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Clinical paper

Timing of brain computed tomography and accuracy of outcome prediction after cardiac arrest



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Abstract

Aim: Gray–white-matter ratio (GWR) calculated from head CT is a radiologic index of tissue changes associated with hypoxic-ischemic encephalopathy after cardiac arrest (CA). Evidence from previous studies indicates high specificity for poor outcome prediction at GWR thresholds of 1.10–1.20. We aimed to determine the relationship between accuracy of neurologic prognostication by GWR and timing of CT.

Methods: We included 195 patients admitted to the ICU following CA. GWR was calculated from CT radiologic densities in 16 regions of interest. Outcome was determined upon intensive care unit discharge using the cerebral performance category (CPC). Accuracy of outcome prediction of GWR was compared for 3 epochs (<6, 6–24, and >24 h after CA).

Results: 125 (64%) patients had poor (CPC4–5) and 70 (36%) good outcome (CPC1–3). Irrespective of timing, specificity for poor outcome prediction was 100% at a GWR threshold of 1.10. Among 50 patients with both early and late CT, GWR decreased significantly over time ($p=0.002$) in patients with poor outcome, sensitivity for poor outcome prediction was 12% (7–20%) with early CTs (<6 h) and 48% (38–58%) for late CTs (>24 h). Across all patients, sensitivity of early and late CT was 17% (9–28%) and 39% (28–51%), respectively.

Conclusion: A GWR below 1.10 predicts poor outcome (CPC4–5) in patients after CA with high specificity irrespective of time of acquisition of CT. Because GWR decreases over time in patients with severe HIE, sensitivity for prediction of poor outcome is higher for late CTs (>24 h after CA) as compared to early CTs (<6 h after CA).

Keywords: Prognostication, Cardiac arrest, Grey-white-matter-ratio (GWR), Computed tomography (CT), Outcome prediction, Therapeutic hypothermia

Introduction

After resuscitation from cardiac arrest (CA), patients face a high probability of death or survival in unresponsive wakefulness due to hypoxic-ischemic encephalopathy (HIE).^{1,2} Studies have shown that features of the clinical examination alone lack sufficient discrimination for accurate neurologic prognostication, especially

since a subset of patients with HIE remains unconscious for days to weeks after CA.³ Several prognostic tests such as EEG and neurological examination are reported to predict poor outcome with close to 100% specificity, but all these tests may be confounded by inconsistencies in test performance or lack of expertise in interpreting the results. Some reliable prognostic tests (e.g. somatosensory evoked potentials, SSEP) are not routinely available in many centers treating patients after CA. In response to the issues,

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current guidelines recommend a multimodal approach to outcome prediction following CA.⁴

In contrast to neurophysiologic tests (SSEP and to some extent EEG), head CT is widely available and is therefore an important option for prognostic testing in CA patients. Previous studies have demonstrated the value of head CT in the prediction of poor outcome.^{5–17} Most of these studies investigated CT performed within 24 h after CA and found low sensitivities for prediction of poor outcome. Few studies have included CTs performed at later time points.^{5,7,8} An important head CT finding in patients with severe HIE is the loss of differentiation of gray and white matter¹⁸ which can be quantified in specific regions as the ratio of radiologic densities in gray versus white matter (gray–white-matter-ratio, GWR). Recent studies point to a threshold of around 1.15, below which poor outcome is highly likely in patients after CA.^{7–10,15}

In clinical practice, CA survivors commonly undergo an early head CT upon hospital admission to evaluate for neurological causes of CA (e.g. aneurysmal subarachnoid hemorrhage). Retrospective studies evaluating the prognostic value of CT have largely focused on the hyperacute post-CA period, using images acquired within the first hours after admission. Little is known about the time course of GWR changes in CA patients. Tissue changes resulting in altered radiologic densities and GWR may occur over the course of hours to days in CA patients with severe HIE. Accordingly, the predictive value of head CT, in terms of neurologic outcome, may change significantly over this period.^{7,16} We therefore aimed to investigate time-dependent GWR changes in a large cohort of CA patients treated with targeted temperature management (TTM).

Materials and methods

Subjects

Study subjects (CA patients with head CT) were retrospectively identified from our prospective database of patients with cardiac arrest admitted to the Charité Cardiac Arrest Center of Excellence. Data from some of these patients have already been part of previous studies not focusing on head CT.^{7,8} Patients were eligible if they had suffered a non-traumatic CA, were ≥ 18 years of age and had undergone at least one brain CT within 10 days after CA. All patients were treated with Targeted Temperature Management (TTM, 33 °C for 24 h) adhering to the current guidelines.⁴ Head CT were ordered at the discretion of the clinical team: early CT scans (<6 h after CA) when there was a concern for a subarachnoid hemorrhage or other primary intracranial disorder as a cause of cardiac arrest; later CT scans were mainly obtained for prognostication of neurological outcome (along with neurological examination, SSEP, NSE serum concentration, EEG). A registration of this study was not ensued. The study was approved by our hospital ethics committee (EA2/066/17).

Study outcome was determined upon ICU discharge by treating physicians and/or consulting neurologists using the cerebral performance category (CPC) score.¹⁹ We defined CPC1–3 as good outcome and CPC4–5 as poor outcome; Patients with CPC3 were assigned to the good outcome group because of the early determination of CPC (at ICU discharge), in order not to assign a falsely pessimistic outcome to patients who may improve during rehabilitation. Considering the overall small number of patients with CPC3, assigning CPC3 to the poor outcome group would not have made a difference in the analysis of our data.

WLST was considered only in comatose patients after multimodal prognostication including neurological examination, SSEP, EEG, serum NSE concentration and brain imaging. According to a local interdisciplinary standard for prognostication, which was adapted to current research over time, prognostication was undertaken a minimum of 72 h after cardiac arrest and frequently delayed until 7 days or more after CA.²⁰

CT acquisition and GWR calculation

Only non-contrast enhanced head CT scans were analyzed. The scanners used in this study were GE Revolution GSI, GE Revolution EVO, GE LightSpeed VCT (GE Healthcare, Little Chalfont, UK). The examinations were performed following a standard head CT protocol at a voltage of 120–140 kV with a slice thickness of 5 mm. CTs with signs of (intracerebral) hemorrhage or stroke were excluded from the study.

The rater who determined the gray–white-matter ratio (K.J.S.) was blinded to the clinical outcome at the time of GWR determination. Circular regions of interest (ROI, 0.1 cm²) were placed manually in gray and white matter areas (caudate nucleus, putamen, thalamus, posterior limb of internal capsule, forceps minor of the corpus callosum, medial cortex and medial white matter at the level of the centrum semiovale as well as the high convexity area) as described previously.⁶ Mean GWR was calculated using data from four gray matter and four white matter ROIs in each hemisphere (16 ROIs in total). Fig. 1 shows example images for different GWR ratios illustrating the relationship between CT image and GWR.

Statistical analysis

The results are tabulated as arithmetic mean \pm standard deviation or as median and interquartile range. The statistical analysis was performed using IBM SPSS Statistics (SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) and MATLAB Statistics Toolbox (MathWorks, Natick, Massachusetts, USA). The Gaussian distribution of the data was tested using the Lilliefors test and the Shapiro-Wilk test. The Pearson Correlation coefficient was calculated to test for a correlation between the GWR and t-ROSC. We determined specificities and sensitivities for prediction of poor outcome (CPC4–5) at different GWR cutoff values (1.10, 1.13, 1.16). 95% confidence intervals were calculated using the Wilson Score method. To explore time-dependent discrimination of outcome categories by GWR, we did a receiver-operating characteristic (ROC) curve analysis at the three different epochs. For analysis, the data were grouped (a) according to the dichotomized CPC, and (b) into 3 epochs according to time elapsed between CA and head CT. The three epochs were: early (less than 6 h after CA), intermediate (6–24 h after CA) and late (more than 24 h after CA). Test characteristics including sensitivity, specificity and AUC were compared between epochs. To investigate the association of CPC score, timing of CT, age, initial rhythm and cause of arrest with GWR, a binary logistic regression was performed.

Results

During the study period 679 patients were admitted to the ICU after CA among whom 206 patients underwent a head CT. Of these 206 patients 11 were excluded (e.g. due to acute intracerebral hemorrhage or stroke). We thus analyzed data of 195 patients who

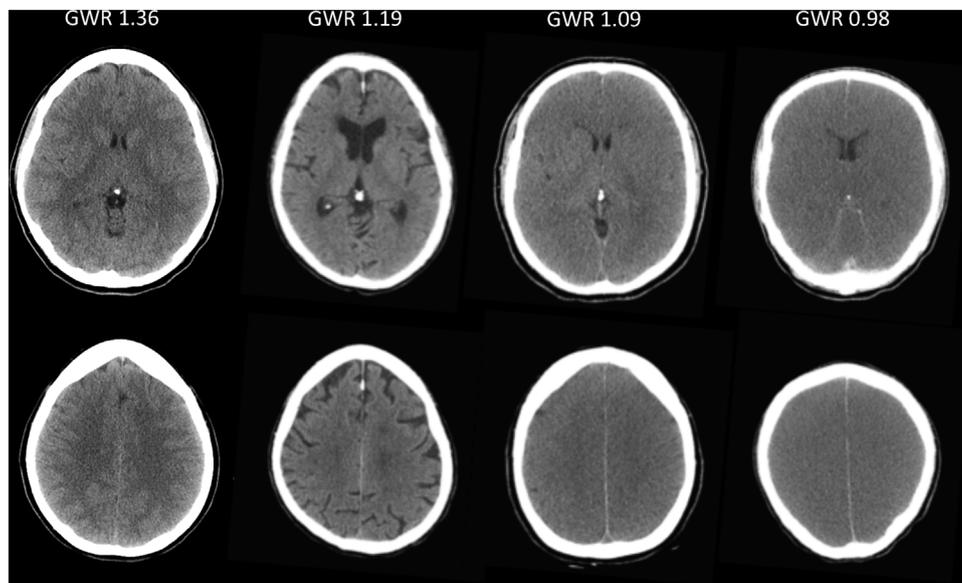


Fig. 1 – CT image examples for different GWR illustrating the progressive loss of differentiation between gray and white matter with decreasing GWR.

underwent 245 head CTs. Fifty of the 195 patients had both an early (<24 h, mostly 0–6 h after CA) and late (>24 h after CA) CT. Characteristics of the study patients are provided in Table 1. The mean age was 59 years, 28% were female. 79% were OHCA patients, 46% had a cardiac cause and 34% a respiratory cause of arrest. Neurological outcome at ICU discharge was CPC1 in 35 (18%), CPC2 in 27 (14%), CPC3 in 8 (4%), CPC4 in 11 (6%) and CPC5 in 114 patients (58%): thus, 70 patients (36%) were classified as having a favorable outcome and 125 (64%) were classified as having a poor outcome at discharge.

GWR and timing of head CT

Fig. 1 demonstrates the severity of CT changes at a GWR of 1.09 — severe diffuse brain edema is evident on visual inspection. One

hundred and six patients underwent a CT scan within 6 h after CA, 31 patients between 6 and 24 h and 108 patients more than 24 h after CA; 50 of the 195 patients had both an early and late CT. The median time of CT acquisition for the early epoch was 2 h 30 min after CA arrest (1:06; 3:37), 9 h and 20 min for the intermediate epoch (7:29; 16:52) and 107 h for the late epoch (52; 135). Mean GWR in these three epochs was 1.23 ± 0.09 , 1.22 ± 0.07 and 1.19 ± 0.11 , respectively. Among the patients who underwent both early and late CT mean GWR (\pm standard deviation) of the initial CT was $1.22 (\pm 0.08)$ and in the follow up CT $1.18 (\pm 0.12)$ ($p=0.007$).

Association of GWR with baseline data

Mean GWR was higher for patients with OHCA compared to IHCA patients (1.24 ± 0.09 versus 1.21 ± 0.08 , $p=0.04$). Mean GWR was

Table 1 – Demographics of study population.

	ALL (n = 195)	CPC1–3 (n = 70)	CPC4–5 (n = 125)
Age (years)	59 (17)	54 (21)	64 (23)
Female sex	54 (28%)	18 (26%)	36 (29%)
Out of hospital CA	154 (79%)	56 (80%)	98 (78%)
Cause of arrest			
Respiratory	67 (34%)	17 (24%)	50 (40%)
Cardiac	89 (46%)	44 (63%)	45 (36%)
Other	28 (14%)	8 (11%)	20 (16%)
Unknown	11 (6%)	1 (1%)	10 (8%)
Shockable rhythm	78 (40%)	39 (56%)	39 (31%)
Time to ROSC (min)	15 (8–25)	15 (8–30)	15 (8–22)
Time on ventilator (h)	164 (79–330)	216 (124–425)	126 (52–230)
APACHE	31 (23–37)	31 (19–36)	32 (24–37)

ROSC: return of spontaneous circulation, ICU: intensive care unit, CPC: cerebral performance category, APACHE: acute physiology and chronic health evaluation.

slightly higher in patients who had a primary cardiac cause of CA at 1.23 (± 0.07) than in patients with respiratory cause at 1.20 (± 0.1 , $p=0.04$). There was no statistically significant relationship between the time to achieve ROSC and GWR (Pearson correlation: $r=0.009$, $p=0.451$).

Prognostic value of GWR

The ROC curves for GWR discrimination of outcome categories are compared between the 3 epochs in Fig. 2. AUCs with 95% CI were 0.70 (0.61–0.80) within the first 6 h, 0.71 (0.52–0.90) between 6 and 24 h and 0.80 (0.72–0.88) after 24 h. In the ROC comparison we found no significant differences (ROC A versus B $p=0.946$, ROC A versus C $p=0.142$, ROC B versus C $p=0.406$).

A scatterplot of the relationship between GWR and outcome for each epoch of imaging is shown in Fig. 3. No patient with good neurological outcome (CPC1–3 at ICU discharge) had a GWR below 1.10; the lowest GWR in a favorable outcome patient was 1.13 (a patient with CPC1 and CT performed within 6 h after CA). Table 2 shows sensitivities and FPR for different GWR cut-off values at the three time epochs. Sensitivity and specificity of GWR < 1.13 was 35% and 100% (NPV 0.46 and PPV 1.0) for the entire cohort of patients. In patients with poor outcome, GWR significantly decreased from early (<24 h after CA) to late (>24 h) time points ($p=0.007$). Logistic regression indicated that timing of CT was independently associated with GWR ($p=0.001$).

Previous studies have found different cut-offs for prediction of poor outcome with specificity close to 100%.^{5–8,11,13} Considering these previous studies and our current findings, the limited sample size of our and previous studies and potential small variations in GWR among different scanners,²¹ we chose a cut-off of 1.10 for further analysis, which in our view represents a reasonable balance between high specificity for poor outcome prediction (close to 100%) and clinically useful sensitivity for detection of severe HIE. Overall sensitivity of poor outcome prediction at this cut-off was 27% (with no false positives). For patients ($n=106$) who received a CT scan within the first 6 h after CA, sensitivity was 17%, for CTs performed 6–24 h after CA ($n=31$) sensitivity was 10% and for CTs performed more than 24 h after CA sensitivity was 39%. Sensitivity for poor outcome prediction did not relevantly change when patients with CPC3 were assigned to the poor outcome group (25% versus 27%). Sensitivity of poor outcome prediction at a GWR cut-off of 1.10 was 24% for late CTs in patients with cardiac cause of arrest and 44% in patients with respiratory cause.

GWR in patients with repeat head CTs

A total of 50 patients underwent CT at two epochs (first CT within the first 24 h after CA, second CT more than 24 h after CA). Of these 50 patients, 17 had a CPC score of 1–3 and 33 had a CPC4–5. Mean GWR of the early measurement was 1.22 (± 0.08) and mean GWR at the later time point was 1.18 (± 0.12), $p=0.007$. Mean early GWR of the subgroup with poor outcome was 1.20 (± 0.08) and mean late GWR was 1.14 (± 0.11 , $p=0.002$). Sensitivity for poor outcome prediction at a GWR threshold of 1.10 for this subgroup of patients with both, early and late CT was 12% (7–20%) for early and 48% (38–58%) for late CTs.

A GWR change (dGWR) of -0.18 from early to late CT predicted poor outcome (CPC4–5) with 100% specificity and 24% sensitivity. Thus, in our limited cohort, an absolute GWR cut-off outperformed dGWR in poor outcome prediction.

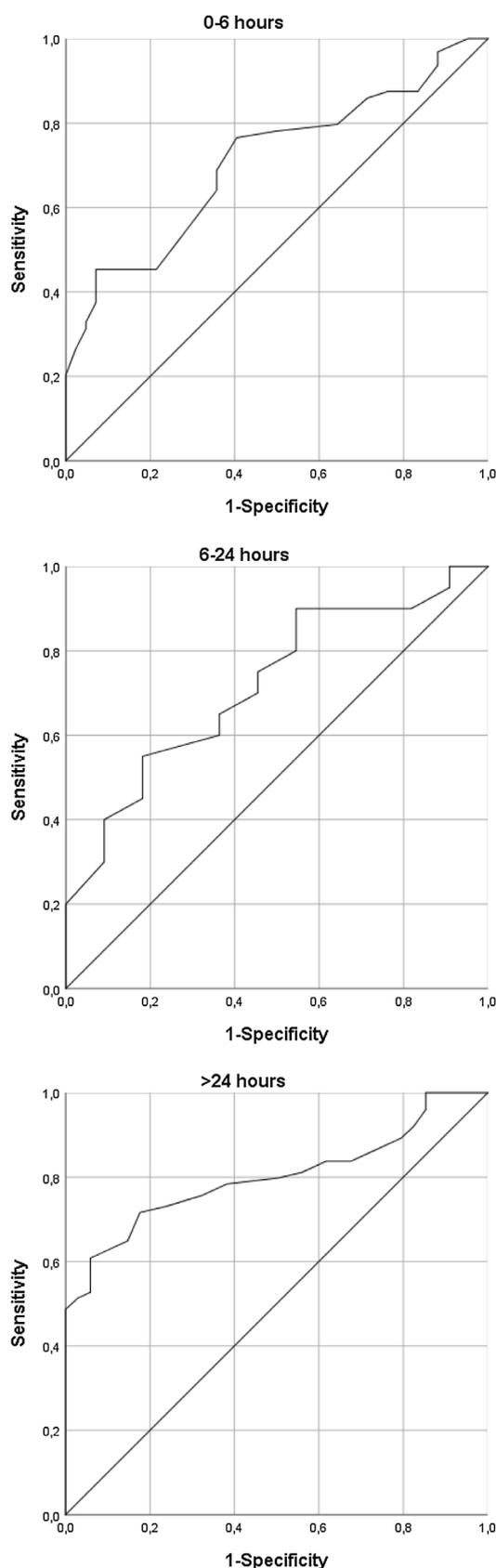


Fig. 2 – ROC curves for the different epochs. AUCs (95% CI) were 0.70 (0.61–0.80) for head CT performed within the first 6 h after CA, 0.71 (0.52–0.90) for CT between 6 and 24 h and 0.80 (0.72–0.88) for CT performed more than 24 h after CA.

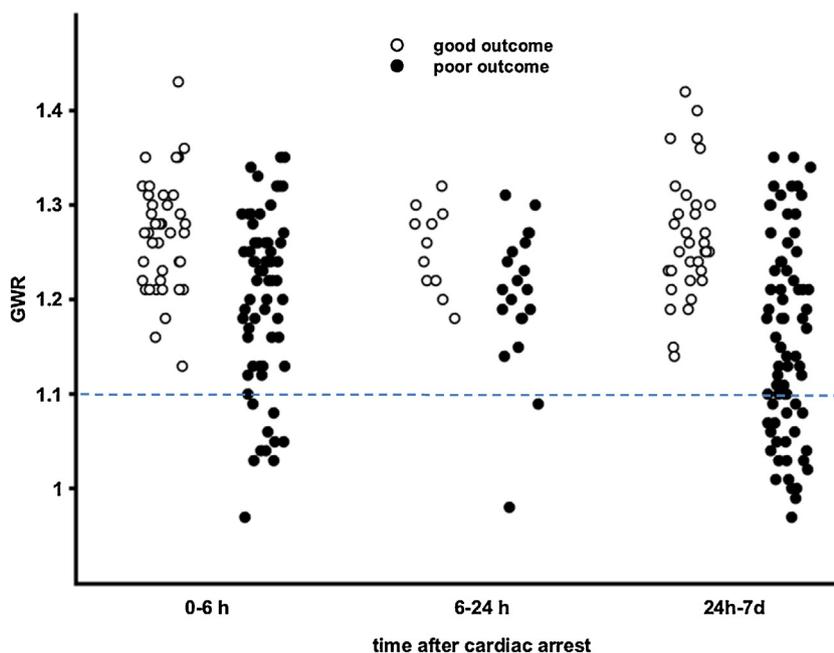


Fig. 3 – Scatter plot (each GWR is represented by one dot) of the relationship between GWR and outcome for different CT timings. Note that the lowest GWR in a patient with CPC1–3 was 1.13 with no apparent change of the GWR cut-off over time.

Table 2 – Statistics for prediction of poor outcome (CPC4–5) at three different GWR thresholds and for the three time epochs, 0–6, 6–24 and >24 h after CA.

Time from CA to brain CT	GWR cut-off level	Specificity	Sensitivity	Number of patients				
				True positive	False positive	True negative	False negative	Total
0–6 h	1.10	1.00 (0.90–1.00)	0.17 (0.09–0.29)	11	0	42	53	106
	1.13	1.00 (0.90–1.00)	0.20 (0.11–0.32)	13	0	42	51	
	1.16	0.98 (0.87–1.00)	0.27 (0.17–0.40)	17	1	41	47	
6–24 h	1.10	1.00 (0.68–1.00)	0.10 (0.02–0.31)	2	0	11	18	31
	1.13	1.00 (0.68–1.00)	0.10 (0.02–0.31)	2	0	11	18	
	1.16	1.00 (0.68–1.00)	0.20 (0.07–0.43)	4	0	11	16	
>24 h	1.10	1.00 (0.87–1.00)	0.39 (0.28–0.51)	29	0	34	45	108
	1.13	1.00 (0.87–1.00)	0.41 (0.30–0.53)	33	0	34	41	
	1.16	0.94 (0.79–1.00)	0.53 (0.41–0.65)	39	2	32	35	

Logistic regression model

Logistic regression analysis indicated that timing of CT ($p=0.001$), outcome ($p=0.003$) and age were independently associated with GWR, but not etiology of arrest ($p=0.518$).

Discussion

The main findings of this study are (1) In patients with HIE following CA, a GWR < 1.10 at any time in the first days after CA predicts poor outcome with high specificity (100% in our cohort). (2) In patients with

poor outcome, GWR decreased significantly from early (<24 h after CA) to late (>24 h) time points. (3) Sensitivity of GWR for predicting poor outcome increases with time: it was higher for late (39% >24 h after CA) than for early head CT (17% <6 h after CA).

Gray–white-matter ratio (GWR) and prediction of poor outcome

Head CT is a ubiquitously available diagnostic tool. GWR has emerged as quantitative method to assess the severity of HIE. Several studies have demonstrated the high specificity of GWR to predict poor outcome in patients after cardiac arrest with thresholds ranging from 1.10. to 1.22.^{7,10,12,15,17} Potential reasons for the

differences in thresholds include small sample sizes (with a small number of patients with good outcome), methodological differences in GWR determination and differences in CT scanners used, imperfect interrater agreement, differing characteristics of the patient cohorts and cohort selection. Differences in the selection of gray and white matter region of interest for GWR calculation may substantially influence the cut-offs for outcome prediction. For example, in one study the threshold calculated with an automated whole brain GWR approach was considerably lower than the threshold obtained using 16 manually defined ROIs GWR⁹ — possibly because the whole brain method assigned volumes at the border of gray and white matter to either category, thereby diminishing the calculated mean difference.

Here we analyzed 16 manually placed ROIs as described by Metter et al. and several subsequent studies.^{6,7} Consistent with these prior studies we found 1.13 as the lowest GWR in a patient with good outcome. Oh et al. found significant variances in Hounsfield units (HU) when using different CT scanners but only minor differences in GWR values.²¹ Taking small sample sizes and minor variations in GWR by use of different scanners into account, we chose to include a small 'security margin' in our proposed cut-off. Using a cut-off of 1.10 in our study did not relevantly decrease sensitivity for detection of poor outcome as compared to 1.13 as is depicted in [Table 2](#). [Fig. 1](#) visualizes the severity of CT changes at a GWR of 1.09 — severe diffuse brain edema is evident on visual inspection.

In summary, we suggest that as a part of a multimodal approach to prognostication after cardiac arrest, a GWR cut-off of 1.10 may be used when implementing the manual 16 ROI method.

Using this method in our study population we observed a false positive rate of 0%; however more studies on patients with late CT imaging are necessary to confirm our findings and establish the sensitivity of CT for poor outcome detection.

Timing of head CT

Observations made in patients with stroke suggest that brain water content rises slowly over many hours after ischemia onset.²² When CT was acquired in the early post-CA phase, sensitivity of GWR for poor outcome prediction was low (17%). This result is consistent with other studies in which CT was done early after cardiac arrest.¹⁰ One study found no difference in sensitivity of GWR between early CT and late CT.⁶ Similar to previous studies,^{7,23} we found a significant increase in the sensitivity of GWR to predict poor outcome from 12% in the early epoch to 48% in the late period among 50 patients who had underwent both an early and a late CT. In contrast to previous studies, the fact that early and late CTs were performed in the same patients in this subgroup excludes a potential patient selection bias.

Overall, our data suggest that head CT for outcome prediction should be obtained at least 24 h after ROSC. The sensitivity for these late CTs in our study was comparable to that of other established predictors of poor outcome such as somatosensory evoked potentials (SSEP) or serum neuron specific enolase.^{24–28}

Etiology of CA and predictive value of head CT

As in a previous report,¹¹ the sensitivity of GWR for poor outcome prediction was higher for patients with a respiratory cause of arrest as compared to patients with cardiac cause. However, in a logistic regression analysis, outcome, timing of CT and age were independently associated with GWR but not etiology of arrest.

Limitations

There are several limitations of our study. First, in our institution, neuroimaging is recommended as an additional prognostic test in those patients who remain comatose after the end of TTM. Subjects selected for analysis in this study are thus a subset of CA patients who underwent a head CT, potentially limiting generalizability of our findings. However, we did not find a significant difference in age, gender, t-ROSC or cause of cardiac arrest in the patient group with CT as compared to those who had not received head CT. Second, GWR was determined by a single rater (KJS, after extensive GWR method training) without independent verification. Although size and shape of ROIs as well as anatomical landmarks have been clearly defined, inter-rater variability has to be taken into account as a potential problem for generalizability of our results. Inaccuracy of ROI placement can influence the calculation of GWR. Therefore expertise in performing the measurements is essential when using GWR in outcome prediction. As an alternative automated methods would be very useful in this context and are currently being investigated. Third, measured radiological densities may differ relevantly between different CT scanners and scanner settings. The effect on GWR seems to be minor,²¹ but needs to be considered if GWR determination is implemented on a scanner different from the ones used in our study. Fourth, the results of the head CTs were known to treating physicians and may have influenced decisions to withdraw intensive care. In principle, this may have led to a self-fulfilling prophecy. However, at our institution we use a conservative multimodal approach for prognostication and withdrawal decision making including a considerable observation period (of at least seven days in most patients). Fifth, we determined outcome at ICU discharge. Thus, we cannot exclude that long-term outcome groups were different from the ones determined at ICU discharge. In an effort to address this and in contrast to studies using long-term outcome, we assigned CPC3 to the good outcome category. Only few patients, however, were discharged with CPC3. A good neurological long-term outcome is highly unlikely for patients discharged with CPC4 (unresponsive wakefulness or coma).²⁹

Conclusions

A GWR of <1.10 determined manually using the method described above is a highly specific and moderately sensitive predictor of poor outcome in patients after CA. The sensitivity for poor outcome prediction increases from early (<6 h) to late (>24 h after CA) CTs, as the GWR decreases over time in patients with severe HIE. CT performed >24 h after CA is therefore an important option for a multimodal approach to neuroprognostication.

Disclosures

K.J. Streitberger reports no disclosures, C. Endisch reports no disclosures, C.J. Ploner reports no disclosures, R.D. Stevens reports no disclosures, M. Scheel reports no disclosures, M. Kenda reports no disclosures, C. Storm reports honoraria for lectures, travel costs and research support from Bard Medical, Zoll Medical, Phillips and Covidien and received research support from Deutsche Herzstiftung and C. Leithner reports honoraria and travel costs from Bard Medical.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.resuscitation.2019.09.025>.

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