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ORIGINAL WORK

Cerebral Infarction Observed on Brain MRI in Unconscious Out-of-Hospital Cardiac Arrest Survivors: A Pilot Study

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Abstract

Background: Cumulative evidence regarding the use of brain magnetic resonance imaging (MRI) for predicting prognosis of unconscious out-of-hospital cardiac arrest (OHCA) survivors treated with targeted temperature management (TTM) is available. Theoretically, these patients are at a high risk of developing cerebral infarction. However, there is a paucity of reports regarding the characteristics of cerebral infarction in this population. Thus, we performed a pilot study to identify the characteristics and risk factors of cerebral infarction and to evaluate whether this infarction is associated with clinical outcomes.

Methods: A single-center, retrospective, registry-based cohort study was conducted at Severance Hospital, a tertiary center. Unconscious OHCA survivors were registered and treated with TTM between September 2011 and December 2015. We included patients who underwent brain MRI in the first week after the return of spontaneous circulation. We excluded patients who underwent any endovascular interventions to focus on "procedure-unrelated" cerebral infarctions. We assessed hypoxic–ischemic encephalopathy (HIE) and procedure-unrelated cerebral infarction separately on MRI. Patients were categorized into the following groups based on MRI findings: HIE (−)/infarction (−), infarction-only, and HIE (+) groups. Conventional vascular risk factors showing $p < 0.05$ in univariate analyses were entered into multivariate logistic regression. We also evaluated if the presence of this procedure-unrelated cerebral infarction lesion or HIE was associated with a poor clinical outcome at discharge, defined as a cerebral performance category of 3–5.

Results: Among 71 unconscious OHCA survivors who completed TTM, underwent MRI, and who did not undergo endovascular interventions, 14 (19.7%) patients had procedure-unrelated cerebral infarction based on MRI. Advancing age [odds ratio (OR) 1.11] and atrial fibrillation (OR 5.78) were independently associated with the occurrence of procedure-unrelated cerebral infarction (both $p < 0.05$). There were more patients with poor clinical outcomes at discharge in the HIE (+) group (88.1%) than in the infarction-only (30.0%) or HIE (−)/infarction (−) group (15.8%) ($p < 0.001$). HIE (+) (OR 38.69, $p < 0.001$) was independently associated with poor clinical outcomes at discharge, whereas infarction-only was not ($p > 0.05$), compared to HIE (−)/infarction (−).

Conclusions: In this pilot study, procedure-unrelated cerebral infarction was noted in approximately one-fifth of unconscious OHCA survivors who were treated with TTM and underwent MRI. Older age and atrial fibrillation might be associated with the occurrence of procedure-unrelated cerebral infarction, and cerebral infarction was

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not considered to be associated with clinical outcomes at discharge. Considering that the strict exclusion criteria in this pilot study resulted in a highly selected sample with a relatively small size, further work is needed to verify our findings.

Keywords: Out-of-hospital cardiac arrest, Induced hypothermia, Cerebral infarction, Hypoxia–ischemia, brain, Prognosis

Introduction

Post-cardiac arrest (CA) brain injury is a common cause of morbidity and mortality in out-of-hospital cardiac arrest (OHCA) survivors. This includes hypoxic–ischemic encephalopathy (HIE), cerebral infarction, and a variety of neurologic manifestations, such as intractable myoclonus, cognitive decline, and parkinsonism [1]. Recent advances in integrated post-CA care, greatly contributed by targeted temperature management (TTM), shed light on the treatment of unconscious OHCA survivors, with both higher chances of survival and better neurologic recovery [2].

Cumulative evidence regarding brain magnetic resonance imaging (MRI), particularly diffusion-weighted imaging (DWI), for identifying HIE, a powerful and reliable method to predict the neurologic outcome of unconscious OHCA survivors treated with TTM, is available [3, 4]. In real clinical practice, we have sometimes found diffusion-restricted lesions, suggesting the occurrence of cerebral infarction in unconscious OHCA survivors treated with TTM. It is hard to distinguish cerebral infarction from HIE, because both can show restricted diffusion and coexist [5, 6]. However, HIE tends to present as restricted diffusions predominantly in the gray matter, such as the cortex, basal ganglia, thalami, hippocampi, or cerebellum, whereas cerebral infarction may show patterns of a large-artery occlusion, embolism, or small-artery occlusion [5–7]. Nevertheless, previous studies only focused on the presence of diffusion-restricted lesions, which mainly considered HIE and showed that they could predict the prognosis of unconscious OHCA survivors. However, they did not investigate the differential impact of cerebral infarction and HIE on the prognosis [3, 4].

Until now, there has been only one preliminary study describing the characteristics of embolic infarction [8]. In this retrospective study, among the 77 patients who underwent induced hypothermia after CA, only two patients (3% of included patients, mean age 73 years) developed a clear embolic stroke; however, no features were found among these two patients that could distinguish them from the others [8]. This finding might be due to the paucity of stroke cases in their cohort. Theoretically, however, unconscious OHCA survivors treated with TTM have a high risk of developing cerebral infarction because of premorbid cardio-cerebrovascular risk factors, such as coronary and valvular heart diseases, low cardiac output, and arrhythmia [1, 9], as well as adoption of endovascular interventions, including percutaneous coronary intervention (PCI), intra-aortic balloon pump (IABP), and percutaneous cardiopulmonary support (PCPS) [10–13]. Furthermore, TTM is also associated with several complications, including dysrhythmias and hemodynamic instability, which in turn increase the incidence of cerebral infarction [14], although TTM generally increases the rate of a favorable neurologic outcome and reduces mortality [2, 15].

The overall aim of this pilot study was to identify the characteristics and risk factors for development of procedure-unrelated cerebral infarction and to evaluate the association between the infarction and the neurologic outcome at discharge in unconscious OHCA survivors treated with TTM. Cerebral infarction and HIE based on MRI were evaluated separately to predict the prognosis of unconscious OHCA survivors treated with TTM.

Methods

Patients and TTM

This is a retrospective registry-based pilot study performed in a single tertiary center. Unconscious OHCA survivors were prospectively enrolled according to the inclusion and exclusion criteria presented below and treated with integrated team-based TTM, encompassing the departments of emergency medicine, cardiology, pulmonology, anesthesiology, and neurology, since September 2011.

The inclusion criteria were as follows: OHCA patients aged >18 years who had stable vital signs after resuscitation but remained unconscious [defined as Glasgow coma scale (GCS) $\leq$8]. Patients with preexisting coma prior to CA, hemodynamic instability [mean blood pressure (BP) <60 mmHg despite vasopressor use], history of terminal illness, severe coagulopathy associated with bleeding, pregnant women, and those with a "do-not-resuscitate" status were excluded.

TTM, as a pre-scheduled sequence in our hospital, was performed as follows: hypothermia was induced within 4 h after CA, hypothermia was maintained for 24 h, and rewarming and maintenance of normothermia were performed for at least 48 h. The target temperature

for maintenance therapy was initially set at 32–34 °C [2]. During the study, there was no research conducted in non-cardiogenic OHCA survivors; thus, we decided to study the same targets in this population. From April 2014, based on the Nielsen study [15], the target temperature was changed for cardiogenic CA to 33–36 °C, and that for non-cardiogenic CA was maintained at 32–34 °C.

We retrospectively collected data of unconscious OHCA survivors who underwent TTM from September 2011 to December 2015.

MRI Acquisition Protocol and Definition of Cerebral Infarction and HIE

Although the proper timing and value of MRI have not yet been validated for use in neurologic prognostication in unconscious OHCA survivors [16], brain MRI was scheduled at 72 h after the return of spontaneous circulation (ROSC) per protocol in our hospital, which was based on a previous study [3]. In cases where MRI could not be performed owing to the patients' unstable state, it was delayed and performed when the treating physicians believed that the patient could safely undergo MRI. For this study, we included the unconscious OHCA survivors treated with TTM who underwent brain MRI within 7 days of their ROSC. There is no definite scientific evidence about the proper time window of MRI until now. Moreover, in real clinical practice, the time window of MRI is influenced by the patients' condition and treating physicians' judgement. Nevertheless, we tried to make our own inclusion criteria based on previous researches. Many studies on HIE for the neurologic prognostication in unconscious OHCA survivors used the MRI time window of within 7 days of ROSC [3, 4, 6]. With regard to evaluating cerebral infarction, an abnormal signal intensity on DWI within 24 h of stroke onset was detected in 100% of the studied patients, and the detection rate remarkably decreased after 10 days (60%) [17]. Consequently, to evaluate both cerebral infarction and HIE, we included patients who underwent MRI within 7 days of CA [3, 4, 6, 17]. The brain MRI protocol included DWI with B values of both 1000 and 3000, apparent diffusion coefficient (ADC), fluid-attenuated inversion recovery (FLAIR), and gradient echo (GRE) sequences. All scans were acquired by using a Philips 3.0 Tesla scanner (Philips Achieva; Philips Medical System, Best, The Netherlands).

We defined cerebral infarction as a lesion with both discrete DWI-high and ADC-low signal findings [5], and only if the lesion is not in conjunction with HIE (described below) on DWI or FLAIR images (Fig. 1a, b). HIE was regarded as a lesion showing relatively symmetric and diffuse DWI-high and ADC-low signals, involving the cerebral cortex, deep gray nuclei (basal ganglia and thalamus), cerebellum, or brainstem; of which, the whole configuration does not follow arterial cerebrovascular territories (Fig. 1c) [6, 18]. Two neurologists who were blinded to the clinical findings reviewed the MRI scan and determined whether a cerebral infarction or HIE was present. In case of disagreement, the diagnosis was made with the help of a neuroradiologist.

We additionally excluded patients who underwent any endovascular interventions, including PCI, IABP, or PCPS before the MRI study, because of the well-established relationship between these interventions and cerebral infarction [10–13], which is not the focus of our

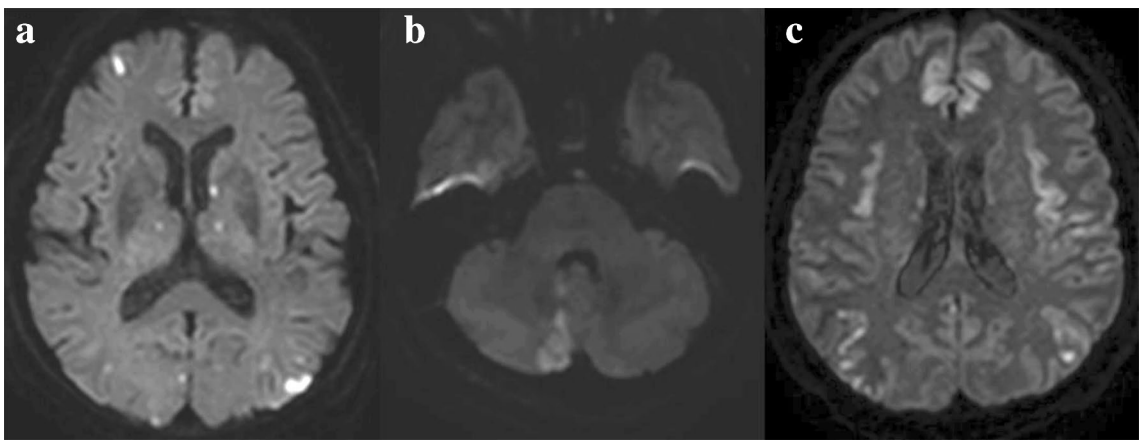

Fig. 1 Illustrative MRI scans (DWI) showing cerebral infarction (**a**, **b**) and HIE (**c**) lesions. **a**, **b** Cerebral infarction was defined as the presence of discrete DWI-high and ADC-low signal findings, and only if the lesion is not in conjunction with HIE on DWI or FLAIR images. **c** HIE was regarded as a lesion, showing diffuse DWI-high and ADC-low signals involving the cerebral cortex, deep gray nuclei (basal ganglia and thalamus), cerebellum, or brainstem, which are not typical for vascular territories. *ADC* apparent diffusion coefficient, *DWI* diffusion-weighted imaging, *FLAIR* fluid-attenuated inversion recovery, *HIE* hypoxic–ischemic encephalopathy, *MRI* magnetic resonance imaging

study. A cerebral infarction that occurred in patients who did not undergo endovascular procedures was referred to as a procedure-unrelated cerebral infarction and that in patients who underwent endovascular interventions was termed as a procedure-related infarction.

Considering the strong effect of HIE on prognosis in the previous study [4], we categorized the patients into the following three groups: patients with HIE [$n=42$, HIE (+) group], patients with cerebral infarction-only [$n=10$, infarction-only group], and patients with neither HIE nor cerebral infarction [$n=19$, HIE (−)/infarction (−) group]. The remaining four patients with both HIE and cerebral infarction were further classified into the HIE (+) group.

Clinical Work-Up and Definition of a Poor Clinical Outcome at Discharge

Clinical work-up data were obtained in a prospective and standardized manner at predefined time points. Neurologic examinations, including pupil light reflex (PLR) and GCS [19, 20], were performed at the initial presentation and MRI acquisition, considering the frequent use of sedatives. Brain computed tomography was performed immediately in most cases (135 out of 156 patients, 86.5%) to predict the need for hyperosmolar therapy. Additionally, somatosensory evoked potentials (SSEPs) were performed at approximately 72 h after ROSC according to our protocol [21].

The clinical outcome of the patients was assessed at discharge, using the Glasgow–Pittsburgh cerebral performance category (CPC) scale [22]. A CPC of 1 indicates full recovery, a CPC of 2 indicates moderate disability, and a CPC of 3 indicates severe neurologic disability but with preserved consciousness. Patients with a CPC of 4 are comatose or in a persistent vegetative state, and a CPC of 5 indicates death. A poor clinical outcome at discharge was defined as a CPC of 3–5 at discharge [23].

Statistical Analysis

Statistical analysis was performed using R version 3.5.2 (http://www.R-project.org). Descriptive statistics of continuous variables are presented as median and interquartile range (IQR), because all of them were not normally distributed. For the statistical test of difference among the three groups described earlier, the Chi-squared test or Fisher's exact test was used for categorical variables, followed by the Bonferroni post hoc method. For continuous variables, we performed the Kruskal–Wallis test followed by the Dunn–Bonferroni post hoc method. To determine the clinical factors that were independently associated with the occurrence of infarction, a logistic regression analysis for the presence of infarction, regardless of the presence of HIE, was conducted. Variables with $p<0.05$ in the univariate analyses were entered into each multivariate model. The results of the logistic regression analysis are presented as odds ratios (ORs) and 95% confidence interval (CI), and two-sided p values of <0.05 were considered statistically significant. A poor clinical outcome at discharge and the relationship with each clinical variable, including the three predetermined groups based on MRI lesions, were determined through the univariate and multivariate logistic regression analyses, respectively.

Results

The flowchart of this study is depicted in Fig. 2. Data of 223 adult unconscious OHCA survivors who were enrolled in the registry were reviewed. Four patients who regained alertness soon after ROSC, four patients whose brain computed tomography (CT) scan showed cerebral hemorrhage, 26 patients with unstable vital signs, three patients who underwent surgery, and 30 patients whose caregivers refused further work-up or aggressive care (do-not-resuscitate) failed to complete the entire TTM protocol and were excluded. Among the remaining 156 patients who were enrolled and who completed TTM, 94 patients (60.3%) underwent a technically adequate brain MRI scan within 7 days of ROSC.

The baseline characteristics and differences according to the presence of MRI scan among all 156 OHCA patients who completed TTM are summarized in Supplementary Table 1. Patients who underwent MRI were more likely to have a shockable rhythm and were less likely to undergo PCPS than those who did not undergo MRI. Patients without an MRI scan showed a worse prognosis at discharge, and eventually a higher mortality. However, there was no difference in demographic and baseline clinical characteristics. Moreover, clinical variables during the TTM, such as initial neurologic examination and median temperature, were not different.

Among the unconscious OHCA survivors who completed TTM and underwent MRI ($n=94$), eight patients showed a discrepancy between the neurologists regarding the presence of cerebral infarction (Cohen's kappa = 0.798). As aforementioned, 23 patients who underwent endovascular interventions were additionally excluded from our main analysis; of these, 11 (47.8%) patients had an infarction (procedure-related infarction), compared to 14 (19.7%) patients who did not undergo endovascular interventions and had procedure-unrelated infarctions ($p=0.017$) (Supplementary Table 2).

Finally, unconscious OHCA survivors with complete TTM and MRI who did not undergo endovascular interventions ($n=71$) were included in the analyses (Fig. 2).

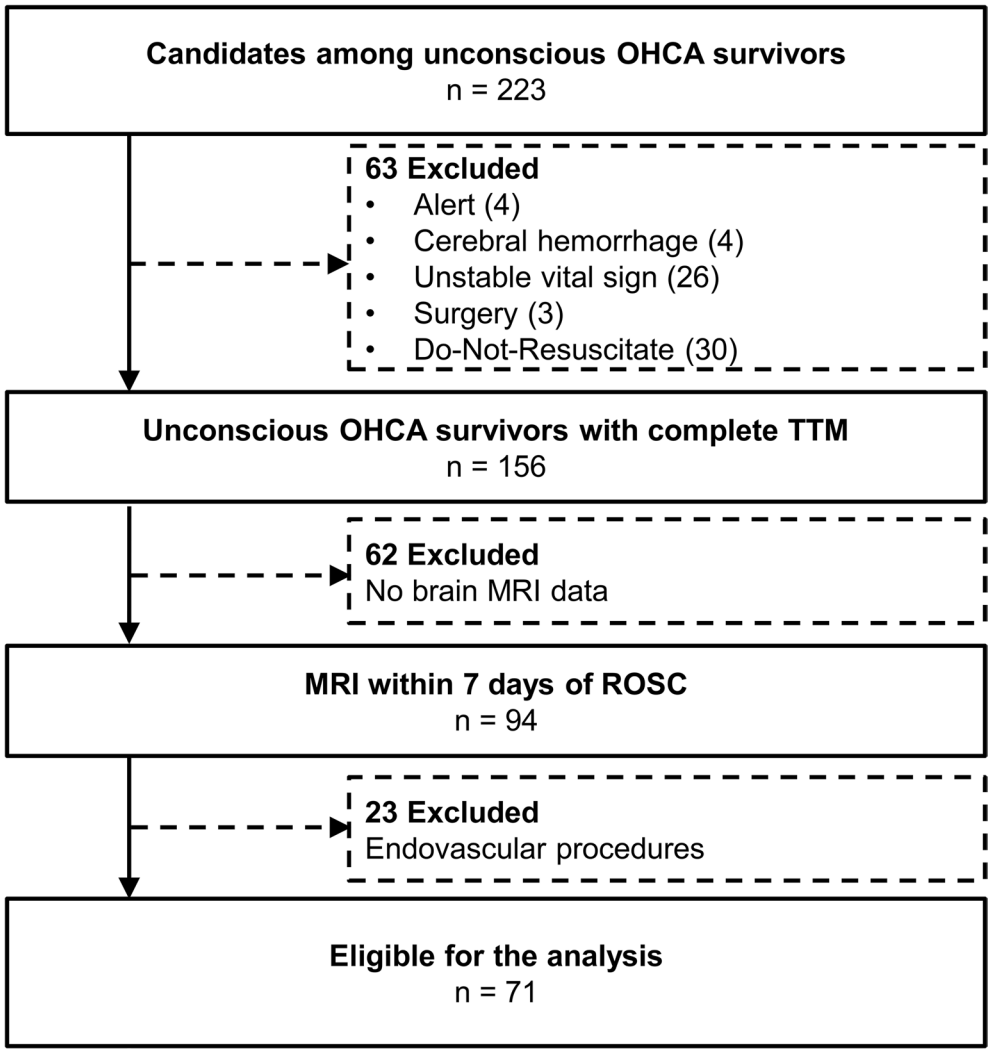

Fig. 2 Flowchart of patient selection. *MRI* magnetic resonance imaging, *OHCA* out-of-hospital cardiac arrest, *ROSC* return of spontaneous circulation, *TTM* targeted temperature management

Characteristics of Procedure-Unrelated Cerebral Infarction

The median time from ROSC to MRI scan was 77.2 h (IQR, 66.1–91.7). Procedure-unrelated cerebral infarction was observed in 19.7% (14/71) of the patients. There were six patients with vessel studies, including computed tomography angiography (CTA) or magnetic resonance angiography (MRA), and none of them showed relevant artery stenosis. According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification [7, 23], 12 patients were classified as having "cardioembolism". Two patients with medium-risk potential cardiac sources of embolism (lone atrial fibrillation and hypokinetic left ventricular segment) were classified as having "incomplete evaluation." The DWI scans of each patient showing characteristics of cerebral infarction according to the abovementioned classification are presented in Supplementary Fig. 1, and the clinical characteristics of each patient are shown in Supplementary Table 3. Border zone infarctions were observed in 57.1% of the patients (8 out of 14 patients with infarction, 1st and 2nd rows of Supplementary Fig. 1). All border zone cerebral infarctions ($n=3$) were located at the external border zone. The other border zone infarctions ($n=5$) were located at the cerebellum.

Comparison of Characteristics According to the Presence of HIE and Cerebral Infarction

The baseline characteristics of 71 unconscious OHCA survivors after categorization into three groups based on their MRI features are summarized in Table 1.

Table 1 Baseline characteristics of unconscious OHCA survivors according to the MRI findings

	Total ($n=71$)	HIE (−)/infarction (−) ($n=19$)	HIE (+) ($n=42$)	Infarction-only ($n=10$)	p value
Baseline characteristics					
Age, years	58.0 [49.5–68.5]	58.0 [43.5–63.0]	57.0 [49.0–67.0]	70.5 [68.0–79.0][a,b]	0.014
Sex, men	53 (74.6)	16 (84.2)	31 (73.8)	6 (60.0)	0.356
Hypertension	36 (50.7)	10 (52.6)	18 (42.9)	8 (80.0)	0.106
Diabetes	19 (26.8)	5 (26.3)	11 (26.2)	3 (30.0)	0.969
Dyslipidemia	13 (18.3)	4 (21.1)	6 (14.3)	3 (30.0)	0.481
Old CVA	13 (18.3)	3 (15.8)	6 (14.3)	4 (40.0)	0.159
Atrial fibrillation	15 (21.1)	3 (15.8)	8 (19.0)	4 (40.0)	0.276
CAOD	14 (19.7)	4 (21.1)	7 (16.7)	3 (30.0)	0.626
CKD	12 (16.9)	3 (15.8)	8 (19.0)	1 (10.0)	0.781
Smoking, PYRS	2.0 [0.0–30.0]	14.0 [1.0–30.0]	0.0 [0.0–15.0]	13.0 [0.0–30.0]	0.258
Antithrombotics before admission	27 (38.0)	6 (31.6)	14 (33.3)	7 (70.0)	0.079
Anticoagulation after admission	43 (60.6)	12 (63.2)	22 (52.4)	9 (90.0)	0.088
Arrest characteristics					
Witnessed	48 (67.7)	15 (78.9)	25 (59.5)	8 (80.0)	0.215
Bystander CPR	46 (64.8)	13 (68.4)	27 (64.3)	6 (60.0)	0.898
Cardiogenic cause	40 (56.3)	16 (84.2)	18 (42.9)[a]	6 (60.0)	0.010
Shockable rhythm	31 (43.7)	12 (63.2)	14 (33.3)	5 (50.0)	0.085
CPR duration, min	19.0 [8.0–28.5]	11.0 [4.5–18.5]	24.0 [17.0–35.0][a]	9.0 [6.0–12.0][b]	< 0.001
Work-up					
GCS at initial	3.0 [2.0–4.5]	4.0 [3.0–6.0]	2.0 [2.0–3.0][a]	3.0 [2.0–6.0]	0.002
PR (+) at initial	34 (47.9)	12 (63.2)	13 (31.0)	9 (90.0)[b]	0.001
GCS at MRI scan	2.0 [2.0–7.5]	10.0 [7.5–15.0]	2.0 [2.0–3.0][a]	5.5 [2.0–9.0][b]	< 0.001
PR (+) at MRI scan	47 (66.2)	18 (94.7)	20 (47.6)[a]	9 (90.0)	< 0.001
Any sedatives at MRI scan	33 (46.5)	6 (31.6)	21 (50.0)	6 (60.0)	0.267
Absent N20 on SSEPs ($n=59$)	27 (45.8)	1 (8.3)	25 (64.1)[a]	1 (12.5)	< 0.001

Data are expressed as median [IQR] or a number (%)

CAOD coronary artery occlusive disease, *CKD* chronic kidney disease, *CPR* cardiopulmonary resuscitation, *CVA* cerebrovascular accident, *GCS* Glasgow coma scale, *HIE* hypoxic–ischemic encephalopathy, *MRI* magnetic resonance imaging, *OHCA* out-of hospital cardiac arrest, *PR* pupil light reflex, *PYRS* pack-years, *SSEPs* somatosensory evoked potentials

[a] Bonferroni-adjusted $p < 0.05$ in comparison with HIE (−)/infarction (−) group

[b] Bonferroni-adjusted $p < 0.05$ in comparison with HIE (+) group

Thirty-three (46.5%) patients received sedatives during the MRI scan day. The infarction-only group was older than the HIE (−)/infarction (−) (Bonferroni-adjusted $p=0.015$) or HIE (+) group (Bonferroni-adjusted $p=0.027$). Moreover, the infarction-only group was more likely to preserve PLR at the initial presentation (Bonferroni-adjusted $p=0.006$) and have better GCS at the time of MRI scan (Bonferroni-adjusted $p=0.021$) than the HIE (+) group. On the other hand, the HIE (+) group had a longer duration of cardiopulmonary resuscitation (CPR) than the infarction-only (Bonferroni-adjusted $p<0.001$) and HIE (−)/infarction (−) groups (Bonferroni-adjusted $p=0.003$). In addition, the HIE (+) group was less likely to have a cardiac origin of arrest (Bonferroni-adjusted $p=0.018$), more likely to have worse GCS at the time of the MRI scan (Bonferroni-adjusted $p<0.001$), and absent N20 on SSEPs (Bonferroni-adjusted $p=0.006$) than the HIE (−)/infarction (−) group.

Conditions Related with the Occurrence of Procedure-Unrelated Cerebral Infarction

Univariate logistic regression analyses revealed that an increase in age ($p=0.002$), atrial fibrillation ($p=0.006$), or shorter duration of CPR ($p=0.016$) was associated with the occurrence of procedure-unrelated cerebral infarction (Table 2). In the multivariate logistic regression analysis, every 1-year increase in age and atrial fibrillation was related to a 1.1-fold (OR 1.11, 95% CI 1.04–1.20, $p=0.006$) and 5.8-fold (OR 5.78, 95% CI 1.23–31.31,

Table 2 Logistic regression analyses for the occurrence of cerebral infarction

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Baseline characteristics				
Age, years	1.11 (1.05–1.2)	0.002	1.11 (1.04–1.20)	0.006
Sex, men	0.36 (0.1–1.26)	0.101		
Hypertension	2.98 (0.99–11.9)	0.092		
Diabetes	1.71 (0.46–5.85)	0.402		
Dyslipidemia	1.28 (0.26–5.07)	0.737		
Atrial fibrillation	6.13 (1.70–23.05)	0.006	5.78 (1.23–31.31)	0.030
CAOD	1.14 (0.23–4.44)	0.858		
Old CVA	2.13 (0.5–8.09)	0.275		
Smoking, PYRS	0.99 (0.96–1.02)	0.609		
Use of antithrombotics	2.67 (0.81–9.18)	0.107		
Arrest characteristics	(−)			
Witnessed	1.25 (0.36–5.03)	0.733		
Bystander CPR	0.46 (0.14–1.53)	0.202		
Shockable rhythm	0.66 (0.18–2.17)	0.505		
CPR duration, min	0.92 (0.86–0.98)	0.016	0.93 (0.86-0.99)	0.053

Variables, which showed $p < 0.05$ in the univariate analyses (age, atrial fibrillation, and CPR duration), were included in the multivariate analysis. Data are given as odds ratio (95% confidence interval)

CAOD coronary artery occlusive disease, *CPR* cardiopulmonary resuscitation, *CVA* cerebrovascular accident, *PYRS* pack-years

$p = 0.030$) higher risks of procedure-unrelated cerebral infarction, respectively (Table 2).

Clinical Outcomes at Discharge

After a median hospitalization duration of 16.5 days (IQR, 11.1–26.9 days, range 5.1–296.7 days), the HIE (+) group demonstrated poorer clinical outcomes at discharge ($p < 0.001$, Fig. 3). Six (8.5%) patients died (CPC 5) at discharge (5 [11.9%] in the HIE (+) group, one patient [5.3%] in the HIE (−)/infarction (−) group, and none in the infarction-only group).

A poor clinical outcome at discharge was associated with non-shockable rhythm, longer CPR duration, and HIE (+) in the univariate analyses (Table 3). In the multivariate analysis, HIE (+) was independently associated with a worse clinical outcome at discharge (OR 38.69, 95% CI 6.77–359.90, $p < 0.001$), whereas infarction-only was not ($p > 0.05$), compared to HIE (−)/infarction (−) (Table 3).

Discussion

In this pilot study, procedure-unrelated cerebral infarction was observed in approximately one-fifth of unconscious OHCA survivors who were treated with TTM and who underwent MRI. A high proportion of procedure-unrelated infarction cases might be associated with a cardioembolic origin, and these cases also demonstrated a border zone pattern. Older age and atrial fibrillation might be associated with the occurrence of procedure-unrelated infarction. Regarding the prognosis, HIE was considered to be associated with poor clinical outcomes

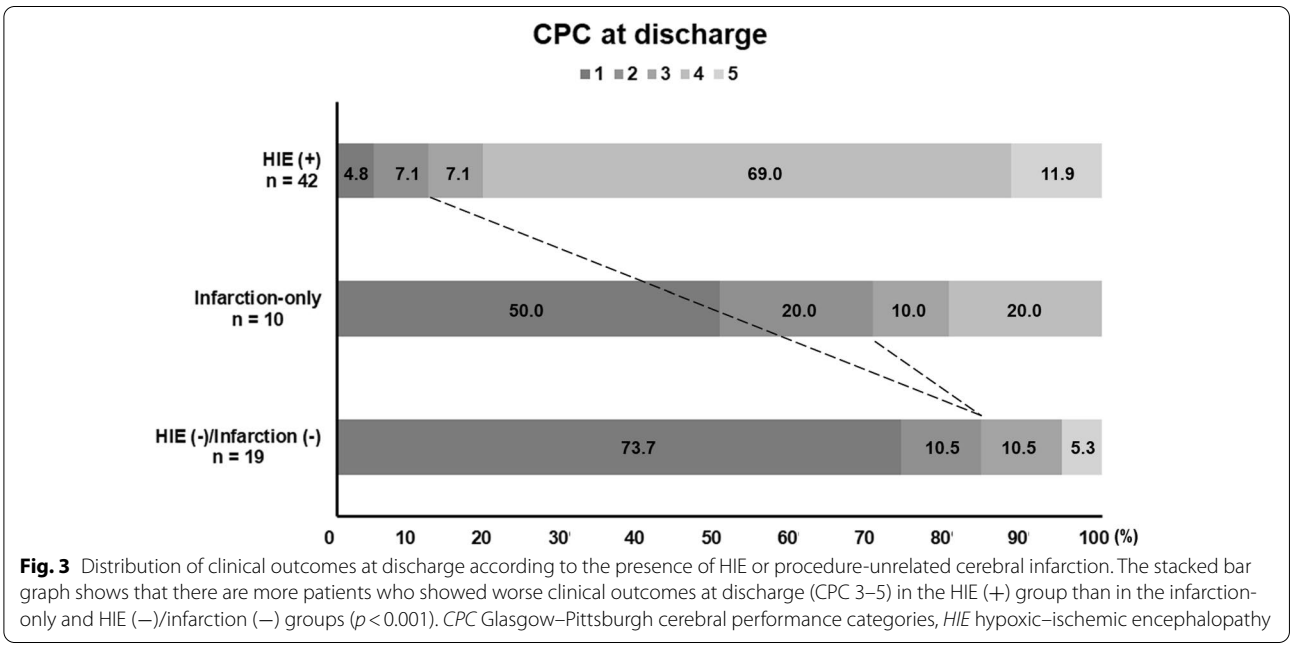

Fig. 3 Distribution of clinical outcomes at discharge according to the presence of HIE or procedure-unrelated cerebral infarction. The stacked bar graph shows that there are more patients who showed worse clinical outcomes at discharge (CPC 3–5) in the HIE (+) group than in the infarction-only and HIE (−)/infarction (−) groups ($p < 0.001$). *CPC* Glasgow–Pittsburgh cerebral performance categories, *HIE* hypoxic–ischemic encephalopathy

Table 3 Logistic regression analyses for poor clinical outcomes at discharge

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Baseline characteristics				
Age, years	1.02 (0.99–1.05)	0.174		
Sex, men	0.50 (0.14–1.54)	0.246		
Hypertension	1.05 (0.40–2.73)	0.924		
Diabetes	3.21 (1.01–12.46)	0.063		
Dyslipidemia	1.59 (0.46–6.41)	0.482		
Atrial fibrillation	0.69 (0.22–2.21)	0.520		
CAOD	0.58 (0.18–1.92)	0.370		
Old CVA	1.59 (0.46–6.41)	0.482		
Smoking, PYRS	1.00 (0.98–1.02)	0.993		
Use of antithrombotics	0.92 (0.34–2.47)	0.860		
Arrest characteristics				
Witnessed	0.42 (0.13–1.20)	0.116		
Bystander CPR	0.80 (0.29–2.16)	0.662		
Shockable rhythm	0.14 (0.04–0.39)	< 0.001	0.08 (0.01–0.36)	0.003
CPR duration, min	1.05 (1.01–1.09)	0.019	1.03 (0.97–1.09)	0.368
Patient category				
HIE (−)/infarction (−)	1		1	
Infarction-only	2.29 (0.35–15.32)	0.376	2.29 (0.27–21.77)	0.444
HIE (+)	39.47 (9.53–222.87)	< 0.001	38.69 (6.77–359.90)	< 0.001

Variables, which showed $p < 0.05$ in the univariate analyses (shockable rhythm, CPR duration, and MRI category), were included in the multivariate analysis. Data are given as odds ratio (95% confidence interval)

CAOD coronary artery occlusive disease, *CPR* cardiopulmonary resuscitation, *CVA* cerebrovascular accident, *HIE* hypoxic–ischemic encephalopathy, *MRI* magnetic resonance imaging, *PYRS* pack-years

at discharge in this highly selected patient population, whereas cerebral infarction did not show a statistically significant association.

The procedure-unrelated cerebral infarction was more frequently observed in our study than in the previous preliminary report, which might be due to the difference in the methods used. For example, in the previous study, only clear embolic stroke lesions were counted [8]. Unconscious OHCA survivors treated with TTM usually have not only underlying cardio-cerebrovascular risk factors but also hemodynamic instability [1, 9]. TTM also increases the risk of dysrhythmias and hemodynamic instability [14], despite its well-established benefit [2, 15]. In our study, in accordance with the previous research [9], older age and atrial fibrillation might be associated with the occurrence of procedure-unrelated cerebral infarction. In fact, according to the TOAST classification [7, 24], most of the cases could be classified as cardioembolism. Other conventional cardiovascular risk factors [9], such as hypertension, diabetes, or history of old cerebrovascular accidents, did not show an association with the occurrence of cerebral infarction in the univariate analysis. However, the infarction-only group had a consistently higher proportion of each cardiovascular risk factor than the HIE (−)/infarction (−) group, although there was no statistical difference (Table 1). This observation could be attributed to the small sample size in this study.

According to the TOAST classification [7, 24], all of the infarction cases were found to be related with cardioembolism (two patients with medium-risk potential cardiac sources of embolism). Atrial fibrillation, myocardial infarction, and akinetic/hypokinetic left ventricular segment were found to be the main causes of cardioembolism. Although there were only six patients with vessel studies in whom no stroke-relevant artery stenosis was found, we postulate that cardioembolism is the major mechanism of cerebral infarction in unconscious OHCA patients treated with TTM. It is well known that border zone infarction constitutes approximately 10% of all brain infarction cases; however, it accounted for nearly half of the patients in this study [25, 26]. The external cerebral border zone infarction is mainly caused by embolic pathogenesis, whereas the internal cerebral border zone infarction is related with hemodynamic compromise [25, 26]. The pathomechanism of cerebellar border zone

infarction is known to be either arterial disease or cardioembolism [27, 28]. In this study, all cerebral border zone infarction cases were located in the external border zone, which also highlights the potential causative role of cardioembolic pathogenesis. Although vessel stenosis was not evaluated in most patients, we speculated that both hemodynamic compromise (cardiac arrest itself) and embolism, which were common in unconscious OHCA survivors treated with TTM, might contribute to the frequent occurrence of border zone infarction in this study. A future study that includes cerebral angiography in unconscious OHCA survivors might be needed to thoroughly investigate the pathomechanism of infarction found among them.

Poor clinical outcomes at discharge was highly suspected to be associated with HIE (+) and non-shockable rhythm in the multivariate analyses, which is in line with the results of previous studies [4, 29]. However, unexpectedly, infarction-only did not seem to be associated with a poor outcome in unconscious OHCA survivors who were treated with TTM and underwent MRI. This contradicts that, in general, cerebral infarction is one of the well-established predictors of poor outcomes [30]. There is a possibility that an infarction might be an epiphenomenon of cardiac diseases in unconscious OHCA survivors.

It is difficult to clarify the extent of the relationship between MRI findings and the clinical outcome of unconscious OHCA survivors treated with TTM. Our finding should be interpreted threefold. First, our results concerning the prognostic factors of unconscious OHCA survivors with TTM were consistent with the previous findings. A few researchers suggest that the presence of HIE lesion on MRI is among the most powerful predictors of the clinical outcome in OHCA patients [4]. A study using quantitative DWI MRI showed that decreased ADC value and volume of HIE lesion is correlated with poor prognosis with high specificity [31]. Moreover, it is well known that non-cardiogenic CA and non-shockable rhythm are predictors of poor clinical outcomes [4, 29], which were common in the HIE (+) group in our group comparison. Second, we could not draw a conclusion on whether infarction-only is related with the outcome. The strict definition of cerebral infarction in the current study might have rendered the number of patients insufficient to observe an effect of infarction on the clinical outcome. Similarly, the number of patients in each group might mask the differential relationships of cerebral infarction and HIE. Although not significantly different, the percentage of well-known predictors of poor clinical outcomes, such as non-cardiogenic cause of arrest, non-shockable rhythm, absent PLR, and lower GCS [4, 19, 20, 29], were the highest in the HIE (+) group, followed by the infarction-only group, and the lowest in the HIE (−)/infarction (−) group (Table 1). The proportion of patients with poor clinical outcomes was also decreased in the same order (Fig. 3). This implies the possibility that the difference in occurrence and effect of each condition might be more apparent with a larger number of patients in each group. Third, patients without MRI who were suspected of having a higher burden of cerebral infarction could have been excluded. Although there was no statistical difference in the cardiovascular risk factors between patients who underwent MRI and those who did not (Supplementary Table 1), considering that MRI was not taken in medically unstable patients, there still exists a possibility of excluding an unneglectable number of patients with cerebral infarction, which is probably associated with poor clinical outcomes.

The overall rate of cerebral infarction after PCI is not high, ranging from 0.2 to 0.4% [11, 12, 32]. However, we found that cerebral infarction was relatively common in patients with endovascular procedures (47.8%, Supplementary Table 2). Previous studies reported that the risk factors for the development of post-intervention cerebral infarction were underlying cardiovascular risk factors, urgency of procedures, history of carotid disease, and placement of IABP [11, 32]; all of which could contribute to the more frequent occurrence of procedure-related infarction in our study than in previous reports.

There are several limitations in our study. First, there were only 71 patients included in this pilot study. Given the small sample size, we can only speculate on the implications of the study findings. Larger trials are needed to verify our findings. Second, the included patients were highly selected. Among 156 unconscious OHCA survivors with complete TTM, 62 patients without brain MRI were excluded. Considering this aspect, the results of this study should be interpreted carefully. Third, the diagnosis of cerebral infarction was not fully consistent. Although the inter-rater reliability between the two neurologists showed a substantial strength of agreement [33], distinguishing infarction from HIE was difficult in a few cases. Fourth, we did not evaluate the focal neurologic deficits related to infarction. The CPC used for prognostication and the PLR and GCS used for the neurologic examination due to frequent use of sedatives in the current study approximate the patients' clinical status. However, the lack of a detailed examination of the focal neurologic deficits makes it difficult to predict the impact of infarction on the awakened patients' activities of daily living. Fifth, cerebral vessel imaging studies were not performed in a significant number of patients. They are needed not only to better categorize patients according to the

TOAST classification but also to investigate the association between vessel stenosis and border zone infarction territory [7, 26].

Conclusions

Our pilot study suggests that procedure-unrelated cerebral infarction on MRI was not rarely observed in unconscious OHCA survivors treated with TTM. The major mechanism of infarction could be classified as cardioembolism. Many of these infarction lesions demonstrated a border zone pattern. Older age and history of atrial fibrillation might be associated with the occurrence of procedure-unrelated infarction. Procedure-unrelated infarction did not seem to be associated with poor clinical outcomes at discharge in these highly selected patients, whereas HIE lesion did. These findings must be interpreted carefully because only unconscious OHCA survivors who completed TTM and underwent MRI were included in this study.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s12028-020-00990-8) contains supplementary material, which is available to authorized users.

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Author Contributions
MB participated in the study design, collection and analysis of data, interpretation of results, and drafted and finalized the manuscript. KHC participated in the study design, interpretation of results, and reviewed and provided the final approval of the version to be published. CO participated in the statistical analysis and revision of critical points in the manuscript. YC participated in the study design and collection of data. KMK participated in the collection of data. SSA participated in the analysis of neuroimaging data. DS provided substantial contribution to the study conception and design. JHH, YSP, JW, YSK, and JK participated in the collection of data and reviewed the manuscript.

Source of Support
None.

Data Availability

The datasets for this manuscript are not publicly available because of protection for personal information. Requests to access the datasets should be directed to KC (zhau@yuhs.ac; zhau@naver.com).

Conflict of interest
The authors declare that the research was conducted in the absence of any personal, commercial, or financial relationships that could potentially be construed as a conflict of interest.

Ethical Approval
The study was approved by the institutional review board of Severance Hospital, Yonsei University Health System. Informed consent was waived owing to the retrospective nature of the study.

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