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**Original Article**



# The Use of Gray-White-Matter Ratios May Help Predict Survival and Neurological Outcomes in Patients Resuscitated From Out-of-Hospital Cardiac Arrest

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**Background:** The gray-white-matter ratio (GWR) measured on brain computed tomography (CT) following return of spontaneous circulation (ROSC) has been reported to be helpful in the prognostication of mortality or comatose status of cardiac arrest victims. However, whether the use of GWR in predicting the outcomes in out-of-hospital cardiac arrest (OHCA) survivors in Taiwan population remains uninvestigated.
**Methods:** This retrospective observational study conducted in a single tertiary medical center in Taiwan enrolled all the non-traumatic OHCA adults (> 18 years old) with sustained ROSC (≥ 20 minutes) during the period from 2006 to 2014. Patients with following exclusion criteria were further excluded: no brain CT within 24 hours following ROSC; the presence of intracranial hemorrhage, severe old insult, brain tumor, ventriculoperitoneal shunt, and severe image artifact. The GWR values were obtained from the density measurement of bilateral putamen, caudate nuclei, posterior limbs of internal capsule, corpus callosum, medial cortex and medial white matter of cerebrum in Hounsfield unit with region of interest of 0.11 $cm^2$, and further compared between the patients who survived to hospital discharge or not and the patients with and without good neurological outcome (good: cerebral performance category [CPC] of 1–2, poor: CPC of 3–5), respectively.
**Results:** A total of 228 patients were included in the final analysis with 59.2% in male gender and mean age of 65.8-year-old. There were 106 patients (46.5%) survived to hospital discharge and 40 patients (17.5%) discharged with good neurological outcomes. The GWR values of patients who survived to hospital discharge was significantly higher than ones of those who failed (e.g., basal ganglion: 1.239 vs. 1.199, $p < 0.001$). Patients with good neurological outcome also had higher GWR values than those with poor outcome (e.g., basal ganglion: 1.243 vs. 1.208, $p = 0.010$). The Area Under Curve of Receiver of Characteristic curve demonstrated fair predicting ability of GWR for survival and neurological outcomes.
**Conclusions:** The use of GWR measured on bran CT within 24 hours following ROSC can help in predicting survival-to-hospital discharge and neurological outcome in OHCA survivors.

**Key words:** *gray-white-matter ratio, survival, neurological outcome, out-of-hospital cardiac arrest*

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## Introduction

Sudden cardiac arrest has been a challenge in clinical practice. In United States, there are 356,000 patients with out-of-hospital cardiac arrest (OHCA) and 209,000 ones with in-hospital cardiac arrest (IHCA) annually. In OHCA victims, the survival-to-discharge was 12% and the good neurological outcome was around 8% in survived patients. However, 25% of IHCA victims survived to hospital discharge.[1] Along with the improvement in emergency medical service (EMS) system,[2,3] science of cardiopulmonary resuscitation (CPR), resuscitation teamwork[4] and post-arrest care,[5] there is significant increase in survival and neurological outcomes in patients who were successfully resuscitated from cardiac arrest. However, the overall good neurological recovery rate is still far from satisfaction, and medical and financial burden of cardiac arrest survivors is quite heavy.[6] Therefore, how to predict the prognosis in cardiac arrest survivors and thus make the further treatment plan constitute an important part in treating those patients, and several prognostication methods including brainstem reflex,[7] electroencephalogram,[8] serum biomarker[9] and brain images[10-12] have been proposed.

The use of neuroimaging including computed tomography (CT), magnetic resonance imaging, positron emission tomography, and single-photon emission CT in predicting outcomes in cardiac arrest survivors has been proposed in last decade and demonstrated various potential in helping prognostication.[10-12] During ischemic brain injury, the edematous change of gray matter results in the attenuation of its density;[13] thus loss of distinction of gray and white matter. The extent of loss of distinction between gray and white matter reflects the severity of ischemic brain injury.[10] Brain CT is frequently performed in early post-arrest period to identify the possible cause of cardiac arrest and to exclude intracranial hemorrhage before therapeutic hypothermia. The measurement of the ratio of X-ray attenuation (Hounsfield units [HUs]) between the gray matter and white matter (GWR) on brain CT image was used to quantify the edematous intensity.[10-12] The normal GWR value of brain is around 1.3 and decreases with cerebral edema. A reduced GWR at the level of basal ganglia was found to be associated with poor outcomes in cardiac arrest survivors.[10,11,14,15] The timing of the presence of cerebral edema varies between studies, from 24 to 72 hours following cardiac arrest.[10,16,17] Studies reported that a GWR value below 1.22 within 24 hours or below 1.18 within 48 hours after return of spontaneous circulation (ROSC) was associated with poor outcome.[18,19]

There is no published study describing the use of GWR in predicting outcomes of cardiac arrest survivors in Taiwan. Whether GWR following ROSC is associated with survival to discharge and neurological recovery in patients successfully resuscitated from cardiac arrest in Taiwanese population remains unclear. Therefore, in the retrospective cohort study, we would like to investigate the association between post-arrest GWR and outcomes in OHCA survivors.

## Method

### Institutional Review Board Approval

The retrospective cohort study was approved by the Institutional Review Board (IRB) of National Taiwan University Hospital (NTUH) (IRB number: 201812008RINC), and the need of informed consent was waived.

### Study Population

This retrospective, single-center observational cohort study conducted in the emergency department of NTUH which is a 2500-bed medical center and provides primary and tertiary care in Taipei City. Taipei is the capital of Taiwan and located in the northern Taiwan with a 2.68 million population in 272 $km^2$.

A total of 1,139 consecutive adult (at least 18-year-old) patients with non-traumatic OHCA had received CPR attempt in the emergency department of our hospital during the period from 2006 to 2014. There were 549 patients gained sustained ROSC (defined as persisted palpable pulses for at least 20 minutes). Among them, brain non-contrasted CT within 24 hours following cardiac arrest had been performed on 271 patients (n = 271). The patients with intracranial hemorrhage (n = 20), severe old insult (n = 6), brain tumor (n = 2), ventriculoperitoneal shunt (n = 1) and severe image artifact (n = 14) were excluded. Two hundred and twenty-eight OHCA survivors with quantified brain non-contrasted CT image were included in the final analysis (Fig. 1). In the enrolled patients, 106 patients survived to hospital discharge and were classified as the survivor group, and 122 patients died during hospitalization and were classified as the

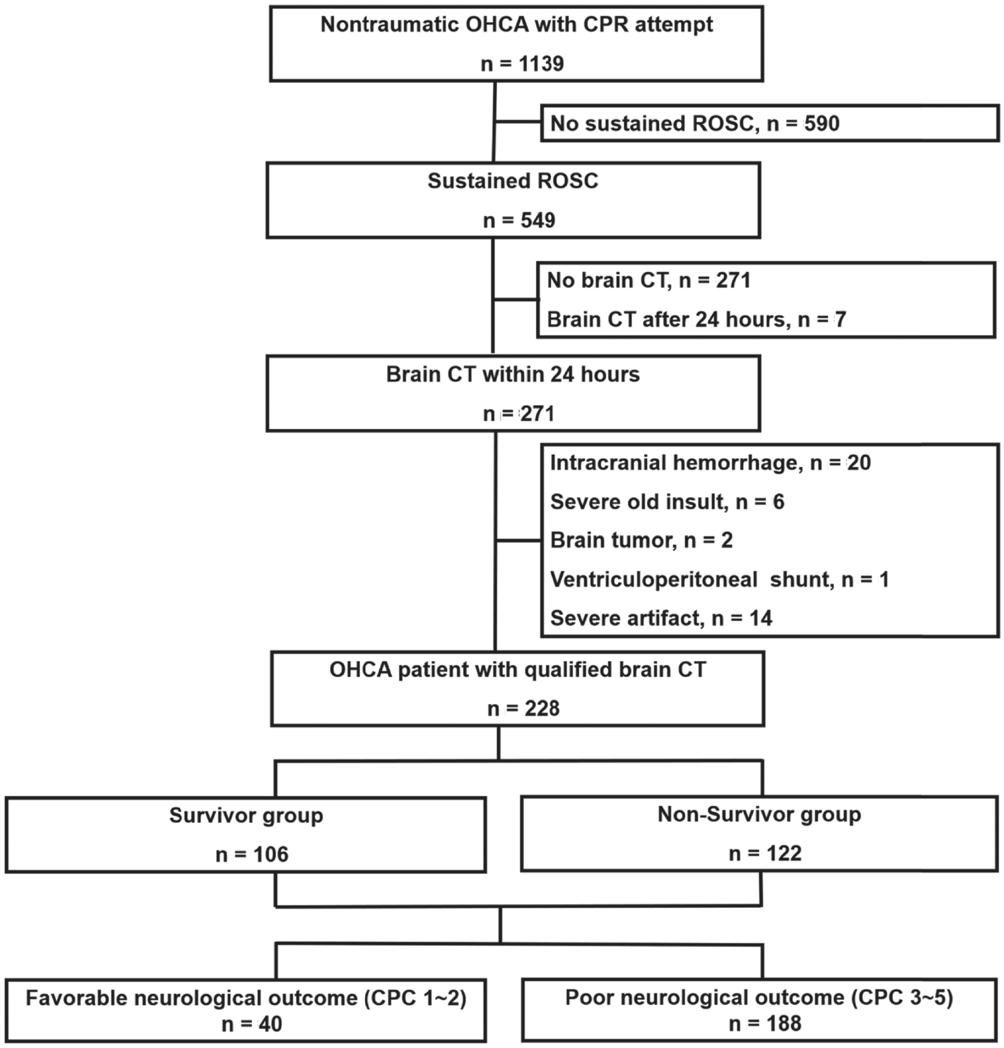



**Fig. 1.** Flowchart of patient enrollment.

CPC: cerebral performance category; CPR: cardiopulmonary resuscitation; CT: computed tomography; OHCA: out-of-hospital cardiac arrest; ROSC: return of spontaneous circulation.

non-survivor group. Forty patients with cerebral performance category (CPC) of 1–2 were classified as the favorable neurological outcome group, and 188 patients with CPC of 3–5 were classified as the poor neurological outcome group.

## Brain CT Measurements

The brain non-contrast CT was performed on 64-row multi-detector scanners (LightSpeed VCT, GE Healthcare, Wauwatosa, WI, USA) in axial mode by the technician on duty who was not involved in the current study. The image parameters were independently reviewed by two physicians respectively (one from emergency medicine and one from radiology department) through Picture Archiving and Communication System. Both of the physicians went through a course of self-training for landmark identification on CT images prior to the study initiation. They were blinded to the patients' clinical information.

The HU that represents the CT density of selective region of interest was measured according to the precedent publications.[20] Circular region of interest with measurement of 0.11 $cm^2$ was placed at the selective area of gray matter and white matter at both of the basal ganglia and cerebrum level. At basal ganglia level, the density of bilateral putamen (PU), head of caudate nuclei (CN), posterior limb of internal capsule (PIC) and corpus callosum (CC) were estimated. The gray matter to white matter ratio of basal ganglia (GWR-BG) was calculated as follow:

$$GWR\text{-}BG = (PU + CN) / (PIC + CC)$$

The density of bilateral medial gray matter (medial cortex, MC) and medial white matter (MW) were measured at two levels, centrum semiovale (MC1, MW1) and high convexity area (MC2, MW2), respectively. The centrum semiovale is located 5 mm just above the last lateral ventricle whereas the high convexity area is located 5 mm just cranial to it. The division of the sum of all gray matter and white matter constitutes the GWR of cerebrum (GWR-C) as shown by the formula below:

$$GWR\text{-}C = (MC1 + MC2) / (MW1 + MW2)$$

The average of GWR-BG and GWR-C gave rise to the average GWR of the brain (GWR-AVE):

$$GWR\text{-}AVE = (GWR\text{-}BG + GWR\text{-}C) / 2$$

In addition, the simplified GWR-BG was also reported as following:

(1) GWR-PUPIC = PU/PIC
(2) GWR-CNPIC = CN/PIC
(3) GWR-PUCC = PU/CC
(4) GWR-CNCC = CN/CC

The GWR calculation was went through twice by each interpreter at different interval in order to estimate the intra-rater consistency. Both of the results of the two interpreters were compared for the determination of inter-rater reliability. The image interpretation performance was evaluated by a third party.

## Data Collection and Outcome Measurement

The baseline characteristics, pre-existing comorbidity, prehospital events, and in-hospital management were retrospectively collected from medical and EMS record by using a pre-designed form. Shockable rhythm meant ventricular fibrillation or ventricular tachycardia. Cardiogenic arrest was impressed when ischemic heart disease, structural heart disease, heart failure or arrhythmias without electrolyte imbalance were considered to be the cause of arrest.[21-23]. The non-cardiogenic causes included respiratory cause, infectious cause, massive GI bleeding, hyperkalemia, central nervous system lesion, and others.[23,24] The causes of cardiac arrest were determined by the primary care physicians in charge who were blinded to the current study. Targeted temperature management (TTM) protocol at NTUH included using cooling devices to decrease patients' body temperature to the targeted temperature (around 33°C) within 4–6 hours after ROSC, maintaining the targeted temperature for 24 hours, and rewarming patients with the increase in 0.25°C every hour till normothermia.[25] The extracorporeal membrane oxygenation (ECMO) and percutaneous coronary intervention (PCI) were defined when the use of ECMO or PCI was applied during CPR or within seven days after cardiac arrest.

The primary outcome of the study was survival-to-hospital discharge. We also concentrated on neurological outcome as the secondary outcome. The neurological outcome was evaluated by using Glasgow–Pittsburgh CPC scores. Favorable neurological outcome was defined as CPC scores of 1 (good performance) and 2 (moderate disability) at discharge. Poor neurological outcome was defined as CPC of 3 (severe disability), 4 (vegetative state), or 5 (death) at discharge.[26] The neurological recovery was assessed by the primary care physicians in charge who were blind to the current study.

These enrolled patients were grouped according to either survival or neurological outcome. Among the enrolled patients, 106 patients (46.5%) survived to hospital discharge (naming the survivor group) and 122 patients (53.5%) failed (naming the non-survivor group). Forty patients (17.5%) with favorable neurological outcome were classified as the favorable group and 188 patients (82.5%) with poor neurological outcome (CPC: 3–5) as the poor group (Fig. 1).

## Statistical Analysis

The categorical variables were expressed in frequencies and percentages with the exploration of chi-square or Fisher's exact test for significance determination. Continuous variables were expressed in means and standard deviations or medians and interquartile ranges according to the normality of distribution. The differences between two groups were determined with independent two-tailed t-test or Mann–Whitney U test. Receiver of characteristic (ROC) curves were plotted in order to measure the GWR performance of outcome prediction as shown by the area under the curve (AUC). Optimal cutoff value with 100% specificity was obtained from the ROC curve. The correspondent sensitivity and its positive predictive value (PPV) were estimated with their 95% confidence interval (95% CI). *p*-value less than 0.05 was considered as statistically significant. All of the results were analyzed with the help of SPSS version 21.0 software (IBM Corp., Armonk, NY, USA).

## Results

Table 1 identified the demographic characteristics of the included 228 OHCA patients with mean age of 65.77 ± 16.68 years. Among them, 135 patients (59.2%) were male. Compared with the non-survivor group, the survivor group had less patients with pre-arrest bed-ridden (1.9% vs. 9.0%, $p = 0.021$), but more patients with initial shockable rhythm (34.0% vs. 11.5%, $p = 0.000$), TTM (63.2% vs. 35.2 %, $p = 0.000$) and PCI (35.8% vs. 8.2%, $p = 0.000$) after ROSC. Patients who survived to hospital discharge were found to be younger (61.74 ± 17.56 vs. 69.28 ± 15.09, $p = 0.001$) and have shorter CPR duration (20.64 ± 15.31 vs. 25.07 ± 15.51, $p = 0.041$) than those who failed. Compared with the poor neurological outcome group, the favorable neurological outcome group had less patients with malignancy (2.5% vs. 15.4%, $p = 0.028$) and cardiogenic arrest (22.5% vs. 57.4%, $p = 0.000$), but more patients with hyperlipidemia (17.5% vs. 5.3%, $p = 0.015$), initial shockable rhythm (52.5% vs. 15.4%, $p = 0.000$), TTM (65.0% vs. 44.7%, $p = 0.020$) and PCI (60.0% vs. 12.8%, $p = 0.000$) after ROSC. Patients with favorable neurological outcome were found to be younger (53.80 ± 17.04 vs. 68.32 ± 15.49, $p = 0.000$) and have shorter CPR duration (18.43 ± 16.15 vs. 23.98 ± 15.26, $p = 0.047$) than those with poor neurological outcome.

When using conventional GWR measurement, the patients in the survivor group had significantly higher values of GWR-BG (1.239 vs. 1.199, $p = 0.000$), GWR-C (1.203 vs. 1.166, $p = 0.000$) and GWR-AVE (1.225 vs. 1.184, $p = 0.000$) than those in the non-survivor group. The simplified GWR method also demonstrated a significantly higher values of GWR-PUPIC (1.256 vs. 1.209, $p = 0.000$), GWR-CNPIC (1.233 vs. 1.207, $p = 0.005$), GWR-PUCC (1.234 vs. 1.175, $p = 0.000$) and GWR-CNCC (1.228 vs. 1.174, $p = 0.000$) in the survivor group than in the non-survivor group. As for neurological outcome, the conventional and simplified GWR measurement demonstrated higher values of GWR-BG (1.243 vs. 1.208, $p = 0.010$), GWR-AVE (1.229 vs. 1.199, $p = 0.008$), GWR-PUPIC (1.253 vs. 1.219, $p = 0.010$), GWR-CNPIC (1.259 vs. 1.213, $p = 0.000$) and GWR-CNCC (1.241 vs. 1.196, $p = 0.017$) in the favorable neurological outcome group than in the poor neurological outcome group except GWR-C (1.197 vs. 1.179, $p = 0.063$) and GWR-PUCC (1.233 vs. 1.203, $p = 0.152$) (Table 2 and Supplement Table 1).

Fig. 2A showed the ROC curves of conventional GWR measurement and the AUC at the setting of specificity of 100% for prediction of in-hospital mortality. The GWR-AVE, as combination of GWR-BG and GWR-C, had a higher AUC to predict in-hospital mortality (0.692, 95% CI: 0.624–0.760) with cut-off value of 1.05 (Fig. 2B). The ROC curves of simplified GWR measurement showed not inferior AUC values from 0.609 to 0.674 (Supplement Fig. 1). As to predict neurological outcome, the conventional GWR measurement also showed an increase of AUC value in GWR-AVE (0.633, 95% CI: 0.553–0.712) with a cut off value of 1.14 (Fig. 3). The ROC curves of simplified GWR measurement in predicting poor neurological outcome showed AUC values from 0.572 to 0.687 (Supplement Fig. 2).

## Discussion

In the current study, we investigated the brain CT image performed within 24 hours after ROSC in OHCA survivors and demonstrated that patients who survived to hospital discharge had higher GWR values than ones who failed. Similarly, patients with good neurological recovery at discharge had higher GWR values than those with poor neurological outcome. To our best knowledge, the study is the first one which investigated the use of GWR in predicting the survival and neurological outcomes for OHCA survivors in Taiwanese population.

Although improvements in CPR and post post-arrest care, the survival-to-discharge rate was approximately 12% and the percentage of good neurological outcome was around 8% in survived cardiac arrest victims. Unfavorable neurological recovery accounts for a heavy burden in both medical and financial aspects. Accurate prognostication is important to avoid pursuing futile treatments when poor outcome is inevitable. Besides, inaccurate neurological prognostication would lead to inappropriate withdrawal of life-sustaining treatment in patients who may otherwise have a chance to achieve good neurological recovery, and thus result in bias in clinical studies. Therefore, how to make an accurate neurological pre-

**Table 1.** Demographic characteristic of patients

| | Total patients N (%) | Survivor group n (%) | Non-survivor group n (%) | | Favorable neurological outcome n (%) | Poor neurological outcome n (%) | |
|---|---|---|---|---|---|---|---|
| | N = 228 | 106 (46.5) | 122 (53.5) | *p*-value | 40 (17.5) | 188 (82.5) | *p*-value |
| Age (years) | 65.77 ± 16.68 | 61.74 ± 17.56 | 69.28 ± 15.09 | 0.001 | 53.80 ± 17.04 | 68.32 ± 15.49 | 0.000 |
| Gender (male) | 135 (59.2) | 70 (66.0) | 65 (53.3) | 0.051 | 27 (67.5) | 108 (57.4) | 0.240 |
| DM | 75 (32.9) | 37 (34.9) | 38 (31.1) | 0.547 | 11 (27.5) | 64 (34.0) | 0.424 |
| Hypertension | 114 (50.0) | 50 (47.2) | 64 (52.5) | 0.426 | 18 (45.0) | 96 (51.1) | 0.486 |
| CAD | 64 (28.1) | 25 (23.6) | 39 (32.0) | 0.160 | 11 (27.5) | 53 (28.2) | 0.930 |
| HF | 31 (13.6) | 13 (12.3) | 18 (14.8) | 0.584 | 5 (12.5) | 26 (13.8) | 0.824 |
| COPD/asthma | 22 (9.6) | 9 (8.5) | 13 (10.7) | 0.581 | 2 (5.0) | 20 (10.6) | 0.383 |
| ESRD | 20 (8.8) | 10 (9.4) | 10 (8.2) | 0.742 | 3 (7.5) | 17 (9.0) | 1.000 |
| Cirrhosis | 2 (0.9) | 0 (0.0) | 2 (1.6) | 0.185 | 0 (0.0) | 2 (1.1) | 1.000 |
| CVA | 28 (12.3) | 12 (11.3) | 16 (13.1) | 0.681 | 4 (10.0) | 24 (12.8) | 0.794 |
| Dementia | 9 (3.9) | 6 (5.7) | 3 (2.5) | 0.310 | 0 (0.0) | 9 (4.8) | 0.366 |
| Bed-ridden | 13 (5.7) | 2 (1.9) | 11 (9.0) | 0.021 | 0 (0.0) | 13 (6.9) | 0.132 |
| Hyperlipidemia | 17 (7.5) | 8 (7.5) | 9 (7.4) | 0.961 | 7 (17.5) | 10 (5.3) | 0.015 |
| Malignancy | 30 (13.2) | 9 (8.5) | 21 (17.2) | 0.052 | 1 (2.5) | 29 (15.4) | 0.028 |
| Witnessed collapse | 158 (69.3) | 80 (75.5) | 78 (63.9) | 0.060 | 30 (75.0) | 128 (68.1) | 0.389 |
| prehospital CPR | 154 (67.5) | 73 (68.9) | 81 (66.4) | 0.691 | 28 (70.0) | 126 (67.0) | 0.715 |
| Initial shockable rhythm | 50 (21.9) | 36 (34.0) | 14 (11.5) | 0.000 | 21(52.5) | 29 (15.4) | 0.000 |
| CPR duration (min) | 22.96 ± 15.54 | 20.64 ± 15.31 | 25.07 ± 15.51 | 0.041 | 18.43 ± 16.15 | 23.98 ± 15.26 | 0.047 |
| Cardiogenic arrest | 111 (48.7) | 48 (45.3) | 69 (56.6) | 0.089 | 9 (22.5) | 108 (57.4) | 0.000 |
| TTM | 110 (60.1) | 67 (63.2) | 43 (35.2) | 0.000 | 26 (65.0) | 84 (44.7) | 0.020 |
| ECMO | 29 (12.7) | 14 (13.2) | 15 (12.3) | 0.837 | 4 (10.0) | 25 (13.3) | 0.570 |
| PCI | 48 (21.1) | 38 (35.8) | 10 (8.2) | 0.000 | 24 (60.0) | 24 (12.8) | 0.000 |
| Highest APACHE II during 24 h | 23.57 ± 7.19 | 26.95 ± 6.56 | 29.42 ± 8.72 | 0.118 | 26.93 ± 7.10 | 28.60 ± 8.06 | 0.467 |

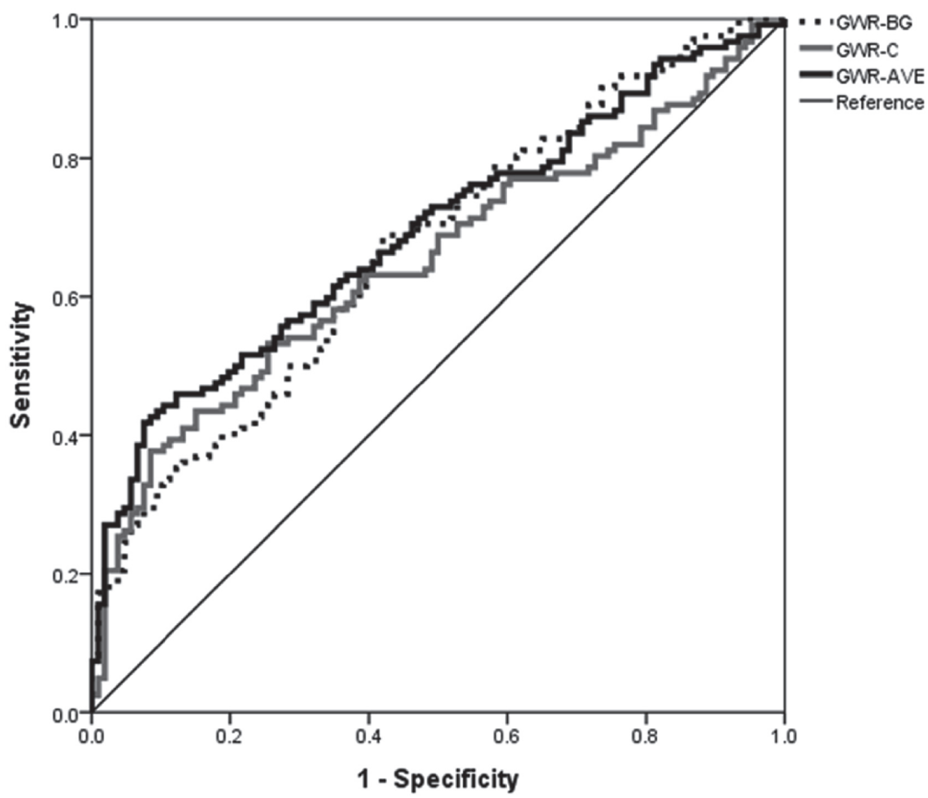
APACHE: Acute Physiology and Chronic Health Evaluation; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; CPR: cardiopulmonary resuscitation; CVA: cerebrovascular accident; DM: diabetes mellitus; ECMO: extracorporeal membrane oxygenation; ESRD: end-stage renal disease; HF: heart failure; PCI: primary coronary intervention; TTM: targeted temperature management.

**Table 2.** GWR between different groups

| | Survivor group median (IQR) | Non-survivor group median (IQR) | *p*-value | Favorable neurologic outcome median (IQR) | Poor neurologic outcome median (IQR) | *p*-value |
|---|---|---|---|---|---|---|
| GWR-BG | 1.239 (1.190–1.282) | 1.199 (1.132–1.250) | 0.000 | 1.243 (1.189–1.280) | 1.208 (1.155–1.259) | 0.010 |
| GWR-C | 1.203 (1.165–1.253) | 1.166 (1.109–1.222) | 0.000 | 1.197 (1.173–1.242) | 1.179 (1.128–1.249) | 0.063 |
| GWR-AVE | 1.225 (1.186–1.255) | 1.184 (1.135–1.228) | 0.000 | 1.229 (1.193–1.251) | 1.199 (1.150–1.244) | 0.008 |

GWR-AVE: average gray matter to white matter ratio of the brain; GWR-BG: gray matter to white matter ratio of basal ganglia; GWR-C: gray matter to white matter ratio of cerebrum; IQR: interquartile range.

(A)



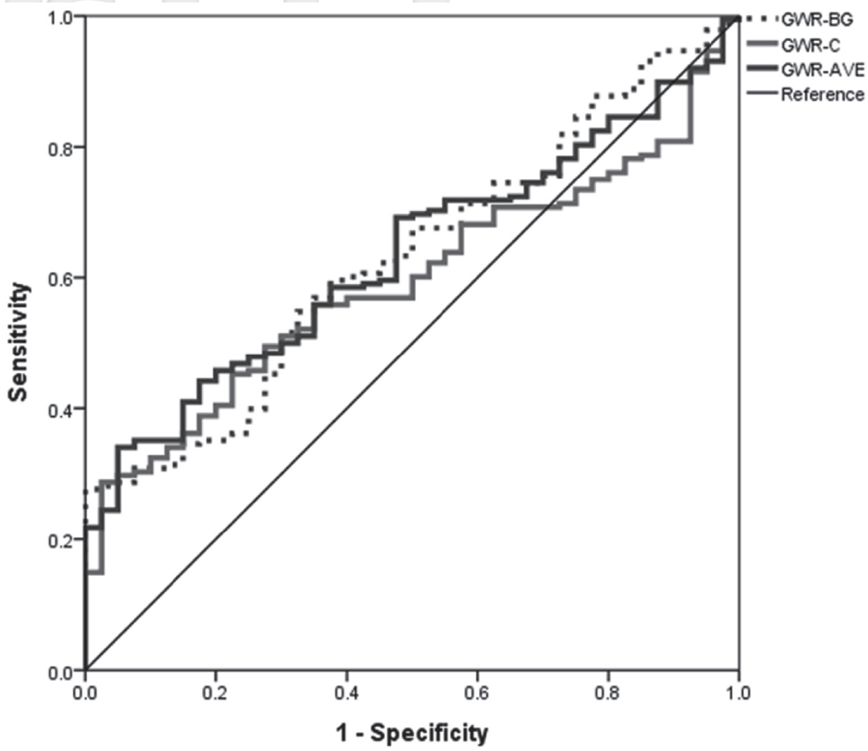

(B)

| | AUC (95% CI) | Cut-off | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | p-value |
|---|---|---|---|---|---|---|---|
| GWR-BG | 0.668 (0.599~0.737) | 1.02 | 8.2 | 100 | 100 | 51 | 0 |
| GWR-C | 0.651 (0.580~0.722) | 1 | 2.5 | 100 | 100 | 47.1 | 0 |
| GWR-AVE | 0.692 (0.624~0.760) | 1.05 | 7.4 | 100 | 100 | 48.4 | 0 |

**Fig. 2.** Receiver of characteristic curve of conventional gray matter to white matter ratio measurement and its predictive performance for in-hospital mortality.

AUC: area under the curve; CI: confidence interval; GWR-AVE: average gray matter to white matter ratio of the brain; GWR-BG: gray matter to white matter ratio of basal ganglia; GWR-C: gray matter to white matter ratio of cerebrum; NPV: negative predictive value; PPV: positive predictive value.

(A)




(B)

| | AUC (95% CI) | Cut-off | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | p-value |
|---|---|---|---|---|---|---|---|
| GWR-BG | 0.630 (0.546~0.715) | 1.162 | 27.7 | 100 | 100 | 22.3 | 0.01 |
| GWR-C | 0.593 (0.514~0.673) | 1.107 | 14.4 | 100 | 100 | 20 | 0.063 |
| GWR-AVE | 0.633 (0.553~0.712) | 1.14 | 20.7 | 100 | 100 | 20.7 | 0.008 |

**Fig. 3.** Receiver of characteristic curve of conventional gray matter to white matter ratio measurement and its predictive performance for poor neurological outcome.

AUC: area under the curve; CI: confidence interval; GWR-AVE: average gray matter to white matter ratio of the brain; GWR-BG: gray matter to white matter ratio of basal ganglia; GWR-C: gray matter to white matter ratio of cerebrum; NPV: negative predictive value; PPV: positive predictive value.

diction in cardiac arrest survivors and thus constitute a further treatment plan play a vital role in treating those patients.

The use of GWR of brain CT following ROSC in predicting in-hospital mortality has been reported in several studies. The patients who successfully survived to hospital discharge had a higher GWR value than those who failed.[16,18,27,28] The predicting power (AUC) of mortality assessed by using ROC curves differs from 0.67 to 0.73 based on different study population, timing of CT performed and sampling area of measurement. Youn et al. showed that an AUC of 0.683 was associated with mortality by using brain CT within 24 hours after cardiac arrest.[27] Another study analyzing brain CT within 24 hours also demonstrated an association between GWR and mortality (basal ganglia AUC: 0.69, cerebrum AUC: 0.67, average AUC: 0.72). Average GWR < 1.20 was proposed to predict in-hospital mortality with a sensitivity of 36%, a specificity of 98%, a PPV of 97%, and a negative predictive value of 46%.[28] In our current study, the survivors also had a higher GWR value than the non-survivors. Besides, the predicting ability of GWRs differs in different sampling areas and ranges from 0.651 to 0.692 (basal ganglia AUC: 0.668, cerebrum AUC: 0.651, average AUC: 0.692). The cut-off values of GWR were from 1 to 1.05, which were lower than previously published manuscript. The difference may be attributed from the setting specificity of 100% and PPV of 100% in our current study to avoid false positive prediction.

The GWRs obtained from brain CT following cardiac arrest have also been used to predicting neurological recovery.[27,29,30] Brain CT performed within 24 hours after ROSC showed an AUC of 0.726 in predicting poor neurological outcome.[27] In combination with optic nerve sheath diameter, GWR provided a better prognostic ability in predicting poor neurological recovery (AUC: 0.67, 95% CI: 0.58–0.76) as compared to each alone. Besides, the combination of optic nerve sheath diameter and GWR improved the sensitivity but not reducing the specificity for predicting poor neurological outcome.[29] By using automated probabilistic GWR segmentation algorithm, Hanning et al. demonstrated a significant better predicting power in automated GWR (AUC: 0.860) for poor neurological outcome than in manual GWR (AUC: 0.699–0.707). The optimal cut-off value of GWR was 1.084.[30] In our current study, the patients with good neurological recovery also had higher GWR values than those with poor outcomes. The AUC of GWR-BG, GWR-C and GWR-AVE were 0.630, 0.593, and 0.633, respectively. The cut-off values of GWR in our current study were from 1.107 to 1.162 with specificity of 100%.

There are some limitations in the current study. As a retrospective study, some important data may not be extracted from medical records. Only the patients with brain CT examination within 24 hours are enrolled which may prone to selection bias, which is somehow unavoidable in retrospective study. Besides, the current study is a single-center one managed in a hospital located in the urban city. The population involved in our study may not represent generalizability to other contexts. And the limited case number in our study may limit the statistical significance. Last but not least, the change of ACLS guidelines during the study period and the improvement of resuscitative quality in the latter years because of the continuous effort of adjusting resuscitative details in our department might influent our result.

## Conclusions

In OHCA survivors in Taiwan, the higher GWRs values were associated with better survival and neurological outcomes with fair predicting ability.

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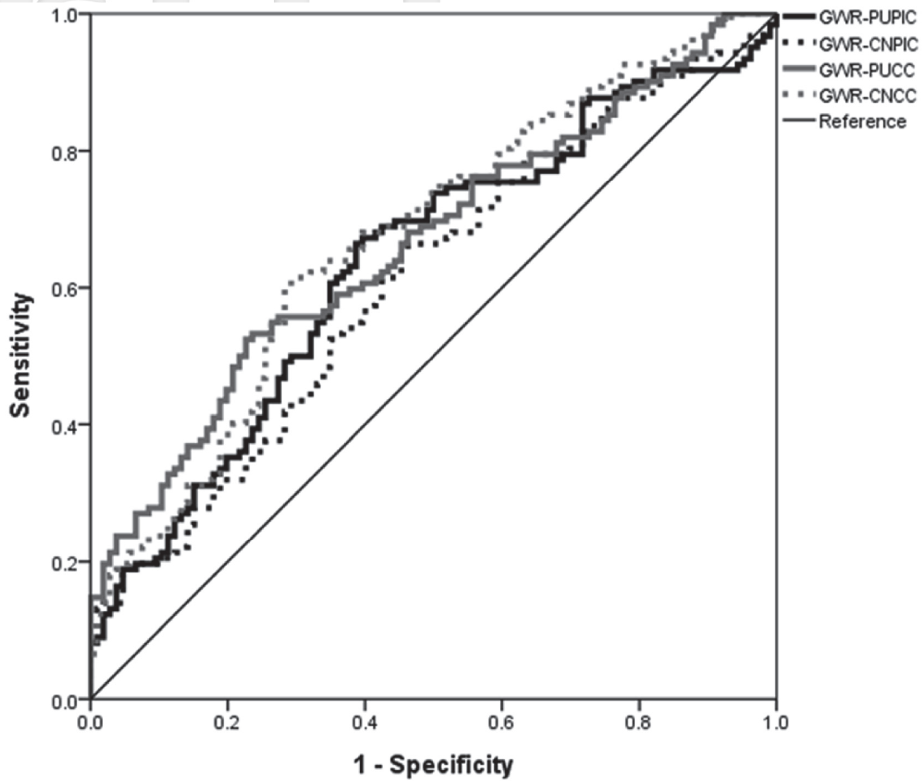
**Supplement Table 1.** GWR between different groups

| | Survivor group median (IQR) | Non-survivor group median (IQR) | *p*-value |
|---|---|---|---|
| GWR-PUPIC[a] | 1.256 (1.198–1.294) | 1.209 (1.168–1.263) | 0.000 |
| GWR-CNPIC[a] | 1.233 (1.178–1.288) | 1.207 (1.151–1.239) | 0.005 |
| GWR-PUCC[a] | 1.234 (1.182–1.299) | 1.175 (1.097–1.255) | 0.000 |
| GWR-CNCC[a] | 1.228 (1.165–1.293) | 1.174 (1.097–1.231) | 0.000 |

| | Favorable neurologic outcome median (IQR) | Poor neurologic outcome median (IQR) | *p*-value |
|---|---|---|---|
| GWR-PUPIC[a] | 1.253 (1.202–1.320) | 1.219 (1.171–1.271) | 0.010 |
| GWR-CNPIC[a] | 1.259 (1.214–1.296) | 1.213 (1.154–1.252) | 0.000 |
| GWR-PUCC[a] | 1.233 (1.172–1.296) | 1.203 (1.139–1.274) | 0.152 |
| GWR-CNCC[a] | 1.241 (1.146–1.298) | 1.196 (1.117–1.254) | 0.017 |

[a]GWR-PUPIC = PU/PIC; GWR-CNPIC = CN/PIC; GWR-PUCC = PU/CC; GWR-CNCC = CN/CC.
CC: corpus callosum; CN: caudate nuclei; GWR: gray matter to white matter ratio; IQR: interquartile range; PIC: posterior limb of internal capsule; PU: putamen.

(A)



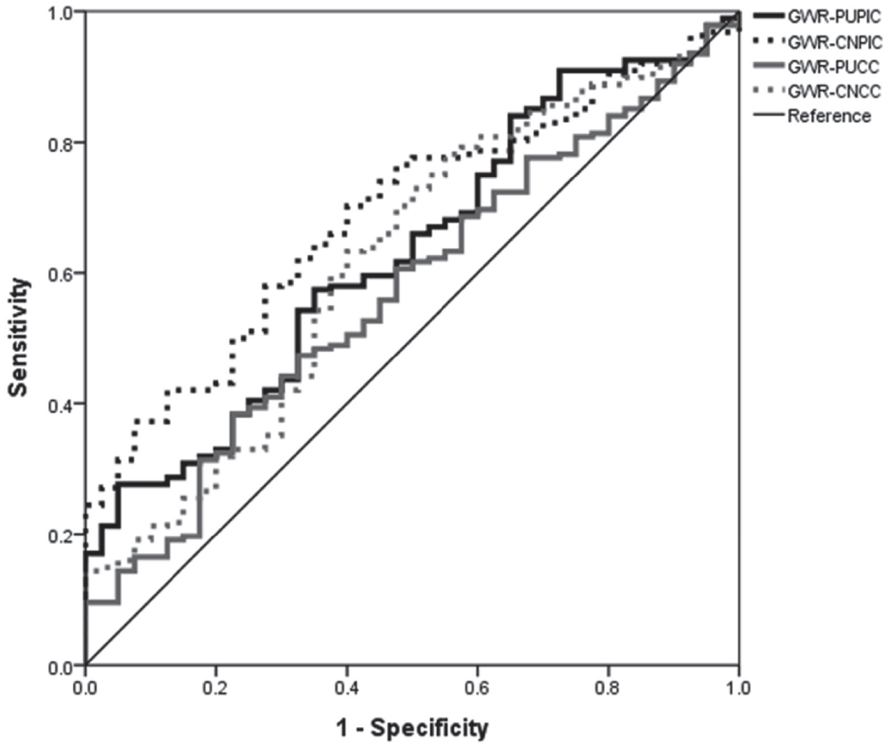

(B)

| | AUC (95% CI) | Cut-off | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | p-value |
|---|---|---|---|---|---|---|---|
| GWR-PUPIC | 0.637 (0.565~0.709) | 1.048 | 8.2 | 100 | 100 | 48.6 | 0 |
| GWR-CNPIC | 0.609 (0.536~0.682) | 0.979 | 8.2 | 100 | 100 | 48.6 | 0.005 |
| GWR-PUCC | 0.663 (0.594~0.733) | 1.06 | 14.8 | 100 | 100 | 50 | 0.733 |
| GWR-CNCC | 0.674 (0.604~0.743) | 0.99 | 6.6 | 100 | 100 | 48.2 | 0.743 |

**Supplement Fig. 1.** Receiver of characteristic curve of simplified gray matter to white matter ratio measurement and its predictive performance for in-hospital mortality.

CC: corpus callosum; CI: confidence interval; CN: caudate nuclei; GWR: gray matter to white matter ratio; NPV: negative predictive value; PIC: posterior limb of internal capsule; PPV: positive predictive value; PU: putamen.

(A)




(B)

| | AUC (95% CI) | Cut-off | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | p-value |
|---|---|---|---|---|---|---|---|
| GWR-PUPIC | 0.630 (0.541~0.720) | 1.149 | 17 | 100 | 100 | 20.2 | 0.01 |
| GWR-CNPIC | 0.687 (0.607~0.766) | 1.152 | 24.5 | 100 | 100 | 21.9 | 0 |
| GWR-PUCC | 0.572 (0.479~0.665) | 1.06 | 9.6 | 100 | 100 | 18.6 | 0.152 |
| GWR-CNCC | 0.620 (0.525~0.716) | 1.06 | 14.4 | 100 | 100 | 19.9 | 0.017 |

**Supplement Fig. 2.** Receiver of characteristic curve of simplified gray matter to white matter ratio measurement and its predictive performance for poor neurological outcome.

CC: corpus callosum; CI: confidence interval; CN: caudate nuclei; GWR: gray matter to white matter ratio; NPV: negative predictive value; PIC: posterior limb of internal capsule; PPV: positive predictive value; PU: putamen.