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# 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☆

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ABSTRACT

*Aim of the study:* Previous studies found that the gray matter to white matter ratio (GWR) on brain computed tomography (CT) could be used to predict poor outcomes in cardiac arrest survivors. However, these studies have included cardiac arrests of both cardiac and non-cardiac etiologies. We sought to evaluate if the GWR on brain CT can help to predict poor outcomes after out-of-hospital cardiac arrest (OHCA) of cardiac etiology.
*Methods:* Using a multicenter retrospective registry of adult cardiac arrest survivors treated with therapeutic hypothermia, we identified survivors of OHCA of cardiac etiology who underwent brain CT within 24 h after successful resuscitation. Gray and white matter attenuations were measured, and the GWRs were calculated as in previous studies. The prognostic values of the GWRs were analyzed, and a logistic regression analysis was performed to determine the contribution of the GWR in predicting poor outcomes (Cerebral Performance Category 3–5).
*Results:* of 283 included patients, 140 had good outcomes and 143 had poor outcomes. Although the GWRs could predict poor outcomes with statistical significance, the sensitivities were remarkably low (3.5% to 5.6%) at cutoff values with 100% specificity. No significant difference in predictive performance was found between the primary predictive model, containing independent poor outcome predictors, and the primary predictive model combined with the GWR.
*Conclusion:* In a cohort of comatose adults after OHCA of cardiac etiology, the GWR demonstrated poor predictive performance and was not helpful in predicting poor outcomes.


*Abbreviations:* CT, computed tomography; ROSC, restoration of spontaneous circulation; GWR, gray matter to white matter ratio; OHCA, out-of-hospital cardiac arrest; KORHN, Korean Hypothermia Network; TH, therapeutic hypothermia; CPR, cardiopulmonary resuscitation; GCS, Glasgow coma scale; HU, Hounsfield unit; CN, caudate nucleus; PU, putamen; PLIC, posterior limb of the internal capsule; CC, corpus callosum; MC, medial cortex; MW, medial white matter; CPC, Cerebral Performance Category; IQR, interquartile ranges; ROC, receiver operating characteristic; AUC, area under the ROC curve; CI, confidence interval; OR, odds ratio.

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## 1. Introduction

Although recent advances in post-cardiac arrest care have been revolutionary for cardiac arrest survivors,[1,2] 45–70% of the survivors still suffer from severe neurologic deficits or die from brain injury.[3–5] Thus, early methods to accurately predict patient outcomes would be useful in making therapeutic decisions and titrating therapy. Various parameters have been used for prognostication in comatose cardiac arrest survivors.[6–8] However, accurate outcome prediction remains difficult, particularly within 24 h of cardiac arrest.

Brain computed tomography (CT) is frequently performed early following restoration of spontaneous circulation (ROSC) to exclude primary brain injury that could result in cardiac arrest and coma. Cerebral edema, a marker of brain injury associated with cardiac arrest, is seen as a loss of gray matter to white matter differentiation on brain CT images. Several previous studies found that gray matter to white matter ratio (GWR), calculated by dividing densities of gray matter by those of white matter, was significantly lower in cardiac arrest survivors with poor outcome relative to patients with good outcome, and thus that decreased GWR could predict poor outcome in cardiac arrest patients.[9–14] Scheel et al.[15] evaluated the prognostic performance of GWR in 98 cardiac arrest survivors, and found a strong association of a low GWR with poor outcome. However, the ability of the GWR to predict outcomes in comatose patients after out-of-hospital cardiac arrest (OHCA) of cardiac etiology needs to be reassessed. Outcomes after OHCA of non-cardiac etiology are generally poor compared to OHCA of cardiac etiology.[16–18] However, previous studies have included cardiac arrests of both etiologies, and did not consider etiology-based differences.[9–15] For example, in the study by Scheel et al.,[15] the arrest etiology was cardiac only in 53% of included subjects.

In this study, we sought to evaluate if the GWR on brain CT could help predict poor outcomes in adult comatose patients after OHCA of cardiac etiology.

## 2. Methods

### 2.1. Data source and population

This was a retrospective observational study using data from the Korean Hypothermia Network (KORHN) retrospective registry, which is a web-based, multicenter registry collection of data from adult (≥18 years) comatose OHCA survivors treated with therapeutic hypothermia (TH).[19] Twenty-four hospitals throughout the Republic of Korea participated in the registry. The Institutional Review Board of each institution approved the study protocol before data collection. Informed consent was waived because of the study's retrospective nature. Briefly, investigators at each hospital were trained to correctly extract data from hospital medical records and transcribe the data into the standardized report form. Investigators reviewed the hospital medical records of all comatose cardiac arrest patients treated with TH and entered the data into the registry. Three clinical research associates examined the input data, corrected suspected errors, provided feedback to investigators at each hospital, and finalized the cases after verification. The data manager then reaffirmed the final input data, reassessed the data for errors, and completed the case with feedback from the clinical research associate and investigators of each hospital. From this registry, we identified subjects who had a brain CT within 24 h after ROSC. Patients whose CT scans indicated parenchymal abnormalities, patients whose CT images were technically inadequate for the determination of cerebral density or patients for whom CT images were not available for analysis were excluded from the analysis.

### 2.2. Data collection

The following variables were collected for each patient: age, sex, underlying diseases, witness of collapse, bystander cardiopulmonary resuscitation (CPR), first monitored rhythm, time from collapse to ROSC, initial glucose level after ROSC, Glasgow Coma Scale (GCS) after ROSC, time elapsed between ROSC and brain CT, time from ROSC to initiation of TH, time from initiation of TH to achieving target temperature, duration of target temperature maintenance, duration of rewarming, and survival status, and neurological outcome at hospital discharge.

An investigator blinded to patient outcomes 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 in previous studies.[9–11,13] Circular regions of measurement were placed over the regions of interest bilaterally (Online Appendix), and the average attenuations were recorded in Hounsfield units (HU). Attenuation values at the level of the basal ganglia were recorded from the caudate nucleus (CN), putamen (PU), posterior limb of the internal capsule (PLIC), and corpus callosum (CC). Values at the centrum semiovale and high convexity levels were recorded from the medial cortex (MC1 and MC2, respectively) and medial white matter (MW1 and MW2, respectively). The average of both sides was recorded as the value for that area. Previous studies used various methods to calculate the GWR,[9–14] and no set rule exists for calculating GWR currently. Thus, various GWRs used in previous studies were calculated: CN/PLIC,[9,10,12] PU/CC,[12] PU/PLIC,[14] $GWR_{basal\ ganglia} = (CN + PU)/(PLIC + CC)$,[11,13] $GWR_{cerebrum} = (MC1 + MC2)/(MW1 + MW2)$,[11,13] Average $GWR = (GWR_{basal\ ganglia} + GWR_{cerebrum})/2$.[11,13] To assess the inter-rater reliability of GWR estimates, a second investigator measured GWR using a randomly selected sample of 10% of the included subjects. To assess the consistency of GWR measurements, the test-retest reliability was measured from another randomly selected sample of 10% of the included subjects.

### 2.3. Outcome measures

The primary outcome was clinical outcome at hospital discharge, which was assessed using the Cerebral Performance Categories (CPC), according to recommendations for outcome assessment in comatose cardiac arrest patients.[20] CPC grades the levels of neuro-functional status after cardiac arrest (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 or median values with interquartile ranges (IQR), as appropriate. Comparisons of continuous variables between independent groups were performed using the independent *t*-test or Mann–Whitney *U* test, as appropriate. Categorical variables were given as frequencies and percentages. Comparisons of categorical variables were performed using the $\chi^2$ test or Fisher's exact test, as indicated. Receiver operating characteristic (ROC) analysis was performed to examine the prognostic performance of GWRs. The comparison of dependent ROC curves was performed using the method of DeLong et al.,[21] while the method of Hanley and McNeil was used to compare the two independent ROC curves.[22] Bonferroni corrections were used to correct for multiple comparisons. Multivariate binary logistic regression analysis was used to calculate the propensity score for poor outcomes in



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