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Original Article

The prognostic value of gray−white matter ratio on brain computed tomography in adult comatose cardiac arrest survivors

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Abstract

Background: Recent studies suggested that the gray−white matter ratio (GWR) determined from brain computed tomography (CT) scans may be a reliable predictor of poor neurological outcomes. The aim of study was to evaluate the association between the GWR and the outcomes in adult comatose cardiac arrest (CA) survivors in Chinese.

Methods: A total of 58 CA patients who had CT scans within 72 h of resuscitation between January 2011 and December 2015 were included in this single-center retrospective study. Gray and white matter attenuations (Hounsfield units) were measured, and the GWRs were calculated according to previous studies. The study analyzed the prognostic values of the GWRs in predicting poor outcomes (Cerebral Performance Category 3−5).

Results: The attenuation values of gray matter were significantly higher in the good outcome group than in the poor one. All GWRs were significantly higher in the good outcome group ($p < 0.05$). A GWR (basal ganglia) < 1.18 predicted poor outcomes with a sensitivity and specificity of 50.0% and 87.5%, respectively ($p = 0.021$). GWR (cerebrum) showed the best predictive performance when CT was performed within 24−72 h ($p = 0.003$). No significant differences were found between GWR and poor outcomes when CT was performed within the first 24 h.

Conclusion: Low GWRs which were obtained from brain CT scans in comatose CA patients after restoration of spontaneous circulation were associated with poor neurological outcomes. GWR from brain CT can be a useful parameter for prognostic prediction aiding to an optimal clinical decision process in comatose CA survivors.

Keywords: Coma; Heart arrest; Prognosis; Tomography; X-ray computed

1. Introduction

In recent years, advances in emergency medicine care and resuscitation treatment strategies such as therapeutic hypothermia have increased the number of survivors of cardiac arrest (CA) and improved the chances of good neurological outcome for these patients.[1] However, 45−70% of the survivors still suffered from severe neurologic deficits or died due to hypoxic ischemic encephalopathy (HIE).[2] Thus, early methods to accurately predict patient outcomes should be useful in making therapeutic decisions and titrating therapy. Various indicators including neurologic exams, electrophysiologic studies, biochemical markers, and neuroimaging have been used for prognostication in comatose CA survivors.[3] Of note, brain computed tomography (CT) is frequently performed early following restoration of spontaneous circulation (ROSC) to exclude primary brain injury that could result in CA and coma.[2]

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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HIE is known to be associated with cerebral edema, which reduces the attenuation of gray matter (GM) on un-enhanced CT scans and results in a loss of differentiation between gray and white matter (WM).[4] Several previous studies found that gray−white matter ratio (GWR), the ratio of attenuation of GM to attenuation of WM, was significantly lower in CA survivors with poor outcomes than those with good outcomes, and thus that decreased GWR could predict poor neurological outcome in CA patients.[5−10] However, there is currently no consensus on a distinct GWR cut-off value that may predict poor outcomes with high specificity. The present study was designed to evaluate the association between the GWR and the neurological outcomes in adult comatose CA survivors in Chinese.

2. Methods

2.1. Study population

The present retrospective study retrieved 58 patients with CA who had brain CT scans within 72 h of resuscitation in the period from January 2011 through December 2015 at the First Affiliated Hospital of Nanjing Medical University (Nanjing, China). Most patients underwent brain CT to rule out a primary intracranial event such as subarachnoid hemorrhage (SAH). All CT examinations were performed using a GE Optima 520Pro CT scanner (GE Healthcare, Tokyo, Japan) with 5-mm slice thickness. Regions of interests (ROI) were placed independently by two expert investigators. Both readers were blinded to outcome and other patient data and to ROI placement by the other reader. Patients with age <18 years, poor baseline neurology, terminal malignancy were excluded from the study. Moreover, patients whose CT scans indicated parenchymal abnormalities and whose CT images were technically inadequate for the determination of cerebral density or were not available for evaluation were excluded from the analysis. The study protocol was reviewed and approved by the Institutional Review Boards for Human Studies of Nanjing Medical University.

2.2. GWR determination

Two investigators reviewed CT scans for each patient using a picture archiving and communication system and identified comparable brain slices at three levels including the basal ganglia, centrum semiovale, and high convexity as reported in previous studies.[8,9] Circular regions of measurement (10 mm^2) were placed over these ROI bilaterally (Fig. 1), and the average attenuations were recorded in Hounsfield units (HU). Attenuation values at the basal ganglia level were recorded from the caudate nucleus (CN), putamen (PU), corpus callosum (CC), and posterior limb of the internal capsule (PIC). Values from the medial cortex and medial white matter were recorded at the level of the centrum semiovale (MC1 and MWM1, respectively) and high convexity area (MC2 and MWM2, respectively). The average of both sides was recorded as the value for that area. Previous studies used various methods to calculate the GWR, and no set rule exists for calculating GWR currently. Thus, four GWRs used in previous studies were calculated: $GWR_{basal\ ganglia}$ (GWR-BG) = (CN + PU)/(CC + PIC), $GWR_{cerebrum}$ (GWR-CO) = (MC1 + MC2)/(MWM1 + MWM2), $GWR_{average}$ (GWR-AV) = (GWR-BG + GWR-CO)/2, and $GWR_{simplified}$ (GWR-SI) = PU/PIC.[4,9] To assess the consistency of GWR measurements, the test-retest reliability was measured from a randomly selected sample of 10% of the included subjects.

2.3. Outcome measurement

The primary endpoint was clinical outcome at hospital discharge, which was assessed using the Cerebral Performance Categories (CPC) score, according to recommendations for outcome assessment in comatose CA survivors. CPC grades the levels of neuro-functional status after CA (CPC 1, good; CPC 2, moderate disability; CPC 3, severe disability; CPC 4, comatose or vegetative state; CPC 5, death). The clinical outcome at hospital discharge was dichotomized as either good (CPC 1 or 2) or poor (CPC 3−5).

2.4. Statistical analysis

Continuous variables were expressed as the mean ± standard deviation (SD) or median with interquartile ranges (IQR), as appropriate. Comparisons of continuous variables between independent groups were performed using the two sample *t* test or Mann−Whitney *u* test, as appropriate. Categorical variables were given as frequencies and percentages. Comparisons of categorical variables were performed by the chi-square test or Fisher's exact test, as indicated. Receiver-operating characteristic (ROC) curve analysis was drawn to identify the optimal cut-off value (to determine maximal sensitivity and specificity) to determine the performance of GWRs in predicting prognosis. The statistical performance of the outcome prediction models was assessed using the area under the curve (AUC) with 95% confidence interval (CI). All the statistical tests were performed in SPSS version 16.0 (SPSS Inc. Chicago, IL, USA). A two-tailed *p* value of less than 0.05 was considered statistically significant.

3. Results

3.1. Clinical characteristics

Clinical characteristics of the included patients were shown in Table 1. A total of 159 adult CA patients recovered spontaneous circulation after resuscitation. Among them, 58 survivors underwent brain CT scans were included in this study. According to the CPC score at hospital discharge, 16 patients (27.6%) were assigned to the good neurologic outcome group and 42 patients (72.4%) were the poor outcome group. In most of pre-CA baseline variables, there were no significant differences between the two groups. However, the present study showed 17.2% of the included CA patients were SAH origin, which indicated poor outcomes.

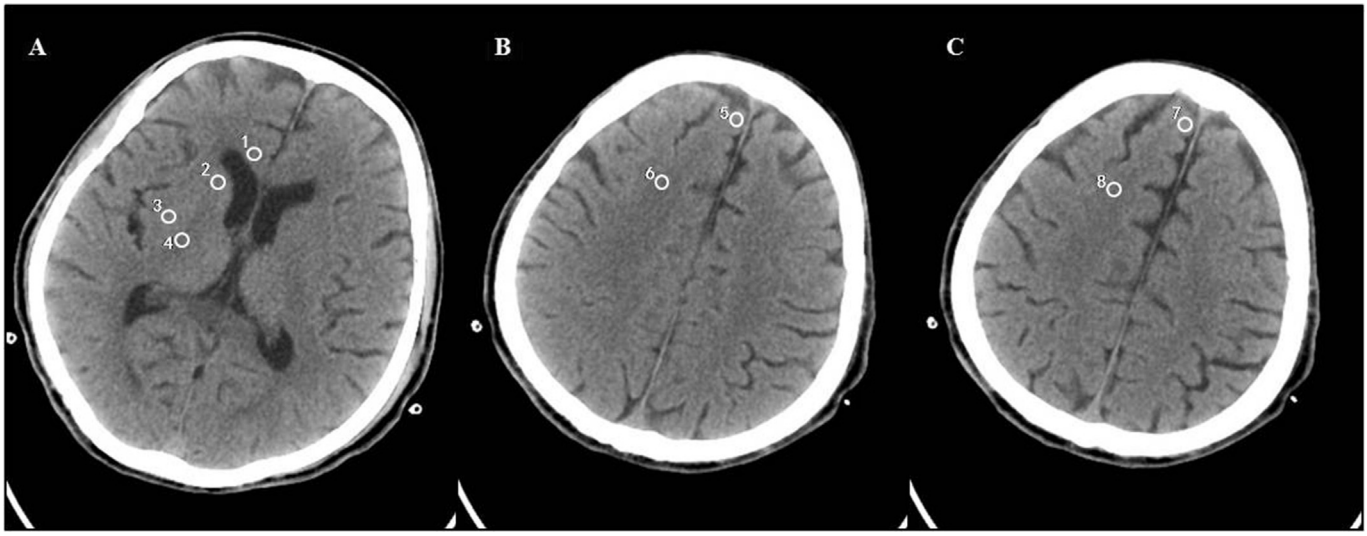

Fig. 1. Circular regions of interest were placed bilaterally in the following regions: *1* corpus callosum, *2* caudate nucleus, *3* putamen, *4* posterior limb of the internal capsule at the basal ganglia level (A), *5* and *6* cortex and white matter at the centrum semiovale level (B), respectively, and *7* and *8* cortex and white matter at the high convexity level (C), respectively.

Table 1
Clinical characteristics of study patients.

Characteristics	Good outcome (N = 16)	Poor outcome (N = 42)	*p*
Age, years, mean ± SD	49.69 ± 22.25	55.74 ± 20.48	0.33
Sex, male, N (%)	9 (56.3)	24 (57.1)	0.95
Underlying disease, N (%)			
Coronary artery disease	1 (6.3)	5 (11.9)	0.88
Hypertension	3 (18.8)	10 (23.8)	0.95
Diabetes	2 (12.5)	4 (9.5)	0.66
Stroke	2 (12.5)	10 (23.8)	0.56
Out-of-hospital CA, N (%)	6 (37.5)	18 (42.9)	0.71
Cardiac etiology, N (%)	4 (25.0)	9 (21.4)	0.74
SAH etiology, N (%)	0 (0)	10 (23.8)	0.05
Time from ROSC to CT, N (%)			
Within 24 h	10 (62.5)	24 (57.1)	0.71
24-72 h	6 (37.5)	18 (42.9)	
GCS score, mean ± SD			
After ROSC	5.13 ± 1.86	3.36 ± 0.88	0.002
At discharge	14.63 ± 0.72	4.61 ± 2.02	<0.001
Outcome			
Hospital stay after ROSC, days, median (IQR)	21.5 (11.0–44.0)	10 (4.0–20.5)	0.008
Survival at discharge, N (%)	16 (100)	23 (54.8)	0.001
Survival at 28days, N (%)	16 (100)	14 (33.3)	<0.001

SD = standard deviation; CA = cardiac arrest; SAH = Subarachnoid hemorrhage; ROSC = return of spontaneous circulation; CT = computed tomography; GCS = Glasgow coma scale; IQR = interquartile range.

Table 2
Attenuation values and gray–white matter ratios.

	Good outcome (N = 16)	Poor outcome (N = 42)	*p*
Density of ROI, HU, median (IQR)			
CN	34.42 (32.96–37.80)	30.95 (27.05–34.90)	0.003
PU	36.91 (30.62–38.07)	30.36 (28.34–34.01)	0.01
CC	29.99 (24.01–31.52)	25.72 (23.00–29.51)	0.06
PIC	28.37 (23.37–30.00)	26.88 (22.34–30.00)	0.49
MC1	38.50 (34.81–39.84)	32.48 (29.66–35.13)	<0.001
MWM1	30.33 (24.32–32.24)	26.59 (22.53–32.35)	0.24
MC2	39.03 (38.06–40.19)	33.40 (29.22–36.53)	<0.001
MWM2	30.51 (24.87–34.04)	26.37 (21.61–31.94)	0.09
Gray–White matter Ratio (GWR), median (IQR)			
Basal ganglia	1.24 (1.20–1.32)	1.19 (1.11–1.25)	0.02
Cerebrum	1.28 (1.17–1.50)	1.15 (1.09–1.38)	0.04
Average	1.23 (1.20–1.42)	1.19 (1.10–1.31)	0.04
Simplified	1.26 (1.20–1.38)	1.16 (1.09–1.29)	0.03

ROI = region of interest; HU = Hounsfield units; IQR = interquartile range; CN = caudate nucleus; PU = putamen; CC = corpus callosum; PIC = posterior limb of the internal capsule; MC1 and MWM1 = medial cortex and medial white matter at the centrum semiovale level respectively; MC2 and MWM2 = medial cortex and medial white matter at the high convexity level respectively.

3.2. Attenuation and GWR on brain CT

Inter-rater reliability of the GWR measurements was excellent with an overall Pearson's correlation coefficient of 0.97 ($p < 0.001$) determined from all measurements combined. The intraclass correlation coefficient of test-retest GWRs was 0.79 ($p < 0.001$). Attenuation values and GWRs were shown in Table 2. The attenuation values of GM were significantly higher in the good outcome group than in poor outcome group. The WM attenuation values failed to show significant differences between the two groups. All four GWRs were significantly higher in the good outcome group (all $p < 0.05$).

3.3. Temporal analysis

A total of 34 CT scans were performed within 24 h (Early), and 24 scans between 24 and 72 h (Late). Regionally, there were significant differences in median HU between the outcome groups for all regions except the PIC in the early cohort. For the late cohort, only the MC1 and MC2 showed significant reductions. Furthermore, All GWRs were significantly higher in

patients with good outcomes than those with poor outcomes in the late cohort. In contrast, no significant difference was found between the outcome groups for all GWRs in the early cohort (Table 3).

3.4. Prognostic performances of GWRs

The prognostic performances of GWRs in predicting poor outcomes were shown in Table 4 and Fig. 2. Although all GWRs could predict poor outcomes with statistical significance, the sensitivities were remarkably low at cut-off values with 100% specificity. The GWR-BG showed the best predictive performance among GWRs. Furthermore, in the late CT performed group, All GWR methods had AUC values between 0.778 and 0.907. On a descriptive level, the AUC value of GWR-CO was even higher (AUC = 0.907) than that of other methods. At 100% specificity, GWR-CO had the highest sensitivity (77.8%, cut-off value 1.20) among all methods.

4. Discussion

As more effective therapies become available there is a need to early identify comatose adult patients after CA with prospect for neurological improvement. Early assessment of the potential of neurological recovery in comatose CA survivors is essential.[11] Different studies suggested GWR measurements in brain CT as an imaging marker for clinical outcome after CA. In a study of 240 comatose CA survivors, Metter et al. showed that an average GWR <1.20 predicted death (AUC = 0.72) with a sensitivity of 36% and specificity of 98%.[6] In a study of 224 comatose CA survivors treated with therapeutic hypothermia, Lee et al. showed that a GWR (PU/CC) < 1.17 predicted poor outcomes (AUC = 0.864) with sensitivity and specificity values of 52.9% and 100%, respectively.[9] Scheel et al. evaluated the prognostic performance of GWR in 98 CA survivors, and found a strong association of a low GWR (GWR < 1.16) with poor outcome.[8] However, Lee et al. indicated that the GWR demonstrated poor predictive performance (AUC of 0.571−0.621) and was not helpful in predicting poor outcomes in a cohort of comatose adults after out-of-hospital CA of cardiac etiology.[2] The present study suggested that a GWR (GWR-BG) < 1.18 predicted poor outcomes with a sensitivity and specificity of 50.0% and 87.5%, respectively.

The change in the attenuation ratio of gray-to-white matter is due to a drop in HU values in GM in patients with cerebral

Table 3
Comparison of attenuation values between patients with good and poor outcome dichotomized by whether CT was performed Early (within 24 h) or Late (24−72 h).

	Early CT performed (N = 34)			Late CT performed (N = 24)		
	Good outcome (N = 10)	Poor outcome (N = 24)	*p*	Good outcome (N = 6)	Poor outcome (N = 18)	*p*
Density of ROI, HU, median (IQR)						
CN	36.79 (33.32−38.13)	30.95 (27.61−34.42)	0.007	32.99 (31.62−36.16)	30.82 (26.57−35.73)	0.18
PU	37.32 (30.13−38.24)	29.92 (28.47−34.08)	0.03	32.72 (30.41−37.80)	30.99 (27.92−34.17)	0.29
CC	30.88 (25.36−32.08)	24.60 (21.93−29.09)	0.02	27.12 (23.81−30.20)	26.56 (24.36−29.88)	0.93
PIC	29.25 (25.25−30.22)	24.21 (21.11−29.36)	0.23	25.74 (23.07−30.09)	27.47 (25.34−30.66)	0.51
MC1	37.00 (34.07−40.49)	31.33 (29.51−34.23)	0.001	38.63 (37.44−39.81)	33.97 (29.40−35.98)	0.003
MWM1	30.50 (26.22−33.66)	23.72 (20.96−28.75)	0.04	27.91 (23.51−31.39)	30.05 (24.65−32.75)	0.27
MC2	39.03 (37.27−39.94)	30.88 (29.21−36.33)	<0.001	38.96 (37.33−40.83)	35.04 (30.92−36.69)	0.006
MWM2	31.81 (28.12−34.61)	23.60 (21.12−31.62)	0.04	28.43 (23.97−31.66)	29.44 (23.77−32.24)	0.84
Gray−White matter Ratio (GWR), median (IQR)						
Basal ganglia	1.24 (1.20−1.32)	1.21 (1.16−1.31)	0.35	1.27 (1.20−1.34)	1.13 (1.05−1.23)	0.02
Cerebrum	1.20 (1.15−1.35)	1.26 (1.10−1.43)	0.88	1.37 (1.28−1.56)	1.12 (1.07−1.21)	0.003
Average	1.21 (1.16−1.33)	1.23 (1.16−1.34)	0.54	1.32 (1.22−1.45)	1.12 (1.06−1.23)	0.005
Simplified	1.26 (1.22−1.38)	1.23 (1.14−1.33)	0.27	1.24 (1.20−1.39)	1.12 (1.06−1.24)	0.05

ROI = region of interest; HU = Hounsfield units; IQR = interquartile range; CN = caudate nucleus; PU = putamen; CC = corpus callosum; PIC = posterior limb of the internal capsule; MC = medial cortex; MWM = medial white matter.

Table 4
ROC-analysis for prediction of poor outcome using different GWR-methods.

GWR	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (95% CI)	*p*
Basal ganglia	1.18	50.0	87.5	91.3	40.0	0.698 (0.559−0.837)	0.02
	1.12	28.6	100	100	34.8		
Cerebrum	1.15	54.8	87.5	92.0	42.4	0.680 (0.538−0.822)	0.04
	1.09	28.6	100	100	34.8		
Average	1.14	38.1	100	100	38.1	0.680 (0.537−0.823)	0.04
Simplified	1.16	50.0	93.8	95.5	41.7	0.692 (0.555−0.829)	0.03
	1.10	28.6	100	100	34.8		

GWR = gray−white matter ratio; AUC = area under the curve; CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value.

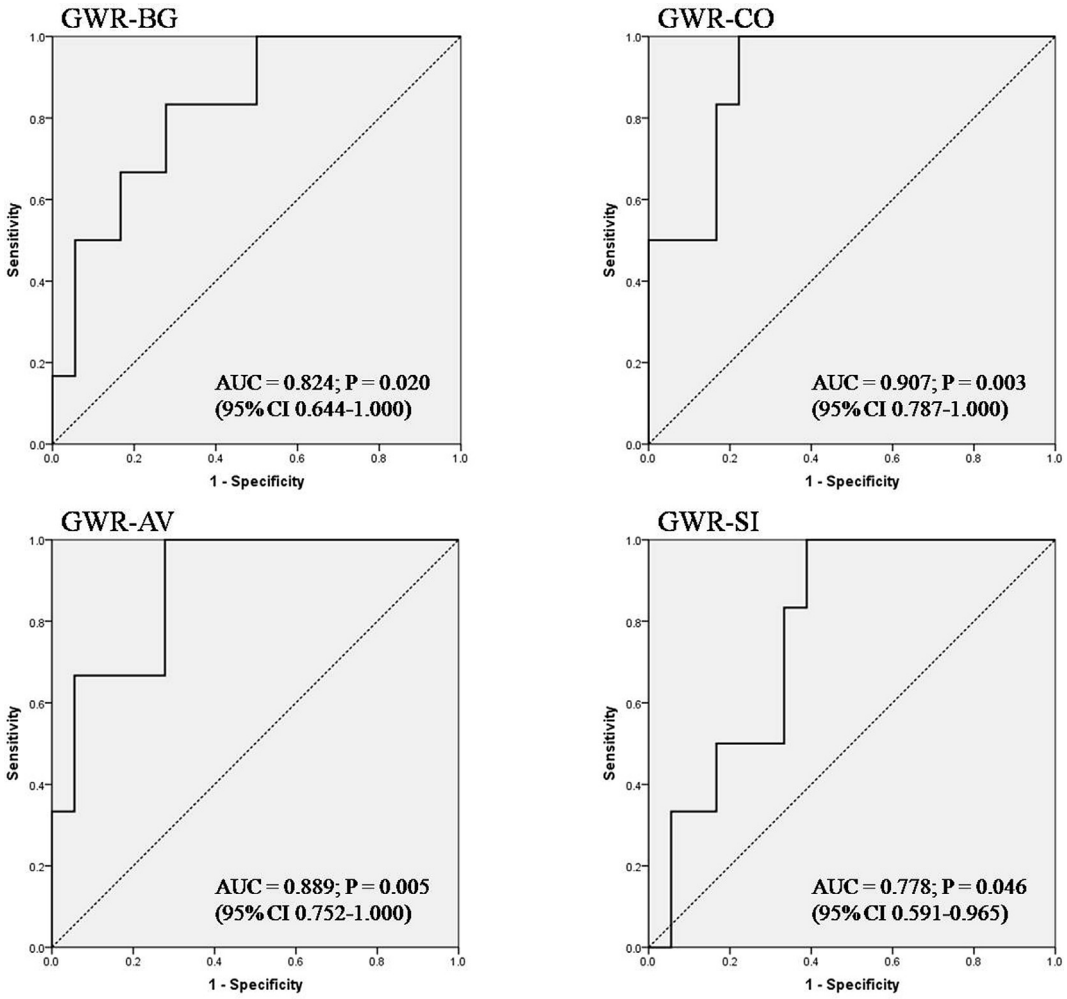

Fig. 2. Receiver-operating characteristic curves for gray–white matter ratio of basal ganglia (GWR-BG), cerebrum (GWR-CO), average (GWR-AV), and simplified (GWR-SI) in the late CT performed group. AUC= area under the curve; CI= confidence interval.

edema.[12] The difference between GM and WM in CT images arises because the higher water content and lower lipid content of the GM result in a higher oxygen concentration and a lower carbon concentration, which increase the level of photoelectric absorption. The greater vulnerability of GM to ischemic/hypoxic events can be explained by its higher metabolic rate, greater blood flow, and susceptibility to excitotoxicity.[13] Increased vascular permeability leading to extravasation of fluid (vasogenic edema) and changes in ion flow due to excitotoxicity (cytotoxic edema) contribute to a preferential accumulation of edema in GM compared to WM.[14] The present study demonstrated that the attenuation values of GM were significantly lower in poor outcome group.

The basal ganglia, in particular, have a high metabolic turnover and are among the first structures to be affected under hypoxic conditions.[15] Also, it appears that edema is more severe in the area of the basal ganglia in general, and in the PU in particular. The PU is anatomically relatively well defined, allowing its reliable identification on CT. The present study therefore chose the PU as the measurement site in GM for the simplified GWR estimation method. For the same reason, the authors chose the PIC as the measurement site in the WM. The WM, such as the PIC, appears to be nearly unaffected during the acute stage of HIE, and HU values are not different between patients with good and poor outcome.[16] The present study also found that the tissue attenuation of WM was not significantly different between good and poor outcome groups.

Several studies have indicated that, in contrast to ischemic strokes, which are not visualized by brain CT for at least 6 h after the onset, cerebral edema after CA becomes recognizable on brain CT at an earlier period.[17] Kim et al. evaluated the prognostic performance of GWR using a brain CT performed within 1 h after ROSC in 167 CA survivors and found a significant association between decreased GWR and poor outcome.[7] Wu et al. found a significant decrease in the density of the PU for CT performed within 24–72 h as compared to within the first 24 h after CA.[5] However, another two studies reported that the arrest-to-brain CT interval was not associated with GWR or its prognostic performances.[2,6] In the present study, GWR-CO showed the best predictive performance when CT was performed within 24–72 h. No significant differences were found between GWR and poor outcomes when CT was performed within the first 24 h. The timing of brain CT has not been uniform in previous studies, whose time from ROSC to

CT was less than 6 h in the majority of cases. Thus, a possibility that a brain CT scan obtained later in the hospital course could be helpful in predicting poor outcomes cannot be disregarded.[18] Further study is required to determine the effects of the timing of brain CT on GWR.

This study also presents several limitations. First, this was a retrospective study with a limited amount and quality of data. Because of the small number of patients, the study population might not have included rare cases of good clinical recovery despite the development of brain edema in the early phase after the event. Moreover, the clinical endpoints of poor CPC at discharge may be subject to error due to later improvement. Therefore, the 100% specificity for the cut-off values the authors identified should be interpreted with caution and needs to be confirmed in further studies. Second, only patients who underwent brain CT scan were included in the study, which might have resulted in selection bias. CT was generally ordered by treating physicians if the cause of the CA was deemed uncertain or if intracranial complications were suspected. The findings require confirmation through further studies with large cohorts in which all comatose patients after CA undergo brain CT scanning. Third, this study cannot definitely rule out the problem of self-fulfilling prophecy by limiting treatment in those patients who are expected to have poor outcome.

In conclusion, the present study demonstrated that a low GWR, as determined from brain CT scans in comatose CA patients after ROSC, was associated with a poor neurological outcome. GWR determination from brain CT can be a useful tool for outcome prediction aiding to an optimal clinical decision process in comatose CA survivors. Further studies in larger patient populations are desirable before a definite recommendation for routine diagnostic use can be made.

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