs alone ($p<0.001$ and $p<0.001$, respectively). When FOUR_B or PCAC is added to this model, the predictive value further improves (AUC of adding FOUR_B: 0.820 ($p=0.014$), AUC of adding PCAC: 0.855 ($p=0.001$)) [Fig 1].

The AUC of combination of GWR and malignant cEEG at 48hrs to predict poor neurological outcome is 0.792 (95% C.I. 0.735–0.841) which is superior to malignant cEEG at 48hrs alone ($p<0.001$). When FOUR_B or PCAC is added to this model, the predictive value is not further improved (AUC of adding FOUR_B: 0.800 ($p=0.786$), AUC of adding PCAC: 0.835 ($p=0.099$)) [Fig 2].

For prediction of mortality, the cutoff value of GW ratio was 1.066 to maintain 0% of FPR (sensitivity 16.47%, 95% CI 11.2–22.9) and FPR of malignant cEEG was 10%. [Supplemental Table 2] For prediction of poor neurologic outcome, the cutoff value of GW ratio was 1.077 to maintain 0% of FPR (sensitivity 15.6%, 95% CI 11–21.1) and FPR of malignant cEEG was 4.5%. Among patients with malignant cEEG, the cutoff value of GW ratio was 1.213 to maintain 0% of FPR (sensitivity 39.71%, 95% CI 28–52.3) for prediction of mortality. Among patients with non-malignant cEEG, the cutoff value of GW ratio was

1.066 to maintain 0% of FPR for prediction of mortality. But the sensitivity (26.47%, 95% CI 18.2–36.1) was higher than that of GW ratio alone (16.47%, 95%CI 11.2–22.9). And among patients with non-malignant cEEG, the cutoff value of GW ratio was 1.077 to maintain 0% of FPR for prediction of poor neurologic outcome. However, the sensitivity (22.22%, 95% CI 15.7–29.9) was higher than that of GW ratio alone (15.6%, 95%CI 11–21.1).

Discussion

We demonstrate that combining the GWR with cEEG was superior to either test alone for predicting in-hospital mortality and neurological outcome after resuscitation from CA. Addition of FOUR_B or PCAC to the above model further improved prediction of mortality. This study quantifies the incremental benefit of each modality in this multimodal approach to prognostication. These findings support current guidelines recommending such an approach and quantify the additive benefit in this population.[20–22]

Prior work has examined prognostic tests such as neurologic examination, SSEP, biomarkers, EEG, brain CT, and MRI in isolation.[9–18] Recent work has tested predictive value of multiple modalities, but the ideal combination is not known.[28–32] Importantly, not all tests are necessary for all patients and some facilities may not offer all of these modalities. Some authors propose a stepwise approach to avoid premature WLST.[33] Recent published guidelines also highlighted a multimodal strategy to minimize erroneous prognostication[21–22]. The European Resuscitation Council and European Society of Intensive Care Medicine suggested using a prognostication algorithm in all comatose patients with an absent or extensor motor response to pain at ≥72 h from ROSC[21]. We propose that such approaches should be tested prospectively.

One novel finding of our study is that malignant EEG patterns are more frequent in patients demonstrating mild edema according to their aGWR than in severe edema patients. We have recently demonstrated heterogeneity in MRI findings between those with malignant and non-malignant cEEG patterns.[34] These data suggest that patients with diffuse cerebral edema may lack the neuronal substrate necessary to generate malignant EEG patterns. Severe edema is more likely to result in profound suppression of EEG. While seizures are common after CA and associated with poor outcome, some patients with seizures will awaken and survive.[35–36] To date, there are no studies in the TTM era evaluating prophylactic antiepileptic medications after CA.

There are several limitations in this study. Generalizability is limited given the single site evaluated. Only subjects receiving both head CT scans and cEEG monitoring were included. While it is our protocol for comatose patients to CT imaging and cEEG monitoring, a large proportion were excluded due to CT image quality, timing of CT, and rapid awakening.[17] This rate of exclusion is similar to prior work.[17] These exclusions may be one reason for the low sensitivity seen for predicting poor outcome and the lower good neurologic outcome rate found in the PCAC II cohort. Another limitation is the lack of standard definition of malignant cEEG. The cEEG studies in this study were completed prior to publication of the new definitions. Similarly, data on reactivity or the presence of a continuous background are

not available for this entire cohort. Such an approach provides data commonly available to clinicians treating this population. Results of prognostication tests were available to the treating physicians, potentially creating a self-fulfilling prophecy. Our median length of stay of 4 (IQR 3, 6) days for non-survivors indicates that early WLST may be limited in this cohort. We did not analyze the other prognostic modalities such as SSEP, biomarker and brain DWI. Future studies are needed to determine the added value of combining these modalities. Finally, the short-term outcome of survival to hospital discharge does not address the full magnitude of recovery, which frequently requires up to one year.[37]

Conclusion

Combining the GWR with cEEG was superior to either individual test alone for predicting in-hospital mortality and neurological outcome after cardiac arrest. Addition of FOUR_B or PCAC to this model improved prediction of mortality but not of poor outcome. These data support a multi-modal approach that incorporates clinical, radiographic, and electrophysiologic data to improve prognostic accuracy for this population. Large, multicenter studies should verify these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Appendix

The Post Cardiac Arrest Service

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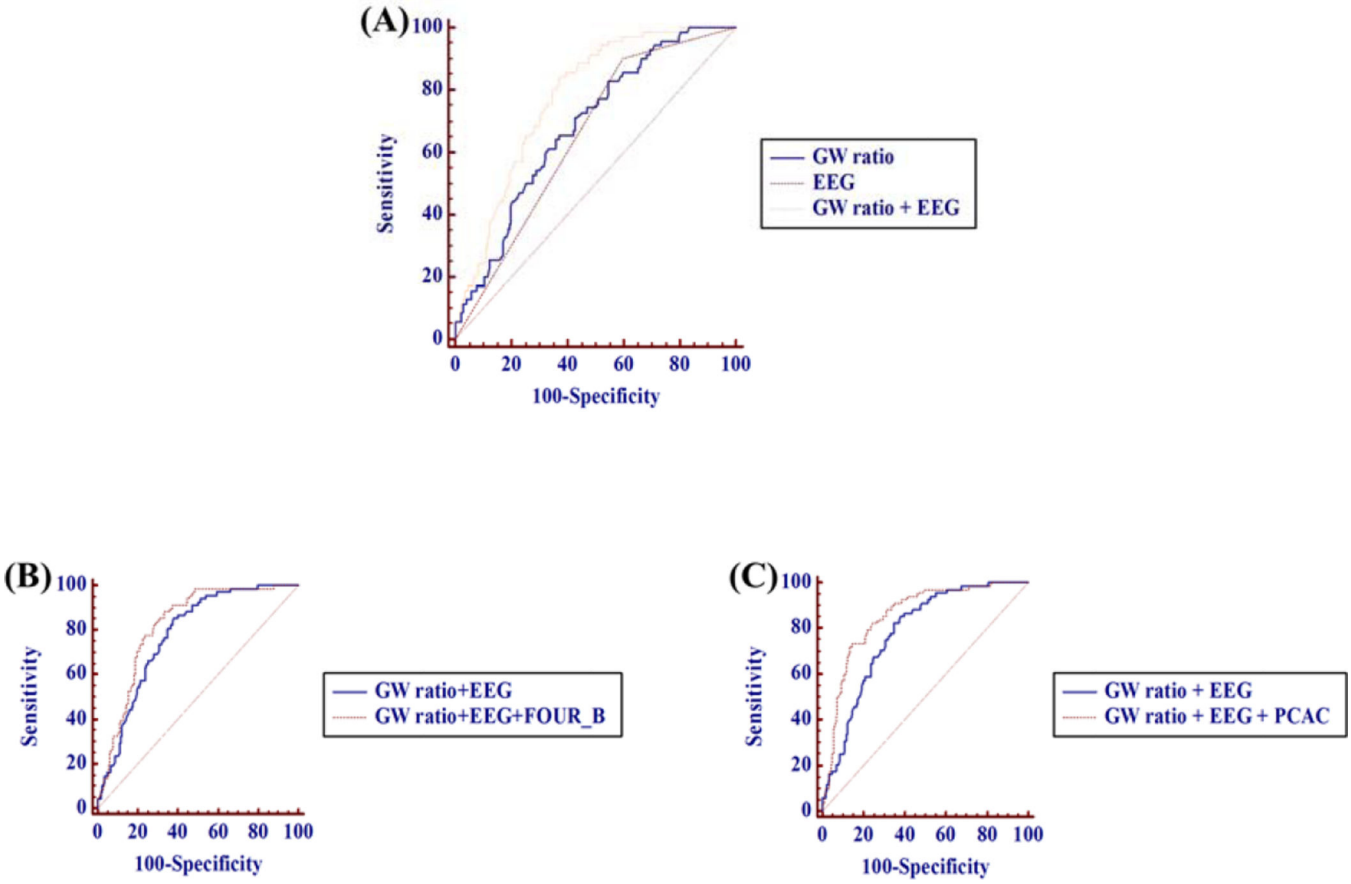

Figure 1. Comparison of ROC curve for predicting mortality

(A) AUC for GW ratio: 0.683, for malignant cEEG: 0.650, for combining GW ratio and malignant cEEG: 0.776 ($p<0.001$, $p<0.001$, respectively) (B) AUC for adding FOUR_B: 0.820 ($p=0.014$) (C) AUC for adding PCAC: 0.855 ($p=0.001$)

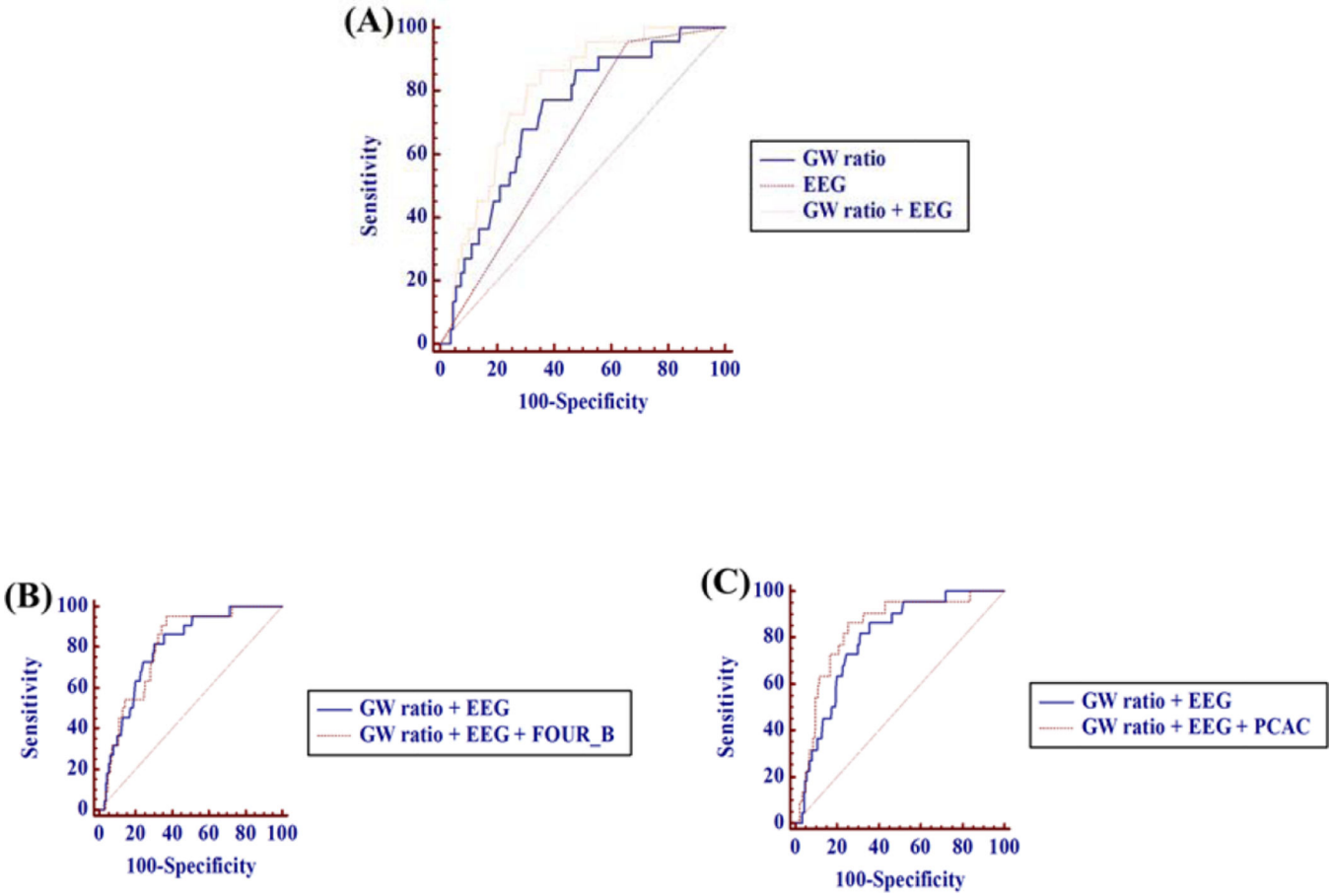

Figure 2. Comparison of ROC curve for predicting poor neurological outcome

(A) AUC for GW ratio: 0.726, for malignant cEEG: 0.647, for combining GW ratio and malignant cEEG: 0.792 ($p=0.067$, $p<0.001$, respectively) (B) AUC for adding FOUR_B: 0.800 ($p=0.786$) (C) AUC for adding PCAC: 0.835 ($p=0.099$)

Table 1

Baseline characteristics of subjects

	Cohort N=240	Survivors N=70	Non-survivors N=170	p
Age, year	56 ± 17	54 ± 18	58 ± 17	0.106
Sex, male	147 (61%)	42 (60%)	105 (62%)	0.799
Initial Rhythm				< 0.001
VF/VT	66 (27%)	33 (47%)	33 (19%)	
PEA	69 (29%)	16 (23%)	53 (31%)	
Asystole	65 (27%)	11 (16%)	54 (32%)	
Unknown	40 (17%)	10 (14%)	30 (18%)	
TH	218 (91%)	64 (91%)	154 (91%)	0.838
LOS, days (IQR)	5 (3, 12)	18 (12, 25)	4 (3, 6)	< 0.001
FOUR_B				< 0.001
FOUR_B=0,1	93 (39%)	9 (13%)	84 (60%)	
FOUR_B=2	62 (26%)	21 (30%)	41 (29%)	
FOUR_B=4	76 (32%)	38 (54%)	38 (27%)	
PCAC				< 0.001
II	61 (25%)	35 (50%)	26 (19%)	
III	33 (14%)	16 (23%)	17 (12%)	
IV	137 (57%)	17 (24%)	120 (86%)	
cEEG, 48hrs				< 0.001
malignant	75 (31%)	7 (10%)	68 (40%)	
non-malignant	165 (69%)	63 (90%)	102 (60%)	
aGWR	1.22 ± 0.11	1.27 ± 0.09	1.20 ± 0.11	< 0.001

Data are expressed mean ± S.D., median (IQR) or percentage.

TH- therapeutic hypothermia; VF/VT- ventricular fibrillation/ventricular tachycardia; PEA- pulseless electrical activity; LOS- length of stay; FOUR- full outline of unresponsiveness; PCAC- Pittsburgh Cardiac Arrest Category; cEEG- continuous EEG; aGWR- Grey-white ratio.

Table 2

Association between initial neurologic examination and GW ratio.

	FOUR_B 0,1 N=93	FOUR_B 2 N=62	FOUR_B 4 N=76
Severe edema GW ratio <1.1	26 (28%)	2 (3%)	6 (8%)
Mild edema GW ratio 1.1–1.2	17 (18%)	11 (18%)	9 (12%)
No edema GW ratio ≥1.2	50 (54%)	49 (79%)	61 (80%)

Table 3

Association between GW ratio and malignant EEG

	Severe edema GW ratio <1.1 N=37	**Mild edema GW ratio 1.1–1.2 N=38**	**No edema GW ratio ≥1.2 N=165**
Malignant EEG at 48hrs	2 (5%)	18 (47%)	55 (33%)
Non-malignant EEG at 48hrs	35 (95%)	20 (53%)	110 (67%)

Table 4

Sensitivity analysis for each single test to predicting mortality and poor neurological outcome

	For mortality				
	AUC	Sensitivity	Specificity	PPV	NPV
Malignant EEG	0.651 (0.586–0.712)	40 (32.6–47.8)	90 (80.5–95.9)	90.7 (81.7–96.2)	38.2 (30.7–46.1)
PCAC > 2	0.751 (0.680–0.822)	84.1 (77.5–89.3)	51.5 (39.0–63.8)	80.6 (73.8–86.2)	57.4 (43.9–70.1)
PCAC > 3		73.6 (66.2–80.2)	75.0 (63.0–84.7)	87.6 (80.8–92.6)	54.3 (43.7–64.6)
FOUR_B=0,1	0.726 (0.663–0.782)	51.5 (43.6–59.4)	86.8 (76.4–93.8)	90.3 (82.4–95.5)	42.8 (34.3–51.5)
GW Ratio≤1.1	0.688 (0.624–0.747)	20 (14.3–26.8)	95.7 (88.0–99.1)	91.9 (78.1–98.3)	33.0 (26.6–40.0)
	For poor outcome				
		Sensitivity	Specificity	PPV	NPV
Malignant EEG	0.650 (0.584–0.711)	33.9 (27.7–40.6)	95.5 (77.2–99.9)	98.7 (92.7–100)	12.7 (8.1–18.8)
PCAC > 2	0.731 (0.627–0.834)	76.6 (70.2–82.1)	54.6 (32.2–75.6)	94.1 (89.4–97.1)	19.7 (10.6–31.8)
PCAC > 3		63.6 (56.7–70.2)	81.8 (59.7–94.8)	97.1 (92.7–99.2)	19.1 (11.8–28.6)
FOUR_B=0,1	0.687 (0.623–0.746)	43.5 (36.7–50.6)	90.9 (70.8–98.9)	97.8 (92.4–99.7)	14.5 (9.1–21.5)
GW Ratio≤1.1	0.729 (0.667–0.785)	16.5 (11.8–22.1)	95.5 (77.2–99.9)	97.3 (85.6–99.9)	10.3 (6.5–15.4)

Table 5

Areas of under the receiving operator characteristic curves for each single test and combined modalities to predicting mortality and poor neurological outcome

	Mortality		Poor outcome	
Single test	**AUC**	**95% CI**	**AUC**	**95% CI**
FOUR_B	0.726	0.663 – 0.782	0.687	0.623 – 0.746
PCAC	0.751	0.680 – 0.822	0.731	0.627 – 0.834
GW ratio	0.688	0.624 – 0.747	0.729	0.667 – 0.785
Malignant EEG at 48hrs	0.651	0.586 – 0.712	0.650	0.584 – 0.711
Combined modality				
FOUR_B + GW ratio	0.772	0.711 – 0.832	0.750	0.663 – 0.836
PCAC + GW ratio	0.814	0.757 – 0.871	0.786	0.706 – 0.866
FOUR_B + malignant EEG at 48hrs	0.787	0.724 – 0.850	0.762	0.675 – 0.849
PCAC + malignant EEG at 48hrs	0.805	0.741 – 0.869	0.802	0.709 – 0.895
GW ratio + malignant EEG at 48hrs	0.776	0.718 – 0.827	0.792	0.665 – 0.782
GW ratio + malignant EEG at 48hrs + FOUR_B	0.820	0.765 – 0.868	0.822	0.742 – 0.850
GW ratio + malignant EEG at 48hrs + PCAC	0.855	0.802 – 0.897	0.835	0.780 – 0.880