TURKISH JOURNAL OF EMERGENCY MEDICINE

Original Article

Access this article online
Quick Response Code:

Website:
www.turkjemergmed.com

DOI:
10.4103/tjem.tjem_255_22

Is gray-white matter ratio in out-of-hospital cardiac arrest patients' really early predictor of neurological outcome?

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Abstract:

OBJECTIVE: This study aimed to evaluate the association between neurological outcome and gray-white ratio (GWR) in brain computed tomography (CT) in patients with return of spontaneous circulation (ROSC) who were brought to the emergency department (ED) due to out-of-hospital cardiac arrest (OHCA).

METHODS: This study has a retrospective design. Patients with ROSC who were brought to the ED due to OHCA and who underwent brain CT in the first 24 h were included in the study. Demographic data, brain CT results (intensities of gray matter and white matter in Hounsfield units and calculated GWR), and hospital outcome were recorded. The cerebral Performance Categories (CPC) score was used as the outcome of the study.

RESULTS: A total of 160 patients were included in the study. 55% of the patients were male and the median age was 75.5. The median brain CT time of the patients was 120 min. 16.3% of the patients were in the good neurological outcome group. When attenuation values and GWRs of the patients were compared according to CPC of patients (good-poor), no statistically significant difference was detected in any parameter except MC2 attenuation ($P > 0.05$ for all values). The patients were separated into groups geriatric and nongeriatric and GWRs were compared. GWRs were lower in the geriatric groups ($P < 0.05$ for all values).

CONCLUSION: Although it is emphasized in the literature that detection of low GWR in brain CT can help the clinical decision process in patients surviving comatose arrest, we think that it is not valid for especially in geriatric patients and in patients who underwent early brain CT after ROSC.

Keywords:

Brain edema, cardiac arrest, gray-white matter ratio, prognostication

Submitted: 02-09-2022
Revised: 24-11-2022
Accepted: 25-11-2022
Published: 02-03-2023

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Introduction

Out-of-hospital cardiac arrests (OHCA) continue to be a significant problem due to high morbidity and mortality rates in our country worldwide.[1,2] One of the important problems in this patient group in terms of emergency service management is the postresuscitation management process of patients with return of spontaneous circulation (ROSC). In last years, advances in prehospital, emergency medical care, and cardiac resuscitation treatment strategies have increased the number of cardiac arrest survivors and improved the chances of good neurological outcomes for these patients.[1] On the other hand, 40%–70% of survivors still develop serious neurological deficits or

How to cite this article: Emektar E, Karaarslan F, Öztürk C, Ramadan S. Is gray-white matter ratio in out-of-hospital cardiac arrest patients' really early predictor of neurological outcome?. Turk J Emerg Med 2023;23:104-10.

EMAT EMERGENCY MEDICINE ASSOCIATION OF TURKEY

BOX-ED section

What is already known on the study topic?

- Although gray and white matter ratio predicts poor neurological outcome in cardiac arrest patients, gray-white ratio (GWR) is mentioned as one of the gaps in adult resuscitation research.

What is the conflict on the issue? Has it importance for readers?

- Is there any relationship between neurological outcomes and GWR in brain computed tomography of patients with comatose arrest patient? We aimed to determine an appropriate threshold value for the prognosis for the gray-white ratio.

How is this study structured?

- This was a single-center, retrospective study that comprises data from 160 cases.

What does this study tell us?

- Low GWR measured in comatose patients who survived arrest is not correlated with poor neurological outcomes, especially in geriatric patients.

die because of hypoxic-ischemic encephalopathy (HIE). Neuropsychiatric problems are recognized in approximately 65% of those discharged from the hospital and irreversible neurocognitive disorders are noticed in 35%.[3] The organ most sensitive to hypoxia is the brain. Changes in the brain tissues of patients with ROSC after cardiopulmonary resuscitation (CPR) are also essential in the determination of the prognosis.[4] Due to the increase in the count of patients developing hypoxic-ischemic brain injury due to CPR efforts in the last years, the number of patients admitted to intensive care units is quite high.[4] This patient group has some medical, ethical, legal, social, and economic problems along. For these reasons, many studies have been conducted for the prediction of prognosis after CPR and are still being carried out.[5] Early methods aiming for accurate prediction of patient consequences can be useful in making therapeutic opinions and managing treatment. Several indicators, containing electrophysiological studies, neurological examinations, neuroimaging, and bio-markers, have been utilized for prognosis in comatose arrest patients. HIE pathophysiology is comprised of primary (ischemic) and secondary (reperfusion) injury which occurs consecutively during cardiac arrest, CPR, and the acute postresuscitation phase.[6] Primary injury in cardiac arrest results from a sudden disruption or decrease of blood circulation that is followed by hypoxemia and results in reduced glucose supply and lack of oxygen in the brain. After HIE, cerebral edema is a recognized complication that causes secondary injury.[7] The tissue density of cerebral gray matter (GM) diminishes earlier compared to the density of white matter (WM), and this certain differentiation can be measured by gray-white ratio (GWR) on brain tomography.[8] HIE is specific and to be associated with brain edema, which diminishes GM attenuation on computed tomography (CT) scans and results in a loss of gray-WM (GWM) differentiation.[5] Several previous studies showed that the GWR, which is the ratio of GM attenuation to WM attenuation, is remarkably lower in arrest patients with poor neuro-outcomes than in patients with good neuro-outcomes, and therefore reduced GWR is associated with a poor neurological condition.[1,4,5,9,10]

In this study, we aimed to determine the association between GWR and neurological outcomes in brain CT of patients with ROSC, who were brought to the emergency department (ED) due to OHCA. In addition, we aimed to determine an appropriate threshold for the prognosis for the GWR within the gaps specified in the resuscitation guidelines.

Methods

Study design and patient population

Our study has a retrospective design. Ethical approval for this study was acquired from Ankara Atatük Sanatoryum Ethics Committee in Ankara on the date of July 7, 2022, with approval number of KAEK-15/2548. Patients with ROSC who were brought to the ED due to OHCA between January 01, 2019, and January 31, 2021, and who underwent head CT in the first 24 h were included in the study. In our study, patients with a palpable pulse in the main arteries for minimum 1 h were accepted ROSC.

Patients who had a traumatic arrest, who did not undergo brain CT, whose CT scans represented parenchymal bleeding, mass, etc., whose CT images were technically insufficient to determine brain density or not suitable for evaluation, and who were aged under 18 were excluded from the study.

Demographic data, comorbid diseases (hypertension and diabetes mellitus), vital signs after ROSC, laboratory values, arrest type, CPR duration, first rhythm on the monitor, brain CT results, and hospital outcomes were recorded from the files of the cases in which ROSC was achieved after OHCA. The patients were separated according to their age (≥65 years old and <65 years old).

Outcome

Modified Rankin Scale, Glasgow Outcome Scale, and Cerebral Performance Categories (CPC) scores were used to evaluate neurological outcome in previous studies.[1,4,11] We used the CPC score as the study outcome. The CPC score is a five-point scale often used evaluate to neurological outcome in research studies and is commonly dichotomized into "good" (CPC 12) versus "poor" (CPC 35) outcome. The CPC score grades the levels of neurostatus after comatose arrest patients (CPC 1, good; CPC 2, moderate disability; CPC 3, severe disability; CPC 4, comatose or vegetative state; and CPC 5, death).[4]

Measurements (gray-white ratio determination)

All CT images were processed using a 16-slice CT scanner (Siemens Sensations, Germany) with 0.3-cm slice thickness and 0.1-cm gap among slices. A researcher who was unaware of the patient's results measured the intensities of WM and GM in Hounsfield units (HU). For each patient, white and GM density measurements were performed symmetrically and bilaterally based on three slices passing through centrum semiovale, basal ganglia, and high convexity level in the head CT images [Figure 1].

In literature studies, different formulas are used to calculate GM/WM ratio.[4,5,9,10]

A region of interest (0.2 cm^2) was placed bilaterally in the posterior limb of the internal capsule (PIC), putamen (PU), caudate nucleus (CN), anterior (rostrum-genu) of the corpus callosum (CC), medial cortex (MC1), and medial WM (MW1 [at the grade of the supraventricular on axial slice]), MC2 and MW2 (at the grade of the high-convexity area). The mean of all measurements in every part was defined as the HU of the site.[1,12] In this study, we used the formulas, GWR-cerebrum (GWR-C) = (MC1 + MC2)/(MW1 + MW2), and GWR-basal ganglia (GWR-BG) = (CU + PU)/(PIC + CC), which were used in previous studies.

Statistical analysis

The analysis of all data used IBM SPSS 20.0 (Chicago, IL, USA) program. Whether the distribution of distinct and continuous numerical variables is suitable for normal dispersion was evaluated by the Kolmogorov–Smirnov test. The continuous numerical variables were indicated as median (interquartile range 2575), and categorical variables as a number of cases and (%). Categorical variables were used with Chi-square or Fisher's exact test and continuous variables with the Mann–Whitney U test. $P < 0.05$ was considered statistically significant.

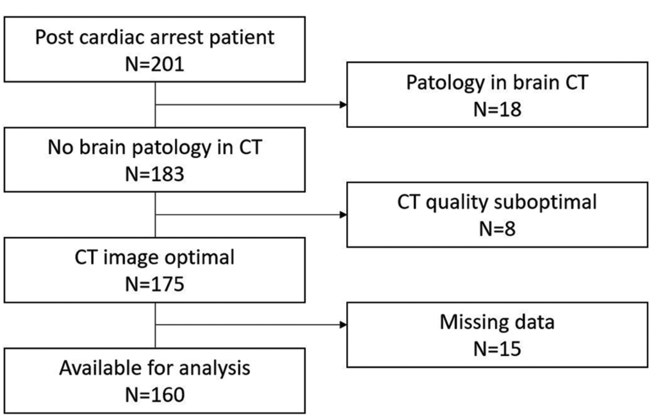

Figure 1: Flowchart of the study

Results

A total of 160 patients were included in the study [Figure 2]. The median age was 75.5 and 55% of the patients were male. The most common comorbidity seen in patients was hypertension (55%). The median brain CT time of the patients was 120 min after ROSC. 16.3% of the cases were in the good outcome group and the 28-day mortality ratio of the cases was 77.5%. Demographic characteristics and laboratory analyses of the two groups are indicated in Table 1. When attenuation values and GWRs of the patients were compared according to CPC of patients (good-poor), no parameter apart from MC2 had any statistically considerable difference ($P > 0.05$ for all values). GWRs and attenuation values of groups were shown in Table 2. The patients were separated into groups as geriatric and nongeriatric and their attenuation values and GWRs were compared. PIC, MW1, and MW2 values were higher; GWRs were lower in the geriatric groups [$P < 0.05$ for all values Table 3].

Discussion

Changes in the brain tissues of patients with ROSC after CPR are essential in determining the prognosis. It is important to find prognostic predictors of neurological outcomes in this patient group. We investigated the association between neurological outcome and GWR in brain CT of patients who were brought to the ED due to OHCA and in which the ROSC was achieved and we think that we reached two important results in this study. Primarily, we showed that a low GWR defined in CT scans is not associated with a neurological outcome in comatose arrest patients after ROSC. Second, these results differ from similar studies in the literature. This may be due to the older age of our patient group and the shorter time of brain CT scan after ROSC. We do not think that GWR measurements obtained from early brain CT images of especially geriatric patients who have coma after arrest can be used as neuroimaging markers.

A multimodal approach in which not only clinical examination but also electrophysiological measurements, imaging studies, and biomarkers are used, has been suggested for prognosis in cardiac arrest survivors.[13-15] Moreover, brain CT after ROSC is also important to rule out brain infarction or hemorrhage.[16,17] Furthermore, brain edema may be used in the prognosis as an indicator of postcardiac arrest brain damage in the initial stage of care after cardiac arrest.[1,4] As more effective treatments

Table 1: Clinical characteristics of patients

Characteristics	Poor (CPC 3-5) (*n*=134)	Good (CPC 1-2) (*n*=26)	*P*
Sex, *n* (%)			
Male	71 (53)	17 (65.4)	0.245
Age (year), median (IQR 25–75)	77 (67-86)	66 (55.5-74.5)	0.001
Comorbidities, *n* (%)			
Hypertension	78 (58.2)	10 (38.5)	0.064
Coronary artery disease	38 (28.4)	10 (38.5)	0.304
Diabetes mellitus	55 (41.4)	4 (15.4)	0.013
Chronic kidney disease	28 (20.9)	3 (11.5)	0.269
Other	41 (30.6)	6 (23.1)	0.572
Vital signs after ROSC, median (IQR 25-75)			
Pulse	88 (74-110)	89 (78.7-110)	0.711
Systolic blood pressure	92.5 (80-112)	101.5 (88.7-114.7)	0.161
Diastolic blood pressure	51 (42-61)	58 (43.5-63.2)	0.434
Body temperature	36.5 (36-37)	36.4 (36-37.1)	0.946
Glasgow Coma Scale	3 (3-3)	3 (3-3)	0.134
Laboratory parameters after ROSC, median (IQR 25-75)			
pH	7.03 (6.88-7.22)	7.07 (6.96-7.29)	0.203
pCO_2	56.3 (40.2-74.8)	54 (41-82)	0.780
HCO_3	14.8 (10-18.9)	18.9 (915-21.5)	0.018
Lactate	8.7 (4.7-12)	6.4 (2.6-10.7)	0.113
Glucose	138 (135-141.2)	138.5 (136-141.2)	0.196
Sodium	157 (110.7-237)	201.5 (136.5-247)	0.307
Creatinin	1.7 (1.16-2.3)	1.2 (0.94-2.1)	0.043
First arrest rhythm, *n* (%)			
Shockable	14 (10.4)	3 (11.5)	0.869
Nonshockable	120 (89.6)	23 (88.5)	
Time from ROSC to brain CT, min, median (IQR 25-75)	120 (60-120)	120 (60-190)	0.352
Survival at 28 days, *n* (%)	8 (7.5)	26 (100)	<0.01

ROSC: Restoration of spontaneous circulation, CT: Computed tomography, CPC: Cerebral Performance Categories, IQR: Interquartile range

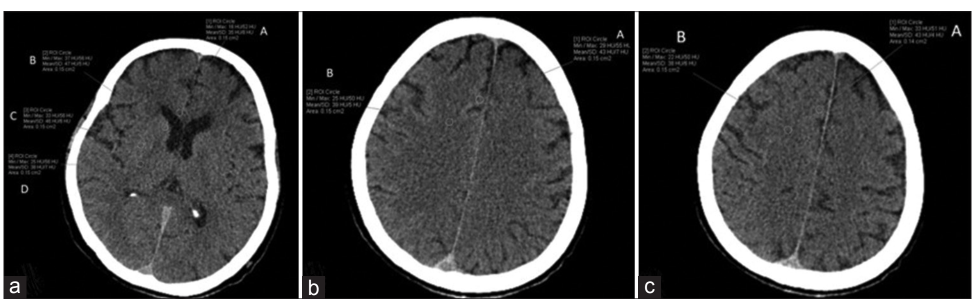

Figure 2: (a-c) Axial noncontrast Head CT images. (a) Regions of interest (ROI) were placed in the following regions; (A) Corpus callosum, (B) Caudate nucleus, (C) Putamen, (D) Posterior limb of the internal capsule at the basal ganglia level. (b) ROI A was placed medial cortex and ROI B was placed white matter at the centrum semiovale level. (c) ROI A was placed medial cortex and ROI B was placed white matter at the high convexity level

become available in recent years, there is a requirement for preliminary identification of adult comatose patients surviving arrest who are expected to achieve early neurological recovery. Early estimation of potential neurological recovery is necessary in comatose survivors. 2020 The American Heart Association guideline mentions prognostication to the GWR as one of the gaps in research on adult resuscitation.[18] Torbey *et al*. evaluated GWR in the cerebrum, centrum semiovale, basal ganglia, and high convexity area, and first noticed that GWR is associated with neurological predictor in comatose arrest patients.[19] In the study managed by Metter with 240 postarrest comatose patients, an average GWR of <1.20 predicted death (area under the curve = 0.72) with a specificity of 98 and % a sensitivity of 36% was reported.[20] Likewise, in the study administered by Scheel to evaluate the prognostic capacity of GWR, a strong correlation was found between low GWR and poor neuro-outcome.[21] We determined a difference between the groups in only the measurements performed in the medial cortex. We found no difference neither in the measurements we performed in other areas or GWR. Evidence from studies over the past 10 years in particular has shown that a reduced GWR strongly predicts worse

Table 2: Comparing of attenuation values and gray-white matter ratios according to neurologic outcome

Density of region of interest, hounsfield units	Median (IQR 25-75)		*P*
	Good (*n*=26)	Poor (*n*=134)	
CN	39 (37-40)	38 (36.7-40)	0.531
Putamen	40 (38-42)	39 (36-40)	0.052
CC	32.5 (30-34)	31 (30-33)	0.363
PIC	32 (30-33)	30 (29-33)	0.265
MC 1	39 (37-40)	38 (36-40)	0.158
Medial white matter at the high convexity level 1	32 (29-32.2)	30 (28-32)	0.158
MC 2	40 (39-40.5)	39 (37-40)	0.022
Medial white matter at the high convexity level 2	33 (32-34)	32 (30-34)	0.104
GWR			
Basal ganglia	1.24 (1.18-1.29)	1.23 (1.18-1.30)	0.969
Cerebrum	1.22 (1.15-1.28)	1.23 (1.17-1.31)	0.490
Average	1.22 (1.18-1.28)	1.23 (1.19-1.30)	0.410

IQR: Interquartile range, CN: Caudate nucleus, CC: Corpus callosum, PIC: Posterior limb of the internal capsule, MC: medial cortex, GWR: Gray-White matter Ratio

Table 3: Comparing of attenuation values and gray-white matter ratios according to age-group

Density of region of interest, hounsfield units	Median (IQR 25-75)		*P*
	≥65 years (*n*=118)	<65 years (*n*=42)	
CN	38 (35-40)	39 (37-40)	0.391
Putamen	38.5 (35-42)	39 (37-40)	0.623
CC	33 (30-34.2)	30 (30-33)	0.059
PIC	32 (30-34.2)	30 (29-32)	0.020
MC 1	38 (35-40)	38 (37-40)	0.153
Medial white matter at the high convexity level 1	31 (30-33)	30 (28-32)	0.007
MC 2	39 (37-40)	39 (37-40)	0.941
Medial white matter at the high convexity level 2	33 (32-35)	32 (30-33.2)	0.003
GWR			
Basal ganglia	1.21 (1.17-1.27)	1.25 (1.18-1.32)	0.028
Cerebrum	1.18 (1.13-1.23)	1.24 (1.19-1.32)	<0.01

IQR: Interquartile range, CN: Caudate nucleus, CC: Corpus callosum, PIC: Posterior limb of the internal capsule, MC: Medial cortex, GWR: Gray-White matter Ratio

neurological outcomes in the years following cardiac arrest.[4,19,21] However, the authenticity of this method is still controversial. Previous analyses have determined that the sensitivity of GWR is affected by several factors including, time from ROSC to brain CT, standardization in the definition of neurological outcomes, measurement sites, and cutoff values of GWR.[11] We also think that time from ROSC to CT is an important factor. We may not have detected a difference because brain CT scans may have been performed in the early period. There is no coronary angiography unit in our hospital. We perform brain imaging, as soon as the patient is stable, to eliminate central pathologies in patients surviving arrest and for whom no apparent etiology can be detected (such as ECG, ST elevation, and MI). The median brain CT time of our patients was 120 min (min-max = 601380 min, 87.5% of them were performed in the first 3 h). In the study of Kim *et al*., in which the brain CT was performed within the next 1 h after ROSC, no statistically significant difference was found when hounsfield attenuation units of poor and good neurological outcome groups were compared, but a significant difference was determined in GWR evaluated from the basal ganglia and cerebrum.[22] On the contrary, in a study evaluating the relationship between neurological and outcome GWR in adult comatose cardiac arrest survivors in China, it was reported that low GWRs are associated with poor neurological outcomes in all patient groups, regardless of brain CT time in comatose arrest patients after ROSC.[23] In this study, patients were separated into two as early (first 24 h) and late (those who underwent brain CT within 24–72 h) according to the CT time. In the early CT group, there was a significant difference in relevant areas when Hounsfield attenuation units of poor and good outcome groups were compared; however, no remarkable difference was found in GWRs evaluated from the basal ganglia (GWR median = 1.24) and cerebrum (GWR median = 1.20). In our results, values measured from the basal ganglia (GWR median = 1.24) and cerebrum (GWR median = 1.22) were similar. These differences might be due to measurement techniques and CT times. Although some studies emphasized that cerebral edema is not visualized by brain CT within the first 6 h and that cerebral edema becomes detectible earlier on brain CT after cardiac arrest, unlike ischemic strokes, the exact time is not clarified yet.

Another reason why there is no difference in GWR that the median age of our patients was higher than in other studies. Normal aging is combined with gradual brain atrophy. Giorgio evaluated 66 healthy subjects aged 23–81, reported a diffuse linear negative association between GM volumes and stated that there is a more localized negative association between WM volumes and age that there is a linear unfavorable association among age, volume, cortical and deep GM parts.[24] Again, Farokhian showed a diffuse decrease in GM volume in the insular, frontal, and cingulate cortex areas, an increase in WM in the occipital and pericentral areas, and a decrease in WM in thalamic radiations in the elderly compared to young people.[25] Compared to the studies in the literature, the age of our sample group was quite high. We divided the patients into geriatric and nongeriatric according to their age, we showed that the GWR values were lower in the geriatric group than in those under 65 years of age. 73.8% of our patients ($n = 118$) were over 65 and these age-related changes may be one of the reasons for no difference.

Another reason may be GWR measurement zones and methods. The sensitivity of GWR has been associated with interobserver variability.[26] Factors affecting the sensitivity of the GWR measurement remain uncertain. In addition, automatic GWR measurement allows the observation of global GWR values as well as isolation of anatomical locations based on brain CT densitometric information. This methodology appears to be more objective and sensitive than manual measurement, and there is a study claiming that the sensitivity of GWR calculated with this automated analysis methodology can reach 92.7%.[11,27]

Limitations

This study has some limitations. Primarily, since our study was retrospective, possible data losses may have affected our results. Secondarily, our patient group mostly included individuals in geriatric age groups. Since the number of our patients with good outcome was not sufficient, we could not perform a logistic regression analysis to evaluate the efficacies of variables (evaluation of brain tomography findings together with other factors affecting neurological outcomes such as age, gender, and comorbidities) that would enable a more accurate interpretation of our study results. Another limitation was that CT scans were performed in the early period. The number of patients who underwent brain CT in the late period was low and the necessary comparisons could not be made. The CPC we use to assess poor neurological outcome at discharge may be subject to fail due to late-period recovery.

Conclusion

In this study, we demonstrated that low GWR measured on CT in comatose patients who survived arrest after ROSC is not associated with poor neurological outcomes. Although it is emphasized in the literature that the detection of low GWR in CT can help the clinical decision process in patients surviving comatose arrest, we think that it is not valid for geriatric patients. We also think that the time of ROSC to CT is an important factor. There is a need for prospective studies with larger cohorts in which CT time can be optimized.

Conflicts of interest

None declared.

Ethical approval

Ethical approval for this study was obtained from Atatürk Sanatoryum Training and Research Hospital Ethics Committee (12/07/2022, number: 2012-KAEK-15/2548).

Informed consent

Written informed consent could not be obtained as it is a retrospective study.

Funding

None declared.

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