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Clinical paper

Grey–white matter ratio measured using early unenhanced brain computed tomography shows no correlation with neurological outcomes in patients undergoing targeted temperature management after cardiac arrest

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Abstract

Aim: This study evaluated whether the grey–white matter ratio (GWR) assessed via early brain computed tomography (CT) within 2 h after the return of spontaneous circulation (ROSC) following cardiac arrest is associated with poor neurological outcomes after 6 months in post-cardiac arrest patients treated with targeted temperature management (TTM).

Methods: This study used data from the Korean Hypothermia Network prospective registry obtained from November 2015 to October 2017 to assess patients with out-of-hospital cardiac arrest (OHCA) who underwent brain CT within 2 h following the ROSC. The primary endpoint was the neurological outcome 6 months post-cardiac arrest (cerebral performance category; CPC). The GWR was measured using early brain CT images. The subgroup analysis examined the difference in GWRs obtained from early and repeated brain CT.

Results: Five-hundred-twelve patients were enrolled. Good (CPC 1–2) and poor (CPC 3–5) neurological outcomes were observed in 162 (31.6%) and 350 (68.4%) patients, respectively. The multivariate logistic regression analysis revealed that the GWR measured using early brain CT was a statistically nonsignificant predictor of poor neurologic outcomes ($p = 0.727$). In patients with poor outcomes, the mean GWR obtained from early and repeated CT images were 1.171 ± 0.058 and 1.091 ± 0.133, respectively ($p < 0.001$); there was no statistically significant difference between the GWRs in patients with good outcomes.

Conclusion: The GWR assessed via early brain CT alone is not an independent factor predictive of poor neurologic outcomes but could be useful when used with repeated CT data.

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Introduction

The early prediction of neurological outcomes in patients with post-cardiac arrest syndrome (PCAS) is important for establishing a treatment plan and determining the appropriate withdrawal of life-sustaining therapy. Although the efficacies of various prognostic tools in determining early neurological prognoses have been investigated, none of these tools have achieved 100% specificity when used alone. Unenhanced brain computed tomography (CT) is frequently performed to evaluate the cause of cardiac arrest in the early stages following the return of spontaneous circulation (ROSC). Accordingly, numerous studies have been performed on associations between poor neurological outcome in patients with PCAS and evaluative modalities measured by early brain CT, such as grey–white matter ratio (GWR) and optic nerve sheath diameter (ONSD).[1–14]

After Torbey et al.[12] reported a lower GWR in patients with post-cardiac arrest than in healthy controls in 2000, several studies have found that CT-measured GWR is significantly lower in post-cardiac arrest patients with poor outcomes than in those with good outcomes.[1,5–8,15–18] In the 2015 American Heart Association (AHA) guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, a Class IIb recommendation stated that the marked reduction of GWR assessed via brain CT within 2 h following cardiac arrest may predict poor outcomes in patients with PCAS without targeted temperature management (TTM).[19] Further, according to the European Resuscitation Council (ERC) and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015, the CT-informed marked reduction of the GWR or sulcal effacement within 24 h following the ROSC may predict poor outcomes.[20] However, these previous studies and guidelines were subject to several limitations: (1) Because the cut-off values of the GWR varied for predicting poor outcomes, they are difficult to apply in clinical settings; (2) the time from cardiac arrest to brain CT following the ROSC was inconsistent; and (3) prior investigations were mostly retrospective, single-centred, and featured small sample sizes.

This prospective, multi-centred, observational study determined whether the GWR measured using early brain CT is associated with poor outcomes in PCAS patients. In addition, we compared the GWRs prospectively obtained from the initial brain CT to those obtained retrospectively from the repeated brain CT to identify changes in the GWR over time and thereby assess neurological outcomes.

Methods

Study design and population

Data were collected between November 2015 and October 2017 from the Korea Hypothermia Network prospective (KORHN-pro) registry (ClinicalTrials.gov Identifier: NCT02827422), a South Korean multi-centre clinical research consortium for TTM established in 2011. The KORHN-pro manages a web-based prospective registry of out-of-hospital cardiac arrest (OHCA) cases treated with TTM to improve post-cardiac arrest care quality and outcomes. This study was approved by the Institutional Review Board (IRB) of each hospital and was registered to the clinical trial registry platform. Informed written consent was obtained for all patients enrolled in this study, and the protocol was approved by the IRB. The inclusion criteria were: (1) age of $\geq$18 years, (2) out-of-hospital cardiac arrest, (3) comatose mental status after the ROSC, (4) performance of TTM, and (5) obtainment of brain CT after the ROSC. The exclusion criteria were: (1) haemorrhagic or ischemic stroke confirmed as the cause of cardiac arrest; (2) cerebral performance category (CPC) of 3 or 4 before cardiac arrest; (3) body temperature below 30 °C upon arrival; (4) PCAS care, including TTM, not provided; and (5) brain CT not obtained within 2 h following the ROSC. Enrolled patients received PCAS care according to the protocol of each hospital. Differences among the hospitals regarding the detailed management of patients with PCAS included the devices used, TTM procedures and shock management; relevant detailed variables were collected using a web-based registry. Each principal investigator of the participating hospitals reviewed the hospital records of the OHCA survivors treated with TTM, circulatory status after the ROSC, circulatory support, neurological status and exam results, TTM procedure, incidence of complications and neurological outcomes at discharge and at 1 and 6 months after the ROSC. The neurological outcomes were investigated by researchers who were blind to the patient data. Researchers called either the surviving discharged patients or their relatives to complete the prepared questionnaire and rate the final CPC. Three clinical research associates monitored the data and assessed their quality by sending queries to the investigators. Finally, a data manager examined the data and decided whether the records could be accepted or needed revision.

Variables

All data were prospectively collected from the web-based registry (http://pro.korhn.or.kr) according to the Utstein guidelines.[21] Time variables for resuscitation were defined as no-flow time (from collapse to the first cardiopulmonary resuscitation [CPR]), and low-flow time (from the first CPR to the ROSC). After the ROSC, we collected variables usually examined within 2 h of the event, including the Glasgow coma scale (GCS), pupillary light reflex (PLR), corneal reflex, mean arterial pressure (MAP), serum lactate levels, duration between the ROSC and brain CT examination and the temperature for TTM. The initial early brain CT was performed before the induction of TTM to confirm the exclusion criteria. The GWR of initial early brain CT was collected prospectively. If a repeated brain CT scan was performed within 7 days of admission, the GWR of the repeated brain CT was collected retrospectively. After admission to the intensive care unit (ICU), the duration of the ICU stay and sequential organ failure assessment (SOFA) scores were recorded for 7 days.

Measurement of grey–white matter ratio

In each hospital, principal investigators reviewed the unenhanced brain CT images and selected three images at specified axial levels (the basal ganglia, centrum semiovale, and high convexity). After the patient information was deleted, these brain CT images were uploaded to the web. The three researchers then measured the GWR according to methods used in previous studies.[16,17] Circular regions of interest (10–15 mm^2) were used to measure Hounsfield units (HUs) on each side and average values were recorded. The interclass correlation coefficient of HUs measured by the three investigators was 0.953 ($p < 0.001$). The basal ganglia level was measured from the caudate nucleus (CN), putamen (PU), posterior limb of the internal capsule (PLIC) and corpus callosum (CC). The centrum semiovale and high convexity levels were measured from the medial cortex (MC1 and MC2) and medial white matter (MW1 and MW2), respectively (Fig. 1). GWRs were calculated by three methods according to previous studies: $GWR_{basal\ ganglia} = (CN + PU) / (PLIC + CC)$, $GWR_{cerebrum} = (MC1 + MC2) / (MW1 + MW2)$, and $GWR_{average} = (GWR_{basal\ ganglia} + GWR_{cerebrum}) / 2$.

Sample size

A previous study estimated the prevalence of poor neurological outcomes to be 60%.[5] To evaluate the GWR using early brain CT as diagnostic tool, the minimum null and the hypothetical hypotheses required 70% and 80% specificity, respectively.[22] The minimum sample sizes were calculated with a significance level of 0.05 and a power of 90%. To achieve a power of 90% for both the sensitivity and specificity, a sample size of 500 and a sample size for poor neurologic outcomes of 300 were required. These sample sizes were calculated by Power Analysis and Sample Size 13 Software (NCSS, LLC. Kaysville: Utah, USA).

Statistical analysis

To assess differences between good and poor neurological outcomes (CPC 1–2 and CPC 3–5, respectively) in patients with post-cardiac arrest, either the independent t-test or Mann–Whitney U-test was performed for continuous variables; and a Pearson's chi-square test or Fisher's exact test, for nominal variables. Continuous and categorical variables are expressed as means ± standard deviations and numbers and percentages, respectively. To determine independent factors for neurological outcomes, a multivariate logistic regression analysis was conducted. All variables were checked for collinearity before multivariate logistic regression. The variation inflation factors were below 2 and were thus proven to be independent. The multivariate logistic regression analysis was conducted on variables with a p-value < 0.1, which was deemed statistically significant for the univariate analysis. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were generated from the multivariate analyses. Significance was set at $p < 0.05$. Statistical analyses were conducted using IBM SPSS statistics version 23.0 (IBM Corp., Armonk, NY, USA).

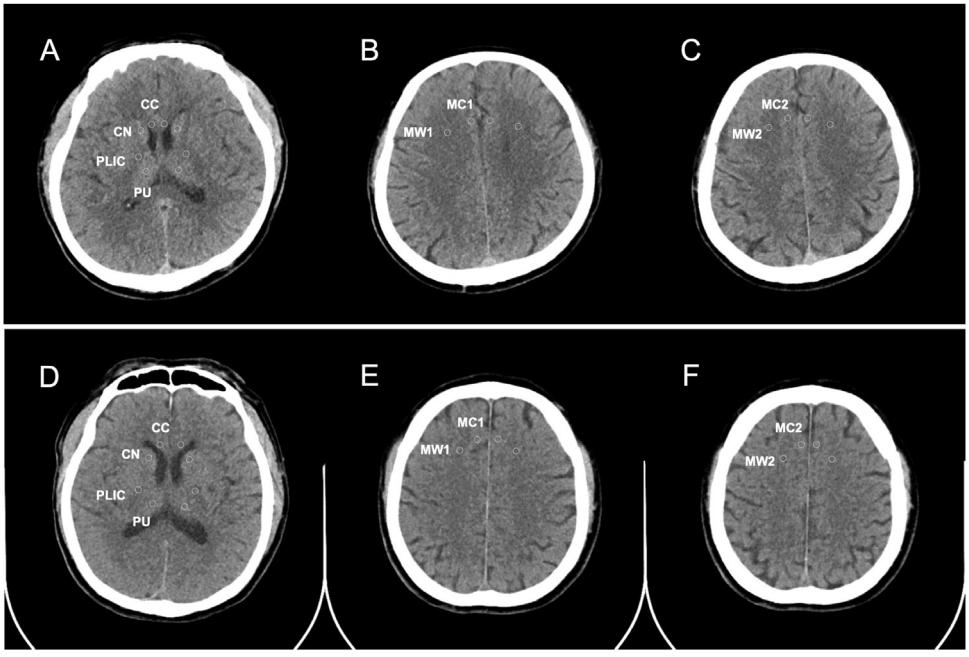

Fig. 1 – Grey–white matter ratio (GWR) measured using early unenhanced brain computed tomography in patients with good and poor neurological outcomes.

A, B and C images reflect a good neurological outcome; while D, E and F reflect a poor neurological outcome. The Hounsfield unit was measured at 3 axis levels: the basal ganglia (A, D), centrum semiovale (B, E), and high convexity (C, F). The corresponding GWRs were 1.240 ($GWR_{basal\ ganglia}$), 1.182 ($GWR_{cerebrum}$) and 1.211 ($GWR_{average}$) in the case of a good outcome, and 1.166 ($GWR_{basal\ ganglia}$), 1.159 ($GWR_{cerebrum}$) and 1.163 ($GWR_{average}$) in the case of a poor outcome. (CC, corpus callosum; CN, caudate nucleus; PLIC, posterior limb of the internal capsule; PU, putamen; MC1, medial cortex of centrum semiovale level; MW1, medial white matter of centrum semiovale level; MC2, medial cortex of high convexity level; MW2, medial white matter of high convexity level).

Results

Participant baseline characteristics

During the study period, 731 patients were enrolled in 20 hospitals, and the corresponding data were recorded in the KOHRN-pro registry. Of the enrolled patients, 219 were excluded (Fig. 2). Concerning the remaining 512 patients, 77 received repeated brain CT within 7 days, 162 (31.6%) had good neurological outcomes and 350 patients (68.4%) had poor neurological outcomes at 6 months after the ROSC. The baseline characteristics of enrolled participants are presented in Table 1. The mean durations between the ROSC and CT examination were 48.80 ± 27.71 min and 50.13 ± 30.47 min for patients with good and poor outcomes, respectively (p = 0.638). Cardiac arrest time was longer in the poor outcome group than in the good outcome group (Table 1).

Patients with good neurological outcomes were younger, and cardiac arrest was more often observed in patients with good neurological outcomes. Bystander CPR and shockable rhythms measured by the emergency medical service (EMS) were more common in the good outcome group than in the poor outcome group. Further, cardiac arrest time was shorter in patients with good neurological outcomes. Following the ROSC, GCS and MAP values were higher in patients with good outcomes than in those with poor outcomes, and PLRs and corneal reflexes were more common in the good outcome group. After admission, ICU-stay duration was shorter and the highest SOFA score 7 days after admission was lower among

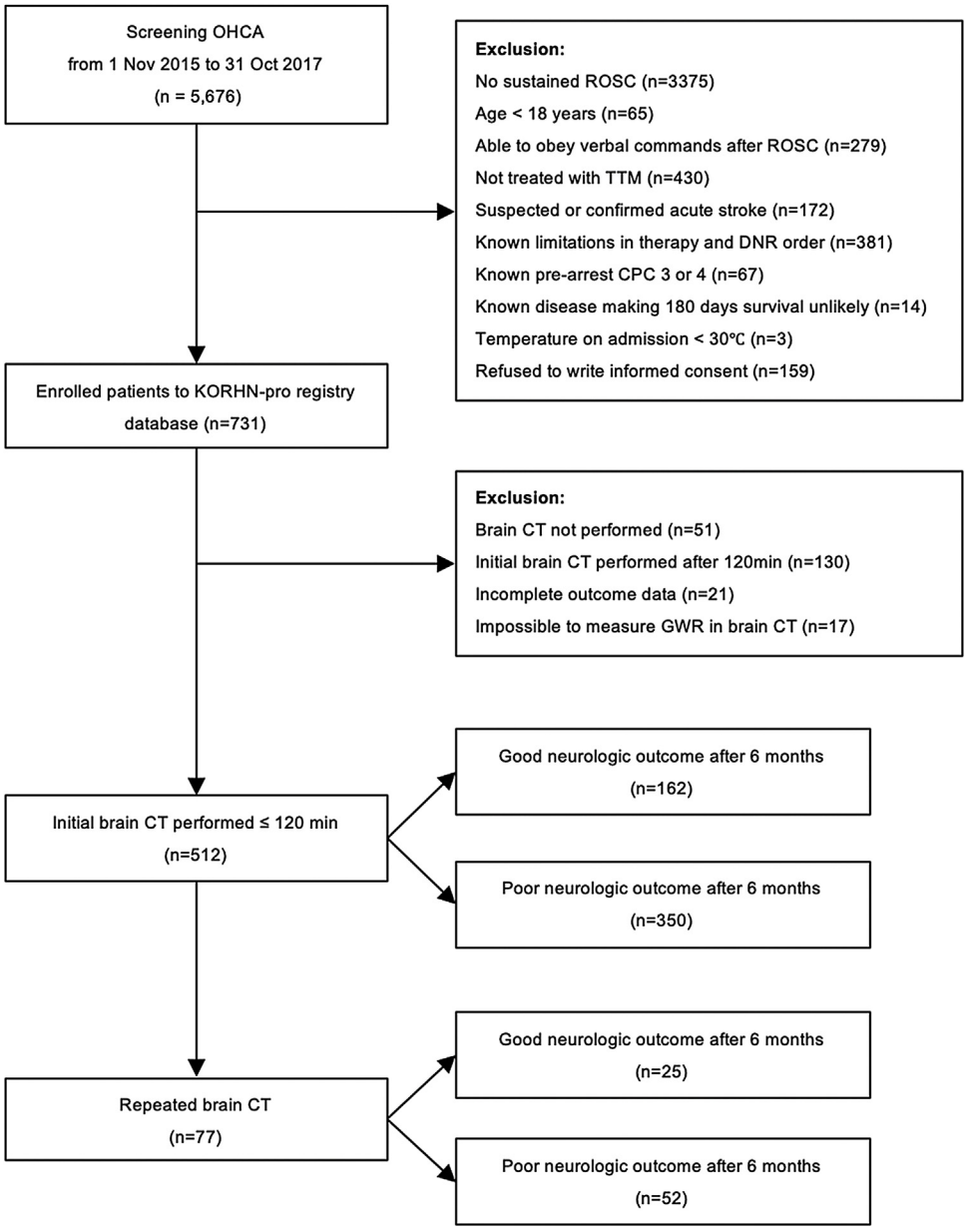

Fig. 2 – Flow chart for patient selection.
(OHCA: Out-of-hospital cardiac arrest, KORHN-pro registry: Korean hypothermia network prospective registry, CT: computed tomography; TTM, target temperature management).

Table 1 – Baseline characteristics and neurologic outcomes 6 months after cardiac arrest.

	Early brain computed tomography scanned within 120 min of the ROSC		
	Good prognoses (n = 162)	Poor prognoses (n = 350)	p-value
Sex (%)			0.039
Male	125 (77.2)	239 (68.3)	
Female	37 (22.8)	111 (31.7)	
Age (year)	53.62 ± 15.01	61.00 ± 16.15	< 0.001
Pre-arrest CPC			< 0.001
CPC1	156 (96.3)	296 (84.6)	
CPC2	6 (3.7)	54 (15.4)	
Cause of arrest			< 0.001
Cardiac origin	148 (91.4)	252 (72.0)	
Non-cardiac origin	14 (8.6)	98 (28.0)	
Witness (%)			< 0.001
Yes	133 (82.1)	208 (59.4)	
No	28 (17.3)	141 (40.3)	
Unknown	1 (0.6)	1 (0.3)	
Bystander CPR (%)			0.041
Yes	108 (66.7)	194 (55.7)	
No	52 (32.1)	155 (44.3)	
Unknown	2 (1.2)	0 (0)	
ECG rhythm in EMS (%)			< 0.001
Shockable	113 (69.8)	57 (16.3)	
Non-shockable	27 (16.7)	242 (69.1)	
Unknown	22 (13.6)	51 (14.6)	
EMS defibrillation (%)			< 0.001
Yes	108 (67.9)	73 (21.2)	
No	29 (18.2)	208 (60.5)	
Unknown	22 (13.8)	63 (18.3)	
Cardiac arrest time (min)			
Down time	3.27 ± 4.74	4.85 ± 6.82	0.003
Low flow time	18.17 ± 14.33	30.51 ± 16.48	< 0.001
ECG rhythm in ED (%)			< 0.001
Shockable	26 (16.0)	16 (4.6)	
Non-shockable	26 (16.0)	263 (75.1)	
Prehospital ROSC	107 (66.0)	56 (16.0)	
Unknown	3 (1.9)	15 (4.3)	
ED defibrillation			0.296
Yes	35 (21.6)	62 (17.7)	
No	127 (78.4)	288 (82.3)	
GCS after the ROSC			< 0.001
≤ 8	146 (90.1)	344 (98.3)	
> 8	8 (4.9)	2 (0.6)	
Unknown	8 (4.9)	4 (1.1)	
Pupillary light reflex (%)			< 0.001
Yes	138 (85.2)	107 (30.6)	
No	24 (14.8)	241 (68.9)	
Unknown	0 (0.0)	2 (0.6)	
Corneal reflex (%)			< 0.001
Yes	93 (57.4)	38 (10.9)	
No	41 (25.3)	285 (81.4)	
Unknown	28 (17.3)	27 (7.7)	
Lactate	7.99 ± 4.71	10.91 ± 5.09	< 0.001
MAP after ROSC	96.54 ± 29.39	86.11 ± 30.26	< 0.001
TTM (°C)			0.408
≤ 34	121 (74.7)	273 (78.0)	
> 34	41 (25.3)	77 (22.0)	
ICU stay (day)	7.06 ± 3.98	9.06 ± 10.50	0.002
Highest SOFA score for 7 days	10.00 ± 2.71	13.15 ± 2.89	< 0.001

Values are expressed as number (%) or mean ± standard deviation as appropriate.
CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; ECG, electrocardiogram; EMS, emergency medical service; ED, emergency department; ROSC, return of spontaneous circulation; GCS, Glasgow coma scale; MAP, mean arterial pressure; TTM, targeted temperature management; ICU, intensive care unit; SOFA, sequential organ failure assessment.

patients with good outcomes. However, the targeted temperature of TTM (≤34 °C and > 34 °C) and defibrillation by the emergency department (ED) did not differ significantly according to neurological outcome (p = 0.408 and p = 0.296, respectively; Table 1).

Grey–white matter ratio

The attenuation of HUs of the three levels (basal ganglia, centrum semiovale, and high convexity) and the calculated GWRs are shown in Table 2. The mean value of grey matter at the three levels was significantly higher in patients with good neurological outcomes (p < 0.001). However, there was no statistically significant difference in the white-matter HU between the two groups. The univariate analysis revealed that the mean $GWR_{average}$ was higher for good neurological outcomes (1.22 ± 0.06) than poor neurological outcomes (1.18 ± 0.07, p < 0.001). Both $GWR_{basal\ ganglia}$ and $GWR_{cerebrum}$ were significantly higher in patients with good neurological outcomes (p < 0.001).

Independent prognostic factors for poor neurological outcomes

The multivariate logistic regression analysis revealed that age (OR = 1.058, p < 0.001), non-shockable rhythm (in EMS: OR = 6.367 and p = 0.029, in ED: OR = 6.767, p = 0.011), absence of a PLR (OR = 3.789, p = 0.005) and corneal reflex (OR = 6.643, p = 0.005) after the ROSC, serum lactate level (OR = 1.095, p = 0.046), and the highest SOFA score in 7 days (OR = 1.224, p = 0.008) were found to be independent prognostic factors for poor neurologic outcomes. However, $GWR_{average}$, $GWR_{basal\ ganglia}$, and $GWR_{cerebrum}$ were statistically nonsignificant predictors of poor neurologic outcomes (p = 0.727, p = 0.731 and p = 0.737, respectively; Table 3).

Grey–white matter ratios of early and repeated brain computed tomography

Of the 77 patients who received repeated brain CT within 7 days of admission, 25 (32.5%) and 52 patients (67.5%) showed good and poor outcomes (Fig. 2), respectively. In the former, there was no statistically significant difference in the GWRs calculated by three methods between early and repeated brain CT ($GWR_{average}$: p = 0.184, $GWR_{basal\ ganglia}$: p = 0.319, and $GWR_{cerebrum}$: p = 0.112). However, in the poor outcome group, there was a statistically significant difference of the mean GWRs between early and repeated brain CT (Fig. 3): for the early and repeated brain CT, the $GWR_{average}$, $GWR_{basal\ ganglia}$ and $GWR_{cerebrum}$ were 1.171 ± 0.058 and 1.091 ± 0.133 (p < 0.001), 1.186 ± 0.070 and 1.088 ± 0.143 (p < 0.001), and 1.156 ± 0.067 and 1.094 ± 0.152, respectively.

Discussion

The 2015 AHA guidelines and ERC guidelines recommend that GWR be used to predict poor neurological outcomes.[19,20] However, details such as the timing of CT scans or TTM use differ between guidelines. Informed by previous studies,[5,6,23,24] the 2015 AHA guidelines define the time at which the CT scan should be performed as within 2 h following cardiac arrest. Since 2015, the GWR has been studied as a useful prognostic tool of neurological outcomes of patients with post-cardiac arrest treated with TTM. In a retrospective multi-centre study, KORHN-pro reported that the GWR derived from brain CT data obtained within 24 h following the ROSC could predict poor outcomes of TTM-treated patients with a 1.13 cut-off value for cardiac aetiology and 1.22 for non-cardiac aetiology.[7,8] A single-

Table 2 – Comparison of the grey–white matter ratio based on early brain computed tomography data for 6-month neurological outcomes.

	Good outcomes (n = 162)	Poor outcomes (n = 350)	p-value
Basal ganglia			
Grey matter			
CN	37.75 ± 3.28	35.78 ± 3.89	< 0.001
PU	37.54 ± 3.49	35.94 ± 3.55	< 0.001
White matter			
CC	30.72 ± 3.28	30.43 ± 3.50	0.371
PLIC	30.16 ± 3.05	29.96 ± 3.26	0.514
Centrum semiovale			
Grey matter			
MC1	34.99 ± 4.00	33.36 ± 4.16	< 0.001
White matter			
MW1	29.17 ± 3.31	28.58 ± 4.01	0.102
High convexity			
Grey matter			
MC2	35.21 ± 4.25	33.66 ± 4.36	< 0.001
White matter			
MW2	29.43 ± 3.72	28.92 ± 0.22	0.183
Grey–white matter ratio			
$GWR_{average}$ ($GWR_{basal\ ganglia}$+ $GWR_{cerebrum}$)/2	1.22 ± 0.06	1.18 ± 0.07	< 0.001
$GWR_{basal\ ganglia}$ (CN+PU)/(PLIC+CC)	1.24 ± 0.07	1.19 ± 0.08	< 0.001
$GWR_{cerebrum}$ (MC1+MC2)/(MW1+MW2)	1.20 ± 0.07	1.17 ± 0.10	< 0.001

CN, caudate nucleus; PU, putamen; CC, corpus callosum; PLIC, posterior limb of internal capsule; MC1, medial cortex at the centrum semiovale; MW1,medial white matter at the centrum semiovale; MC2, medial cortex at the high convexity; MW2, medical white matter at the high convexity; GWR, grey–white matter ratio.

Table 3 – Multivariate regression analysis for poor neurological outcomes 6 months after cardiac arrest.

	Neurological outcome			
	OR	95% CI		p-value
Age (years)	1.058	1.027	1.089	< 0.001
ECG rhythm in EMS				
Shockable				0.023
Non-shockable	6.367	1.206	33.616	0.029
ECG rhythm in ED				
Shockable				0.002
Non-shockable	6.767	1.540	29.727	0.011
Pupil light reflex after ROSC				
Yes				0.021
No	3.789	1.480	9.698	0.005
Corneal reflex after the ROSC				
Yes				< 0.001
No	6.643	2.445	18.049	0.005
Lactate	1.095	1.001	1.197	0.046
Highest SOFA score for 7 days	1.224	1.054	1.422	0.008
Grey–white matter ratio				
$GWR_{average}$				0.727
$GWR_{basal\ ganglia}$				0.731
$GWR_{cerebrum}$				0.737

OR, odds ratio; CI, confidence Interval; ECG, electrocardiogram; EMS, emergency medical service; ED, emergency department; ROSC, return of spontaneous circulation; SOFA, sequential organ failure assessment; GWR, grey–white matter ratio.

centred retrospective study showed that the GWRs were correlated with poor neurological outcomes when obtained from brain CTs performed within 6 h following the ROSC in patients with PCAS who underwent TTM of 33 °C with a 1.13 cut-off value.[1] Furthermore, single-centre retrospective studies demonstrated that GWRs measured via unenhanced brain CTs could predict poor neurological outcomes in patients treated with TTM of 33 °C (cut-off values: 1.21 and 1.1, respectively).[15,18] These studies analysed the predictive value of GWRs for the prognoses of patients who underwent TTM during PCAS care but were limited by their retrospective and single-centred design, small sample sizes, and not having controlled for the time of the brain CT scan.

Our multivariate regression analysis (Table 3) showed that the GWRs measured by early brain CT were not correlated with neurological outcomes at 6 months after the ROSC, although the univariate analysis revealed that GWRs were significantly reduced in the poor neurologic outcome group (Table 2). This result conflicts with those previous. Several differences between the present study and those previous may account for the dispensary. This study featured a prospective and multi-centred design. Moreover, while the time that elapsed before the brain CT scan was obtained ranged from 1 h to 1 week in previous studies,[1,5–8,15–18] we only included cases in which the time between the ROSC and brain CT examinations was within 2 h to reconcile the different definitions of 'initial' and 'early' brain CT used in previous studies. Brain CT scans conducted in the first 2 h following ROSC likely do not allow sufficient time for the formation of cerebral oedema and increased intracranial pressure: factors that may be correlated with adverse outcomes.[10]

Although the GWR assessed through early brain CT could not predict poor neurological outcomes, we speculated that a GWR obtained from a repeated CT and compared to that collected from the early CT could predict a patient's outcome. The enrolled patients were therefore reviewed retrospectively for repeated brain CT performed within 1 week of admission. Repeated brain CT scans were performed in 77 cases; 25 were in the good outcome group and 52 were in the poor outcome group (Fig. 2). In the latter, GWRs of repeated brain CT were significantly lower than those of early brain CT, but there was no statistical difference between the GWRs in the good neurological outcome group (Fig. 3) However, the prognostic value of GWR might be improved. A study that performed CT within 7 days observed that the sensitivity of $GWR_{average}$ was 37.7% at 100% specificity,[17] suggesting that a delayed CT can better predict neurologic outcomes. These findings contrast from those obtained by a study that performed CT within 1 h after ROSC: sensitivities of $GWR_{average}$ and $GWR_{basal\ ganglia}$ at 100% specificity

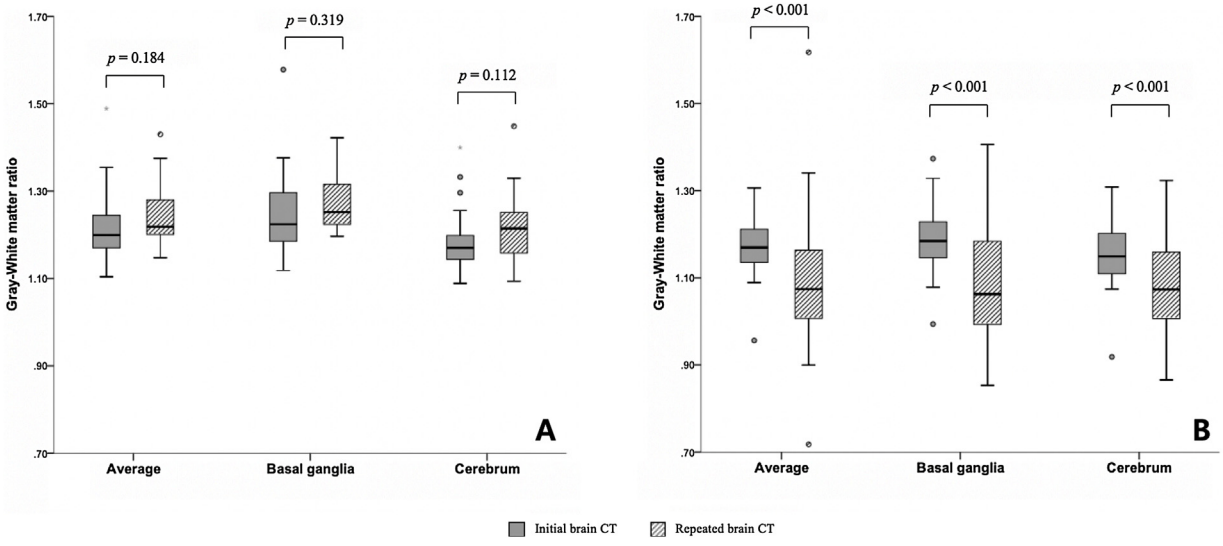

Fig. 3 – A comparison of the grey–white matter ratio calculated using the results from early and repeated brain computed tomography (CT) 6 months after the cardiac arrest.
(A) Good neurological outcome group. (B) Poor neurological outcome group.

were 13.3% and 3.3%, respectively. These finding are similar to the values of to 10.9% and 2%, respectively, found in the present study.[5]

Current guidelines recommend the adoption of multimodal approaches to reduce errors in prognostication,[19,20] and several recent studies have reported prognostic improvement with a multimodal approach that includes GWR values.[1,15,17,18] Imaging modalities reflecting cerebral edema are thought to be less affected by TTM or sedative drugs than other prognostic tools and can be performed relatively earlier. Although the present study found that the obtainment of brain CT within 2 h following ROSC could not predict the neurological outcomes, the optimal timing of scanning brain CT that yields reliable prognostication remains unknown. Further research should ascertain the ideal time at which to perform brain CT for measuring GWR and thereby enhancing the multimodal approach of determining neurologic outcome in patients with PCAS.

This study is subject to several limitations. The information regarding the CT scanner was not documented: the numerous hospitals involved in this multi-centre study each have multiple CT scanners; thus, more than 20 CT scanners were used in this study, and we could not regulate the CT scanner models. This could affect the quality and consistency of CT images as well as the HU and GWR measured by the investigators.[25] Second, we recorded the CT scan timing based on the ROSC because the cardiac arrest time may occur while the patients are not being observed and can thus be based on a caregiver's surmise. Third, the GWRs were not measured by radiologists but rather by emergency physicians. However, the investigators were emergency medicine specialists with more than 10 years of clinical experience; furthermore, the interclass correlation coefficient was 0.953 among the investigators. Finally, with respect to the comparison between the GWRs obtained from early and repeated brain CT, the data of repeated CT was collected retrospectively. A simple univariate analysis was therefore conducted to compare mean GWRs because of the few repeated CTs performed.

Conclusions

The GWR measured using early brain CT within 2 h after the ROSC was not an independent factor predictive of poor neurologic outcomes at 6 months in post-OHCA patients treated with TTM. In patients with poor neurological outcomes, repeated CT GWRs were lower than early brain CT GWRs.

Conflicts of interest

None.

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REFERENCES

1. Chae MK, Ko E, Lee JH, et al. Better prognostic value with combined optic nerve sheath diameter and grey-to-white matter ratio on initial brain computed tomography in post-cardiac arrest patients. Resuscitation 2016;104:40–5.
2. Chelly J, Deye N, Guichard JP, et al. The optic nerve sheath diameter as a useful tool for early prediction of outcome after cardiac arrest: a prospective pilot study. Resuscitation 2016;103:7–13.
3. Choi SP, Park HK, Park KN, et al. The density ratio of grey to white matter on computed tomography as an early predictor of vegetative state or death after cardiac arrest. Emerg Med J 2008;25:666–9.
4. Gentsch A, Storm C, Leithner C, et al. Outcome prediction in patients after cardiac arrest: a simplified method for determination of gray–white matter ratio in cranial computed tomography. Clin Neuroradiol 2015;25:49–54.
5. Kim SH, Choi SP, Park KN, Youn CS, Oh SH, Choi SM. Early brain computed tomography findings are associated with outcome in patients treated with therapeutic hypothermia after out-of-hospital cardiac arrest. Scand J Trauma Resusc Emerg Med 2013;21:57.
6. Lee BK, Jeung KW, Lee HY, Jung YH, Lee DH. Combining brain computed tomography and serum neuron specific enolase improves the prognostic performance compared to either alone in comatose cardiac arrest survivors treated with therapeutic hypothermia. Resuscitation 2013;84:1387–92.
7. Lee BK, Jeung KW, Song KH, et al. Prognostic values of gray matter to white matter ratios on early brain computed tomography in adult comatose patients after out-of-hospital cardiac arrest of cardiac etiology. Resuscitation 2015;96:46–52.
8. Lee BK, Kim WY, Shin J, et al. Prognostic value of gray matter to white matter ratio in hypoxic and non-hypoxic cardiac arrest with non-cardiac etiology. Am J Emerg Med 2016;34:1583–8.
9. Lee DH, Lee BK, Jeung KW, et al. Relationship between ventricular characteristics on brain computed tomography and 6-month neurologic outcome in cardiac arrest survivors who underwent targeted temperature management. Resuscitation 2018;129:37–42.
10. Lee DH, Lee SH, Oh JH, et al. Optic nerve sheath diameter measured using early unenhanced brain computed tomography shows no correlation with neurological outcomes in patients undergoing targeted temperature management after cardiac arrest. Resuscitation 2018;128:144–50.
11. Na MK, Kim W, Lim TH, et al. Gray matter to white matter ratio for predicting neurological outcomes in patients treated with target temperature management after cardiac arrest: a systematic review and meta-analysis. Resuscitation 2018;132:21–8.
12. Torbey MT, Selim M, Knorr J, Bigelow C, Recht L. Quantitative analysis of the loss of distinction between gray and white matter in comatose patients after cardiac arrest. Stroke 2000;31:2163–7.
13. Wang GN, Chen XF, Lv JR, Sun NN, Xu XQ, Zhang JS. The prognostic value of gray–white matter ratio on brain computed tomography in adult comatose cardiac arrest survivors. J Chin Med Assoc 2018;81:599–604.
14. Wu O, Batista LM, Lima FO, Vangel MG, Furie KL, Greer DM. Predicting clinical outcome in comatose cardiac arrest patients using early noncontrast computed tomography. Stroke 2011;42:985–92.
15. Jeon CH, Park JS, Lee JH, et al. Comparison of brain computed tomography and diffusion-weighted magnetic resonance imaging to predict early neurologic outcome before target temperature management comatose cardiac arrest survivors. Resuscitation 2017;118:21–6.
16. Metter RB, Rittenberger JC, Guyette FX, Callaway CW. Association between a quantitative CT scan measure of brain edema and outcome after cardiac arrest. Resuscitation 2011;82:1180–5.
17. Scheel M, Storm C, Gentsch A, et al. The prognostic value of gray–white-matter ratio in cardiac arrest patients treated with hypothermia. Scand J Trauma Resusc Emerg Med 2013;21:23.
18. Youn CS, Callaway CW, Rittenberger JC, Post Cardiac Arrest S. Combination of initial neurologic examination, quantitative brain

imaging and electroencephalography to predict outcome after cardiac arrest. Resuscitation 2017;110:120–5.
19. Callaway CW, Donnino MW, Fink EL, et al. Part 8: post-cardiac arrest care: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2015;132:S465–82.
20. Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine guidelines for post-resuscitation care 2015: Section 5 of the European Resuscitation Council guidelines for resuscitation 2015. Resuscitation 2015;95:202–22.
21. Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein resuscitation registry templates for out-of-hospital cardiac arrest: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Resuscitation 2015;96:328–40.
22. Bujang MA, Adnan TH. Requirements for minimum sample size for sensitivity and specificity analysis. J Clin Diagn Res 2016;10:YE01–6.
23. Choi SP, Youn CS, Park KN, et al. Therapeutic hypothermia in adult cardiac arrest because of drowning. Acta Anaesthesiol Scand 2012;56:116–23.
24. Inamasu J, Miyatake S, Suzuki M, et al. Early CT signs in out-of-hospital cardiac arrest survivors: temporal profile and prognostic significance. Resuscitation 2010;81:534–8.
25. Oh JH, Choi SP, Wee JH, Park JH. Inter-scanner variability in hounsfield unit measured by computed tomography of the brain and effect on gray-to-white matter ratio. Am J Emerg Med 2018;37:680–4.