Useful Computed Tomography Score for Estimation of Early Neurologic Outcome in Post-Cardiac Arrest Patients With Therapeutic Hypothermia

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Background: The Alberta Stroke Program Early CT Score (ASPECTS) is used to assess early ischemic stroke damage. This study compared bilateral ASPECTS (ASPECTS-b) with the gray:white matter ratio (GWR) and quantitative regional abnormality (QRA) to evaluate the prognostic utility of early computed tomography (CT) findings in post-cardiac arrest patients.

Methods and Results: Out-of-hospital cardiac arrest patients with return of spontaneous circulation (ROSC) who underwent brain CT (<6 h after onset) and therapeutic hypothermia were recruited from a university hospital over a 2-year period. General demographics, ROSC characteristics, ASPECTS-b (total score=20 points), GWR, and QRA were assessed. Multivariate logistic regression analysis was used to predict neurologic outcome using cerebral performance category (CPC) at 1 month. The study population was divided into good (n=20; CPC 1–2) and poor (n=47; CPC 3–5) outcome groups. The good (vs. poor) outcome group was younger (mean ±SD age 46.7±11.8 vs. 60.3±17.2 years; P=0.002) and had more initial shockable rhythms (40.0% vs. 8.5%; P=0.002). In addition, the good outcome group had a higher mean ASPECTS-b score (15.3±2.7 vs. 9.0±4.9; P<0.001), despite no differences in QRA and mean GWR. Age and ASPECTS-b were independent predictors of outcome after adjusting for potential confounders.

Conclusions: These findings suggest that an initial CT score (ASPECTS-b) could help estimate early neurologic outcomes in post-cardiac arrest patients treated with therapeutic hypothermia.

Key Words: Cardiac arrest; Coma; Critical care; Hypothermia; Prognosis

Post-resuscitation status after cardiac arrest is a clinical model of hypoxia-ischemia injury. Post-resuscitation care including therapeutic hypothermia (TH) for neuroprotection is based primarily on recognition of brain damage. Previous methods of formal prognostication have focused primarily on identifying patients with an expected poor prognosis to find patients who would gain no further benefit from intensive management. Therefore, formal prognostication should not take place until at least 72 h after the return of spontaneous circulation (ROSC) to minimize the risk of false predictions of poor outcomes and an irrevocable decision to withdraw life support. Because the study of Nielsen et al showed no benefit of therapeutic hypothermia with a target temperature of 33°C compared with 36°C, objective methods to group patients according to the severity of ischemic brain insult are gaining attention. Although there is currently no combination of test methods enabling good prognosis, early estimates of good recovery based on a combination of preliminary tests may support prompt clinical decision making for patients who would benefit from aggressive intensive care or newly developed therapeutic strategies while ischemia-reperfusion (I/R) injury is occurring. Even though clinical manifestations, serological biomarkers, and electrophysiological approaches have been widely used to predict neurological outcome, prognostication of good outcomes is not easy using these methods during the early period (within 24 h) of post-resuscitation care. Brain imaging is a balanced tool that can evaluate the extent of brain damage and enable timely assessment of hypoxic-ischemic insults. In particular, computed tomography (CT) scans are beneficial because of their short acquisition time and ready availability across numerous medical centers. Previous studies of post-cardiac arrest patients using brain CT have focused on the gray:white matter ratio (GWR). Few studies have focused on quantifying the extent of brain injury using brain CT. The Alberta Stroke Program Early CT Score (ASPECTS)
is a widely used screening tool that provides a framework for quantifying the extent of ischemic hypodensity or hypoattenuation in the middle cerebral arterial (MCA) territory.16 The present study compared previous assessment methods with semiquantitative bilateral ASPECTS (ASPECTS-b) to predict neurological outcome using non-contrast brain CT (NCCT) within 6 h after cardiac arrest.

Methods

Study Population

Study subjects were enrolled retrospectively from a prospective out-of-hospital cardiac arrest (OHCA) registry between May 2012 and March 2014. Data on general demographics, as well as clinical and radiological characteristics, were collected. Patients deemed eligible for inclusion in the present study were those who: (1) achieved ROSC after cardiac arrest; (2) underwent NCCT within 6 h after event onset; and (3) underwent therapeutic hypothermia after ROSC. Patients were from the study excluded if: (1) they were <18 years of age; (2) the cardiac arrest was caused by intracerebral mechanisms; and (3) a CT image was not available for analysis.

Patients underwent clinical evaluations, including a check of vital signs, electrocardiogram (ECG), laboratory tests, and sequential organ failure assessment (SOFA).17 Because intracranial causes of cardiac arrest tend to be more common in Asia, accounting for up to 18% of cases, an immediate NCCT was frequently used to identify brain lesions such as intracranial hemorrhage and subarachnoid hemorrhage after cardiac arrest.18 Comatose patients with sustained resuscitation after cardiac arrest were then admitted to the intensive care unit (ICU) for therapeutic hypothermia to 33°C, followed by rewarming at a rate of 0.25°C/h and a maintenance phase for 24 h. Therapeutic hypothermia and post-cardiac arrest care were performed in accordance with the Ajou University Medical Center ICU’s protocol with sufficient sedation, analgesia, and shivering management.

The present study was approved by the Ethics Committee of Ajou University Hospital and the need to obtain patient permission was waived due to the retrospective nature of the study.

Definitions

Post-cardiac arrest care was provided to all patients with ROSC according to the guidelines of the American Heart Association.19 If the first rhythm from the defibrillator was ventricular fibrillation or pulseless ventricular tachycardia, the initial rhythm was defined as shockable rhythm. According to the treatment algorithm, ventricular fibrillation or pulseless ventricular tachycardia belong to the shockable rhythm category, which can be treated with defibrillation.20 Non-shockable rhythms include asystole and pulseless electrical activity. Causes of cardiac arrest were determined on the basis of a patient’s history, ECG findings, echocardiographic findings, cardiac enzyme concentrations, and cardiology consultations. The duration of cardiac arrest was defined as the interval from the time of collapse (presumed time of cardiac arrest) until ROSC. The cerebral performance category (CPC) at 1 month was used as an outcome parameter; it was dichotomized as good (CPC 1–2) and poor (CPC 3–5).

Baseline CT Analysis

NCCT and CT angiography (SOMATOM Sensation 16; Siemens, Erlangen, Germany) were initially obtained for each patient on admission to the emergency department. NCCT was conducted from the skull base to the vertex, with a contiguous 5 mm thickness parallel to the inferior orbitomeatal line. A 50-mL bolus of non-ionic contrast medium (Omnipaque; iodine 300 mg/mL; Amersham Health, Princeton, NJ, USA) was administered into an antecubital vein using a power injector at an injection rate of 4.5 mL/s. The acquisition parameters were 80 kVp (tube voltage) and 120 mAs. CT scanning was initiated 2 s after the start of the injection.

ASPECTS Narrow window and level settings were used to interpret hypoattenuation on the NCCT, centered at the window-level setting of 35 Hounsfield units (HU) and a window width of 35 HU for easy discrimination of gray and white matter.21 To evaluate the extent of bilateral
was analyzed on axial CT cuts at the basal ganglia and supraganglionic levels. With the former, the MCA territory was divided into the caudate nucleus, lentiform nucleus,
The median HUs in ROIs were calculated according to the ICBM atlas at 12 cerebral regions, namely the frontal lobe, temporal lobe, parietal lobe, occipital lobe, cerebellum, caudate nucleus, putamen, thalamus, insula, corpus callosum, posterior limb of the internal capsule, and corona radiate. Results for each area were dichotomized as hypoattenuated (score=1) or not (score=0) compared with the normal controls. A total summed score for the extent of brain damage was calculated using the QRA (range 0–24).

Statistical Analysis

The significance of differences between good and poor outcome groups was analyzed using Student’s t-test or Fisher’s exact test, as appropriate, for continuous and categorical variables, respectively. In order to predict prognoses between the 3 scoring systems (i.e., GWR, QRA, and ASPECTS-b) on an NCCT, the prognostic power for predicting neurologic outcome (CPC 1–2) of each scoring system was investigated by receiver operating characteristic (ROC) analysis. In addition, we investigated the probability of a good outcome based on ASPECTS-b. The probability of good outcome was defined as the proportion of patients with a good outcome at each of the different scores in ASPECTS-b. Data were also stratified into tertiles to determine the sensitivity, specificity, positive predictive value, and FPV in predicting outcome according to ranks of average GWR, QRA, and ASPECTS-b. Potential predictors that were not significant (P>0.1) in the univariate analysis were deleted from the final model.
P<0.05 was considered statistically significant. Unless indicated otherwise, data are presented as the mean±SD.

Results

General Demographics

Overall, 93 patients were screened during the study period and 26 were excluded based on the exclusion criteria (Figure S1). Thus, 67 patients were deemed eligible for inclusion in the present study: 20 patients were in the good outcome group (CPC 1–2) and 47 patients were in the poor outcome group (CPC 3–5). Table 1 outlines the general demographics of all patients (n=67) in the present study. Mean patient age was 56.3±16.9 years, the duration of cardiac arrest was 28.7±16.6 min, and the mean CT acquisition time from onset of cardiac arrest was 124.5±59.9 min.

Compared with the poor outcome group, patients in the good outcome group were younger (P=0.002), had more frequent shockable rhythms at baseline (P=0.002), and had a higher Glasgow Coma Scale (GCS) score after ROSC (P=0.034; Table 1). The causes of cardiac arrest differed significantly between the 2 groups (P=0.027).

Group Comparisons of the GWR, QRA, and ASPECTS-b

Table 1 also presents data for ASPECTS-b, GWR, and QRA according to neurologic outcome. There was no difference in the GWR in the basal ganglia (P=0.101), centrum semiovale (P=0.970), and high convexity (P=0.774) between the 2 groups, and the mean GWR did not significantly differ between the 2 groups. In addition, there were no differences in QRA between the 2 groups (P=0.118). However, compared with the poor outcome group, ASPECTS-b was significantly higher in the good outcome group (9.0±4.9 vs. 15.3±2.7; P<0.001). The inter-rater correlation coefficients were 0.876 for GWR, 0.757 for QRA, and 0.807 for ASPECTS-b. Specifically, the inter-hemisphere correlation coefficient was 0.914 for ASPECTS-b.

Figure 2A shows the area under the ROC curve as an indicator of the prognostic capability of ASPECTS-b. The area under the ROC curve for the prediction of a good outcome (CPC 1–2) was the largest: 0.876 for ASPECTS-b, 0.584 for QRA (score ≤11), and 0.544 for GWR (≥1.13).

Figure 2B outlines the probability of a future good outcome (i.e., the proportion of patients with a good outcome at each of the different scores) according to ASPECTS-b. The probability of a good outcome appeared to be relatively low for an ASPECTS-b score <8, but relatively higher for a score >15 points. Table 2 shows the prognostic performance of GWR, QRA, and ASPECTS-b at 1 month.

The IDI and NRI analyses demonstrated that the new models including ASPECTS-b performed better in terms of predicting good outcome (CPC 1–2) compared with using only the previous methods (Table 3).

Whole-Brain Region-Based Analyses

To determine the primary target areas for imaging analysis, we defined the false-positive rate (i.e., the number of “good outcome” patients with hypoattenuation in a given area
Table 4. Multivariate Regression Analysis for Predicting Good Outcomes

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Estimated OR (95% CI) for predicting good outcomes (CPC 1–2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate model</td>
</tr>
<tr>
<td>Age (decrease per 1 year)</td>
<td>1.06 (1.02–1.10)</td>
</tr>
<tr>
<td>SOFA score ≤11</td>
<td>1.48 (0.32–6.90)</td>
</tr>
<tr>
<td>GCS score after ROSC ≥8</td>
<td>4.89 (1.04–23.0)</td>
</tr>
<tr>
<td>Non-shockable rhythms</td>
<td>0.14 (0.04–0.54)</td>
</tr>
<tr>
<td>Use of a defibrillator</td>
<td>4.38 (1.44–13.30)</td>
</tr>
<tr>
<td>Cardiac causes</td>
<td>4.95 (1.44–17.07)</td>
</tr>
<tr>
<td>Duration of cardiac arrest (decrease per 1 min)</td>
<td>1.03 (0.99–1.06)</td>
</tr>
<tr>
<td>Radiologic features</td>
<td>–</td>
</tr>
<tr>
<td>GWR ≥1.13</td>
<td>3.09 (0.62–15.30)</td>
</tr>
<tr>
<td>QRA (decrease per 1 point)</td>
<td>1.06 (0.98–1.14)</td>
</tr>
<tr>
<td>ASPECTS-b (increase per 1 point)</td>
<td>1.64 (1.27–2.10)</td>
</tr>
</tbody>
</table>

A SOFA score >11 has predictive power for high mortality. A GCS score <8 is predictive of poor outcomes. OR, odds ratio. Other abbreviations as in Tables 1, 3.

Multiplicative Logistic Regression Analysis for Outcome Prediction

Table 4 shows odds ratios (ORs) from multivariate logistic regression analysis predicting good outcomes. Younger age, GCS score ≥8, shokable rhythms, cardiac causes, and higher ASPECTS-b were all significant predictors of a good outcome in univariate analysis. When these factors were entered into a multivariate model for good prognosis, age (OR 1.09; 95% confidence interval [CI] 1.02–1.16; P=0.007) and ASPECTS-b (OR 1.49; 95% CI 1.16–1.92; P=0.002) were significant predictors of good outcomes after ROSC.

Discussion

The present study shows that ASPECTS-b assessment with brain CT, within 6h after ROSC, may be a novel radiologic approach for the easy evaluation of short-term good neurologic prognosis after adjusting for potential confounders. Theoretically, the brain injury process after an acute ischemic stroke is similar to the destructive cascade of the nervous system after ROSC in cardiac arrest syndrome. The aim of the present study was to identify early, achievable CT-based methods to evaluate vulnerable areas against ischemic injury given that a semiquantitative ASPECTS during an initial CT scan is widely used in the acute ischemic stroke field.

Cerebral edema is characterized by decreased X-ray attenuation in the gray matter and a lower GWR (in HU) on brain CT. Most CT-based studies on the GWR have addressed its utility as a reliable predictor of poor neurologic outcomes among cardiac arrest patients. In addition, these studies indicated a specific threshold of GWR (between 1.16 and 1.22) as a predictor of poor outcome. However, the present study showed that GWR was not a significant outcome predictor for post-cardiac arrest patients. This apparent discrepancy may be due to the early CT acquisition time frame (within 6h, and usually around 24h) in the present study, unlike in previous studies. A previous study showed that the rate of detecting a poor outcome using GWR <1.16 was 23% on CT scans obtained with 6h, but that this increased to 60% if scans were obtained from 6h to 7 days. Metter et al reported that attenuation of white matter was not significantly different in 240 subjects with CT scans obtained within 24h when comparing survivors with non-survivors, in contrast with the obvious attenuation of gray matter. Because gray matter is preferentially subject to cytotoxic edema in early ischemic or reperfusion injury after cardiac arrest, the extent of diffuse gray matter damage would be an important early marker for global cerebral insults after cardiac arrest. In addition, it is not easy to obtain precise HU values from multiple brain parenchymal regions from a practical standpoint. Therefore, detection of the extent of global cerebral damage through an intuitive ASPECTS-b using visual contrast between gray and white matter may be more practical than conventional methods based on decreases in GWR.

In addition, the findings of the present study showed that the QRA method, which included whole-brain areas, was not effective in predicting ROSC outcomes. According to our data, a whole-brain region-based assessment including QRA can be misleading. We believe that this result is likely due to contamination of radiological images of the white matter, cerebellum, occipital cortex, and frontal pole areas. White matter has low susceptibility to hypoxic damage, and it is not easy to accurately evaluate the relative hypodensity of white matter on a brain CT. However, ASPECTS primarily focuses on the supratentorial gray matter. In addition, evaluation of the occipital cortex, frontal pole, and cerebellum on brain CT has some limitations due to beam hardening and streak artifacts resulting from bone thickness. Although X-rays can pass through thick bone in these areas, radioactively transmitted energy...
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Precludes full management for cardiac arrest patients. Rather, we argue for the early selection of patients with an expected good prognosis and to give them maximal care while I/R injury is at its peak.

The present study has some limitations. First, the results should be interpreted with caution given that the data were obtained retrospectively from a single referral center. Therefore, larger clinical trials using a prospective design across multiple centers are warranted. Second, clinical interpretation should be performed cautiously in the elderly group because false-positive results were obtained in this group and age was an independent predictor of outcome. Third, the present data lack concomitant surrogate methods (i.e., SEP, EEG, MRI, and serological markers) to evaluate neurological functioning and insults with more precision. Thus, future trials that include such indices would help validate the simple CT-based method used in the present study. Finally, the medical staff were not blinded to the results of evaluations of initial brain CT images. Thus, decisions regarding life-sustaining care could have been influenced by baseline imaging findings. However, in Korea, because of cultural reasons, decisions regarding the withdrawal of life support are very conservative, and so it is likely that knowledge of baseline imaging findings would have had minimal significance in the present study. In previous studies, GWR was measured between 1 and 24 h after cardiac arrest. Although there is limited evidence regarding the optimal time to determine ASPECTS on brain CT, we conducted the brain CT within 6 h after cardiac arrest for consistency with evaluations of acute ischemic stroke.

In conclusion, ASPECTS-b on a brain CT could be a feasible predictor during the early stages among patients with cardiac arrest after ROSC. The ease of use, promptness, and simplicity of ASPECTS-b make it a particularly desirable tool for prognostic evaluation.

Figure 3. (A) False-positive findings, as represented by hypoattenuations, at a fixed radiation dose (tube voltage 120 kVp, X-ray intensity generated in a recording radiograph 214 mAs) in the cerebellum, occipital cortex, and frontal pole regions on brain computed tomography (CT). There are no true lesions on magnetic resonance imaging (MRI), showing some discrepancies between the CT and MRI results. (B) A gradual decrease in the false-positive rate in the occipital cortex is seen on brain CT with an increase from low to high radiation doses (120 kVp; 117, 214, and 270 mAs).

Regardless of the actual score, ASPECTS-b exhibited better discrimination ability to predict a patient's outcome than the QRA and GWR methods. In the present study, ASPECTS-b <8 and >15 points were determined to be clinically applicable cut-off values for outcome prognostication in Figure 2B. There were only 8 cases with a false-positive prediction of a good outcome (i.e., those with a poor outcome despite a good scan and ASPECTS-b ≥15 on a brain CT scan). These 8 patients subsequently experienced medical derangement (n=4), re-arrest after the first ROSC (n=2), acute myocardial infarction (n=1), and neurological deterioration (n=1). There were no cases of a false-positive prediction of a poor outcome (i.e., a good outcome despite a bad scan and ASPECTS-b <9). All false-positive cases were elderly patients (78.8±9.2 years). These findings should help make ASPECTS-b more applicable to identify potential candidates for newly developing intensive neurocritical management. This view may seem to contrast with the current prognostic tendency to withdraw life support when a patient is anticipated to experience poor outcomes. We do not argue for a self-fulfilling prophecy in which early prognostic evaluation and decision is more attenuated. This is demonstrated in Figure 3A, which shows a series of hypodense areas on the brain CT images from normal controls (no lesions on brain magnetic resonance imaging from the same person), representing local artifacts with hypoattenuation in the parenchyma of the cerebellum, the occipital cortex, and the frontal pole areas. Moreover, such artifacts seem to be closely related to our findings whereby the good outcome group had a higher prevalence of false-positive hypoattenuation in the cerebellum, occipital cortex, and frontal poles. Interestingly, such hypoattenuation artifacts can also be more aggravated in the aforementioned areas during a reduction in radiation exposure, such as a decrease in the tube current or tube potential. Figure 3B shows an actual example of these artifacts on a brain CT based on a decrease in tube current.
References


Supplementary Files

Supplementary File 1
Figure S1. Diagram showing the flow of 93 out-of-hospital cardiac arrest (OHCA) patients through the present study.

Figure S2. Frequency of hypoaattenuation in each cerebral region. Please find supplementary file(s): http://dx.doi.org/10.1253/circj.CJ-16-1327