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Severe Cerebral Edema in Substance-Related Cardiac Arrest Patients

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Abstract

Background: Studies of neurologic outcomes have found conflicting results regarding differences between patients with substance-related cardiac arrests (SRCA) and non-SRCA. We investigate the effects of SRCA on severe cerebral edema development, a neuroimaging intermediate endpoint for neurologic injury.

Methods: 327 out-of-hospital comatose cardiac arrest patients were retrospectively analyzed. Demographics and baseline clinical characteristics were examined. SRCA categorization was based on admission toxicology screens. Severe cerebral edema classification was based on radiology reports. Poor clinical outcomes were defined as discharge Cerebral Performance Category scores>3.

Results: SRCA patients (N=86) were younger (P<0.001), and more likely to have non-shockable rhythms (P<0.001), be unwitnessed (P<0.001), lower Glasgow Coma Scale scores (P<0.001), absent brainstem reflexes (P<0.05) and develop severe cerebral edema (P<0.001) than non-SRCA patients (N=241). Multivariable analyses found younger age (P<0.001), female sex (P=0.008), non-shockable rhythm (P=0.01) and SRCA (P=0.05) to be predictors of severe cerebral edema development. Older age (P<0.001), non-shockable rhythm (P=0.02), severe cerebral edema

(P<0.001), and absent pupillary light reflexes (P=0.004) were predictors of poor outcomes. SRCA patients had a higher proportion of brain death (P<0.001) compared to non-SRCA patients.

Conclusions: SRCA results in higher rates of severe cerebral edema development and brain death. The absence of statistically significant differences in discharge outcomes or survival between SRCA and non-SRCA patients may be related to the higher rate of withdrawal of life-sustaining treatment (WLST) in the non-SRCA group. Future neuroprognostic studies may opt to include neuroimaging markers as intermediate measures of neurologic injury which are not influenced by WLST decisions.

Introduction:

Substance use accounts for approximately two-thirds of unintentional overdoses and continues to take many lives each year [1, 2]. Approximately 9.3% of overdoses result in adverse cardiovascular events such as out-of-hospital cardiac arrest (OHCA) [3]. Several studies [4-8] found substance related cardiac arrest (SRCA) patients to be younger, less likely to present with a shockable rhythm, and less likely to have a witnessed arrest. However, prior studies have conflicting results regarding survival, with some showing increased chance of survival [6, 8], and others observing no difference [4, 5, 7].

Survival and discharge outcomes can be biased by variations in withdrawal of life-sustaining treatment (WLST) decisions, which can be influenced by non-neurologic factors [9]. We propose utilizing severe cerebral edema (SCE) as an intermediate objective endpoint related to poor neurologic outcomes to explore the effects of SRCA on the brain. Diffuse cerebral edema is associated with a grim prognosis and poor long-term outcomes [10-12]. The exact mechanism for post-cardiac arrest SCE is not well understood [10-12]. The clinical features associated with early SCE have been investigated [13], but these studies did not focus on SRCA. We hypothesize that the pathophysiologic differences between SRCA and non-SRCA will lead to variable manifestations of SCE, which in turn are associated with poor neurologic outcomes.

Methods:

All analyses were retrospectively performed under local institutional review board approval with waiver of consent (Protocol #2012P000754). Because of the clinical nature of the data, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to Ona Wu (ona.wu@mgh.harvard.edu)

We retrospectively analyzed data from adult OHCA patients (age >= 18 years) admitted to Massachusetts General Hospital (MGH) between 2007 and 2019 whose post-return of spontaneous circulation (ROSC) Glasgow Coma Scale (GCS) scores were consistent with values <= 8. Patients were identified using the Research Patient Data Registry [14] and screening logs from prospective research studies of cardiac arrest patients.

Medical records were reviewed to extract demographic information, to determine whether the arrest was witnessed, and whether the patient underwent targeted temperature management (TTM). Aborted cooling were classified as not TTM treated. Initial arrest type

was classified as either shockable (ventricular tachycardia or ventricular fibrillation) or non-shockable (pulseless electrical activity or asystole). Brainstem reflexes (pupillary, corneal, cough, gag) were extrapolated from the initial neurologic exams. Data were excluded if confounded by sedation. Poor outcomes were defined as discharge Cerebral Performance Category (CPC) score >3 (coma/vegetative state or deceased).

Patients were classified as having an SRCA if one or more of the following criteria were met: drug paraphernalia was present at the scene, witnesses testified to substance use leading up to the cardiac arrest, toxicology screen was positive (based on DSM-5 categories [15], excluding tobacco/caffeine/cannabis) that could not otherwise be explained, or substance use was explicitly stated as a possible etiology of the arrest. Screens were considered positive for alcohol toxicity if the ethanol level was >300 mg/dL. Patients were excluded for the following reasons: positive toxicology screens (opiates/sedatives/stimulants) but cardiac arrest etiology attributed to non-SRCA reason; multiple concomitant acute neurologic conditions (e.g. stroke, hemorrhage, brain tumor or traumatic brain injury); no neuroimaging at MGH.

SCE classifications were made by a reader blinded to SRCA allocation through review of brain CT or MRI reports for explicit mention of herniation, or of more than minimal ventricular effacement. Widespread cortical injury (WCI) was operationally defined as CT hypodensity or T2 hyperintensity on MRI that was attributable to a global hypoxic ischemic event and encompassed more than a single cerebral gyrus or cerebellar folium. For reports that were indeterminate, an experienced neuroradiologist (WAC) blinded to SRCA allocation adjudicated the images. If at least one radiology report was positive for SCE or WCI, patients were considered to have SCE or WCI, respectively. Time-to-SCE and time-to-WCI were calculated as the number of days from arrest to the first report of SCE or WCI, respectively. Subset analyses comparing differences between patients with early (0-1 days post-arrest) and non-early (>1 day) SCE were performed. Similar evaluations were performed for patients with early (0-1 days) and non-early (>1 day) WCI.

Statistical Analyses

Univariable analyses were performed using the Fisher’s Exact Test for categorical variables and the Exact Wilcoxon-Mann-Whitney Test for continuous variables. P-values < 0.05 were considered statistically significant. Subset analyses comparing pooled opioid or sedative (opioid/sedative) related SRCA to non-opioid/sedative-related SRCA were performed. For all multivariable logistic regression analyses, the initial model included demographic information (age, sex) and arrest-related exposure variables (initial rhythm, witnessed arrest and TTM-treatment) known to affect patient outcome. SRCA was included as the primary exposure variable of interest in this study. For poor discharge outcome prediction, we included brain imaging findings, GCS, and brainstem reflexes that were statistically significantly in univariate analyses ($P<0.05$). Variable selection was based on backwards stepwise logistic regression using the Akaike Information Criterion [16]. We compared SCE development between patients with multiple neuroimaging sessions versus single neuroimaging sessions to determine whether multiple imaging sessions influenced SCE detection. Subset analyses were performed for patients who survived to discharge. Causal

mediation analysis (R package mediation version 4.5.0, nonparametric bootstrapping with 100,000 simulations) was used to evaluate the significance of the indirect effects of arrest rhythm on the effects of SRCA on SCE. Statistical analyses were performed using R version 4.0.2 (The R Foundation for Statistical Computing).

Results

Patient Demographics

Records from 729 patients were reviewed. 327 patients met inclusion criteria (see Figure 1). Demographics are shown in Table 1. Of the 86 SRCA patients, 57 were positive for opioids, 34 for sedatives/hypnotics/anxiolytics, 39 for stimulants, 10 for alcohol, 1 for hallucinogens and 14 for other substances. The majority of SRCA cases were polysubstance (N=50). SRCA patients were found to be younger, more likely to have a non-shockable rhythm, and less likely to have a witnessed arrest. No between-group differences were found for sex, TTM treatment, or transfer. SRCA patients had lower post-ROSC GCS scores, were less likely to have brainstem reflexes present, more likely to develop SCE and WCI. Among patients with SCE, time-to-SCE was earlier for patients with only one imaging session compared to patients who underwent multiple sessions (P=0.006) (Supplemental Table 1). However, incidence of SCE development was higher in the SRCA group regardless of whether the patients had multiple (P=0.004) or single (P<0.001) sessions. There were no between-group differences in frequency of poor outcomes and in-hospital mortality. There was a significant difference in cause of death between SRCA and non-SRCA cohorts, with the frequency of brain death higher in the SRCA cohort and WLST higher in the non-SRCA group. Subset analyses comparing opioid/sedative-related SRCA (N=69) to non-opioid/sedative-related SRCA (N=17) showed no statistically significant differences in presentation and imaging findings (Table 2). However, patients with opioid/sedative-related SRCA had higher incidence of poor outcomes than non-opioid/sedative-related SRCA.

Severe Cerebral Edema (SCE) Development

Patients underwent CT (N=160), MRI (N=22) or both (N=145) with median time to first imaging session 0 [0-1] days (Table 1). 72 patients developed SCE. Examples of brain scans with and without SCE are shown in Supplemental Figure 1. Demographic differences between patients with and without SCE are provided in Table 3. Patients with SCE were more likely to be younger and female, have non-shockable rhythm, have SRCA, lower GCS, absent brainstem reflexes, and undergone multiple imaging sessions. They also had worse outcomes, greater in-hospital mortality and died earlier. Brain death rate was higher for the SCE group whereas WLST was higher for the non-SCE cases. Similar results were found for patients with WCI compared to those without (see Table 4), however, patients with WCI were also more likely to have unwitnessed arrests and to have been transferred. WCI was detected later for transferred patients compared to non-transferred patients (3 [2-4] vs 2 [0-3.75] days, P=0.01), likely due to time-to-first scan at the hospital being later for transferred patients (1 [0-3] vs 0 [0-0] days, P<0.001). There were no between-group differences for sex and time-to-death.

Subset analyses between early (N=30) and non-early SCE developers (N=42) (Supplemental Table 2) showed no between-group differences for demographic and baseline information except that time to imaging was earlier in the early SCE group (0 [0-0] vs 1[0-2], P<0.001), and patients in the late group were more likely to undergo multiple imaging studies (P=0.003). In addition, patients with early SCE had earlier deaths (3 [1-4] vs 6 [4-7] days, P<0.001). Patients presenting with early WCI (Supplemental Table 3) were younger (P=0.003), have non-shockable rhythm (P=0.008), have SRCA (P=0.02), less likely to have been transferred (P=0.02), have lower post-ROSC GCS (P=0.01), and less likely to have pupil (P<0.001), corneal (P=0.01) or cough (P=0.04) reflexes. They were also more likely to be imaged earlier (P<0.001) and less likely to have undergone repeat imaging (P<0.003). They were also more likely to have an earlier death (P<0.001), and to die from brain death (P<0.001).

Backwards stepwise logistic regression of a base model involving age, sex, rhythm, SRCA, witnessed arrest and TTM-treatment, resulted in a final model including younger age, female sex, non-shockable rhythm, and SRCA as predictors of SCE development (see Table 3). Significant independent predictors of WCI included younger age, non-shockable rhythm and non-witnessed arrests (Table 4). SRCA (OR 8.66 [3.91 – 19.2, P<0.001) was found to be an independent predictor for non-shockable rhythm controlling for age (OR 1.01 [0.99-1.03] P=0.20) and female sex (OR 2.30 [1.31-4.04], P=0.004). Causal mediation analysis showed that 19% [95% CI 5.0%–40%] of the total effect on SCE was through the effect on rhythm. Controlling for age and sex, the proportion mediated is 27% [95% CI 8.0%–98%] indicating that it was possible that all the effect of SRCA was due to its effect on shockability.

Discharge Outcomes

Demographic differences between patients with favorable (N=89) and poor (N=238) discharge outcomes are shown in Table 5. Post-ROSC GCS scores, pupillary reflexes, cough reflexes, and rates of non-shockable rhythm, SCE, WCI, hospital transfer and TTM treatment were significantly different between outcome groups. Backwards stepwise regression of a base model consisting of age, sex, rhythm, SRCA, witnessed, TTM-treatment, post-ROSC GCS, pupil and cough reflexes and SCE resulted in a final model including older age, non-shockable rhythm, absent pupillary light reflexes, and SCE as significant predictors for poor outcomes with a non-witnessed arrest as a non-significant predictor (see Table 5). Including WCI produced similar findings with a final model with older age (OR 1.06 [1.04-1.08], P<0.001), non-shockable rhythm (OR 2.24 [1.14-4.39], P=0.02), absent pupillary light reflexes (OR 0.39 [0.18-0.83], P=0.015) and WCI (OR 16.1 [6.06-42.58], P<0.001) as significant predictors of poor outcome and SCE (7.51 [0.86-65.71], P=0.07) as a non-significant predictor.

In a separate analysis only including survivors (N = 100), patients with poor outcomes (N = 11) had higher rates of SCE and WCI compared to patients with good outcomes (N = 89) (P < 0.001) (Supplemental Table 4). There was no between-group difference in incidence of SRCA (P = 1.0), GCS (P = 0.71), and brainstem reflexes (P > 0.1). Backward logistic regression of a base model consisting of age, sex, rhythm, SRCA, witnessed, TTM-treatment, and SCE produced a model with only SCE as a significant predictor of

poor outcomes. Repeating analysis including WCI as a covariate resulted in a final model with WCI, SCE and TTM, with only WCI (OR 13.7 [2.54–74.4], P = 0.002) remaining a significant predictor of poor outcomes.

Discussion:

Among cardiac arrest patients initially comatose post-ROSC, SRCA patients are more likely to be younger, have non-shockable rhythms, be unwitnessed, have lower GCS, absent brainstem reflexes, SCE and WCI compared to non-SRCA patients. Furthermore, SRCA patients were more likely to have abnormal findings on early imaging. The higher incidence of SCE in SRCA could be due to the cohort's younger age because SCE is more likely to develop in younger adults [13]. Furthermore, duration of arrest [11, 13], non-shockable rhythm [13] and arrests secondary to respiratory failure [11, 17], which are frequent after opioid overdose [18, 19], have been linked to SCE. In our cohort, we found that SRCA was an independent predictor for non-shockable rhythm, but it is unclear whether or not this was the entire cause of the prevalence of SCE, as the confidence interval on the proportion mediated was 8.0% to 98% when controlling for age and sex.

We observed that females were more likely to have a non-shockable rhythm and develop SCE. Higher rates of non-shockable rhythm in women have been shown previously [20], although the underlying mechanism remains unclear [21]. One prior SCE study did not note a sex-related difference in incidence [13], but that study's definition of SCE was based on the CT-derived ratio of gray-white matter (GWR) of Hounsfield unit values in regions-of-interests drawn in the caudate nucleus and the posterior limb of the internal capsule. We similarly did not find sex as a significant predictor of WCI, suggesting that women may be particularly susceptible to space-occupying cerebral edema whereas WCI is affected primarily by age, arrest duration and non-shockable rhythm as shown in our study and others [13].

Our results support the use of SCE as a neuroimaging intermediate endpoint as an objective measure of neurologic injury. However, the linkage of SCE with neurologic outcomes has not been firmly established [11, 22]. Studies remain few [10, 11, 22, 23] and are often plagued with self-fulfilling prophecy bias [24] in which presence of SCE on imaging may have influenced WLST decisions, including our study. Yet, for survivors, we found that only SCE remained an independent predictor for poor discharge outcome. Furthermore, late SCE was found in 42/72 (58%) of SCE patients, who developed SCE a median of 3 days later. Therefore, SCE may represent an intermediate endpoint that is potentially modifiable by intervention; this needs to be further investigated [10, 11]. Because of our small sample size, between-group differences in baseline presentations between patients who developed early (N=30) and late SCE (N=42) were not found. For early (N=53) vs late (N=110) WCI, we found significant differences, with early developers being younger, having non-shockable rhythms, worse initial neurologic exams and due to SRCA. Future large serial studies are necessary to properly characterize the time course of hypoxic ischemic brain injury.

Our findings of younger age, non-shockable and unwitnessed arrests being more prevalent in SRCA patients are consistent with previous large scale epidemiological studies based

on registries [4-6, 8] and smaller single institution studies [7, 25]. Despite the association between SRCA and a non-shockable rhythm, which confers higher mortality [26], we found no statistically significant difference in discharge outcomes between SRCA and non-SRCA, similar to prior reports [4, 5, 7, 25]. Some investigations have reported SRCA to have a higher survival rate [6, 8], but these studies were not limited to patients who were comatose post-ROSC, and might have included patients who did not have a true cardiac arrest [19]. Differences in our findings from others may be due to our use of a more conservative threshold for poor outcomes (CPC>3, unconscious) compared to studies that used CPC>2 (includes conscious patients with severe disability). We defined poor outcomes as unconsciousness or death prior to discharge because our study was restricted to patients who were comatose after ROSC who would likely take longer to neurologically recover. However, another investigation which involved initially comatose patients, also reported no difference in discharge outcomes [25]. We observed a higher rate of WLST in the non-SRCA cohort, which may be due to their older age. Thus, the worsened neurologic injury experienced by the SRCA cohort might be countered by the higher rates of WLST in the non-SRCA group, perhaps leading to the lack of statistically significant differences in discharge outcomes. Furthermore, our study found a higher incidence of brain death in our SRCA population, similar to a prior report [25], suggesting that SRCA leads to more devastating neurologic insults. This is supported by our SCE and WCI findings and worse initial neurological status.

Our study has several potential limitations. This is a retrospective, single center study in which data was extracted from medical records. Restricting the study to cardiac arrest patients surviving to emergency department arrival or hospital admission may have led to higher overall survival rate compared to epidemiological studies. Our study also did not differentiate between opioid-related SRCA and non-opioid SRCA since the majority of SRCA patients in our study were positive for multiple drug classes, as is typical for this population [19]. Subset analyses pooling opioid/sedative classes did not show significant differences between opioid/sedative SRCA and non-opioid/sedative SRCA except in frequency of poor outcomes. The lack of statistical significance in other variables is likely due to the small sample sizes involved. Future larger studies are needed to address the question whether opioid/sedative SRCA have different outcomes compared to other drug classes.

Another possible limitation of our study is that SCE and WCI classifications were based on radiology reports. We sought to mitigate potential bias by focusing on SCE cases where herniation or ventricular effacement were noted. The strength of this definition is that it is equally applicable to CT and MRI. Previous studies have defined SCE based on GWR thresholds on initial CT [23, 27]. However, no equivalent definitions or thresholds have been reported for MRI. Furthermore, these thresholds are variable across studies and affected by imaging equipment [28, 29]. For these reasons, we based our definition of SCE on findings of herniation and ventricular effacement.

Since our definition of SCE was very conservative, which was a priori chosen to err on the side of specificity for a marker of poor neurologic outcome, we also investigated qualitative assessments for WCI which are likely more sensitive for detection of brain

injury but are more susceptible to greater interrater variability. In contrast to our definition for SCE, definitions for WCI by necessity were different for CT and MRI. We used precise operational definitions for classification to mitigate this variability. Furthermore, WCI reported on neuroimaging may represent a range of pathologies including infarction, dysmyelination and superimposed vasogenic edema [30]. Future studies using quantitative methods based on manually drawn regions of interests [23, 27] and automated methods [31, 32] similar to our previous work [31] might provide additional insight with regards to WCI. As these techniques require sophisticated software or machine learning algorithms, and therefore are harder to incorporate into routine clinical practice, we opted to rely on radiology reported findings as a pragmatic approach.

Our study is also limited by its inability to account for neurologic improvements that occurs following discharge. This shortcoming should be mitigated by our relatively conservative definition of poor neurologic outcome (CPC>3), compared to other studies that have used CPC>2. Another potential confounding factor is that many of the patients included in our study were transferred for advanced management since our hospital is a tertiary care center. It is possible that the patients in our population were more critically ill compared to the general population. We did not find a significant difference in the proportions of transferred subjects among SCE vs non-SCE, however, there was a higher proportion of transferred patients in the WCI vs. non-WCI. Finally, prolonged hypercarbia, particularly with opiates/sedatives, may have been an uncontrolled contributor to SCE, although this was likely corrected quickly after intubation and mechanical ventilation.

Conclusions

SRCA patients were more likely to experience non-shockable rhythms, present with worse neurologic status and exhibit SCE and WCI during their hospitalization. These are all associated with poor neurologic outcomes. There was no statistically significant difference in discharge outcomes between SRCA and non-SRCA patients, which might have been related to variations in WLST decisions. However, SRCA patients had a higher incidence of brain death compared to non-SRCA patients. Prospective multi-center observational studies with standardized imaging and neurologic assessments are needed to improve our understanding of the mechanisms of SCE and brain injury development after SRCA, which may in turn aid the creation of treatment strategies that improve neurologic outcomes in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

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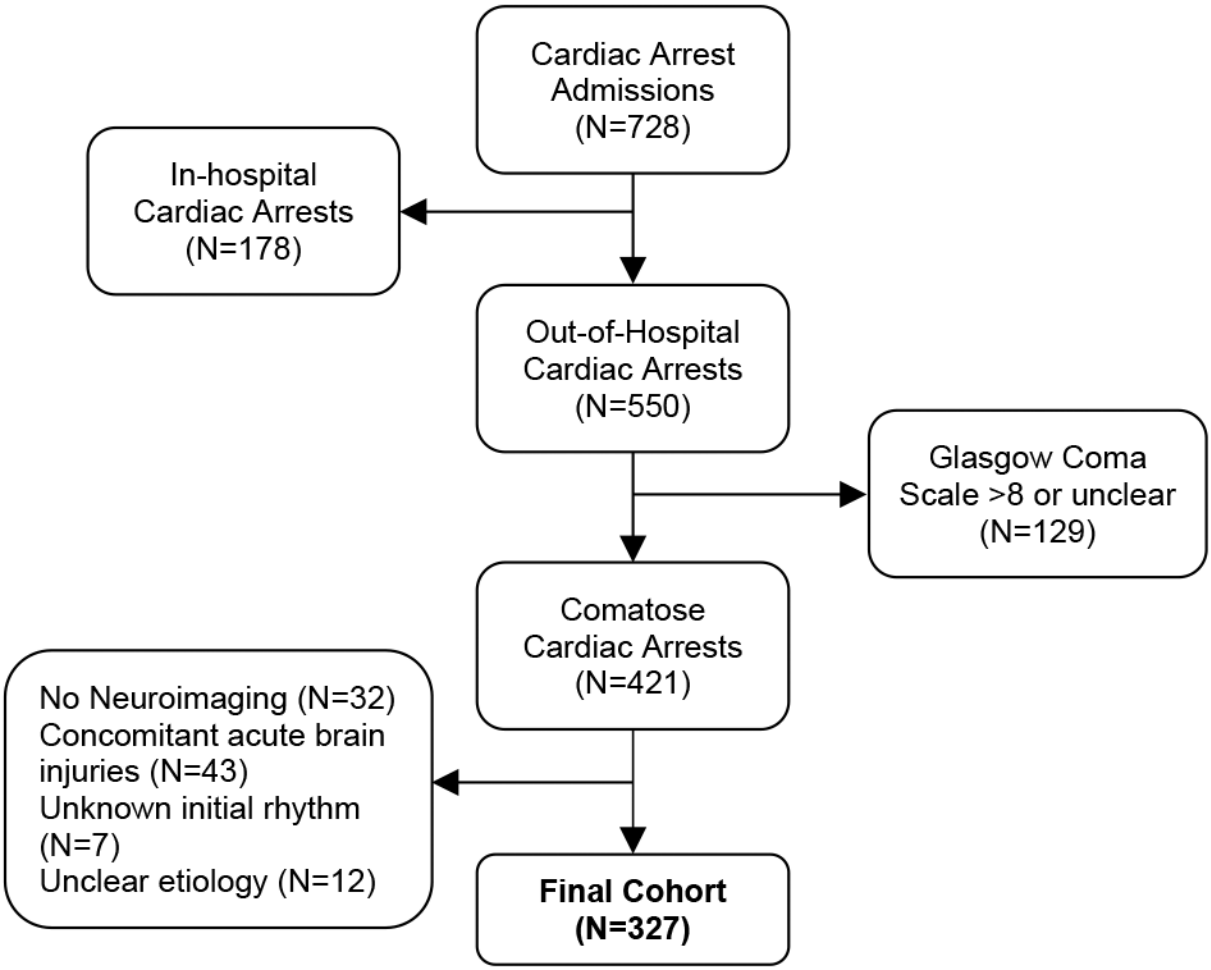

Figure 1:
Flow Diagram Illustrating the Patient Population

Table 1:

Comparison of Substance Related Cardiac Arrests to Non-Substance Related Cardiac Arrests

	Total Arrests (N=327)	Substance Related (N=86)	Non-Substance Related (N=241)	P-Value
Age, years	55 ± 18	42 ± 13	60 ± 17	**P < 0.001**
Sex, female (%)	95/327 (29%)	25/86 (29%)	70/241 (29%)	P = 1.0
Non-Shockable rhythm, yes (%)	210/327 (64%)	77/86 (90%)	133/241 (55%)	**P < 0.001**
TTM, yes (%)	272/327 (83%)	72/86 (84%)	200/241 (83%)	P = 1.0
Target temperature				
33° C	245/272 (90%)	70/72 (97%)	175/200 (88%)	
34° C	2/272 (0.7%)	0/72 (0.0%)	2/200 (1.0%)	
36° C	17/272 (6.3%)	2/72 (2.8%)	15/200 (7.5%)	
33/36° C	4/272 (1.5%)	0/72 (0.0%)	4/200 (2.0%)	
NR	4/272 (1.5%)	0/72 (0.0%)	4/200 (2.0%)	
Witnessed, yes (%)	208/327 (64%)	32/86 (37%)	176/241 (73%)	**P < 0.001**
Hospital Transfer, yes (%)	124/327 (38%)	25/86 (29%)	99/241 (41%)	P = 0.053
Reason				
Advanced Management	87/124 (70%)	22/25 (88%)	65/99 (66%)	
Family Request	17/124 (14%)	0/25 (0%)	17/99 (17%)	
No available beds	7/124 (5.6%)	2/25 (8%)	5/99 (5%)	
Not Documented	13/124 (10%)	1/25 (4%)	12/99 (12%)	
Post-ROSC GCS, median [IQR]	3 [3-4] (N=295)	3 [3-3] (N=81)	3[3-5] (N=214)	**P < 0.001**
Pupillary Light Reflex, present (%)	161/286 (56%)	29/76 (38%)	132/210 (63%)	**P < 0.001**
Corneal Reflex, present (%)	60/266 (23%)	8/73 (11%)	52/193 (27%)	**P = 0.005**
Cough reflex, present (%)	80/217 (37%)	15/63 (24%)	65/154 (42%)	**P = 0.01**
Gag reflex, present (%)	97/241 (40%)	20/69 (29%)	77/172 (45%)	**P = 0.03**
Imaging				
Time-to-first scan, days median [IQR]	0 [0-1]	0 [0-1]	0 [0-1]	P = 0.34
Multiple scans, yes(%)	210/327 (64%)	64/86 (74%)	146/241 (61%)	**P = 0.03**
Severe Cerebral Edema, yes (%)	72/327 (22%)	36/86 (42%)	36/241 (15%)	**P < 0.001**
Time-to-Severe edema, days median [IQR]	2 [0-3] (N=72)	2 [0-3] (N=36)	2 [0.75-3] (N=36)	P = 0.32
Early Severe Cerebral Edema, yes (%)	30/327 (9%)	17/86 (20%)	13/241 (5%)	**P < 0.001**
Cortical injury, yes (%)	163/327 (50%)	62/86 (72%)	101/241 (42%)	**P < 0.001**
Time-to-Cortical Injury, days median [IQR]	3 [1-4] (N=163)	2 [0-3.75] (N=62)	3 [1-4] (N=101)	**P = 0.03**
Early Cortical Injury, yes (%)	53/327 (16%)	27/86 (31%)	26/241 (11%)	**P < 0.001**
Outcomes				
Poor outcome, yes (%)	238/327 (73%)	67/86 (78%)	171/241 (71%)	P = 0.26
In-hospital death, yes (%)	227/327 (69%)	65/86 (76%)	162/241 (67%)	P = 0.17
Cause of Death:				**P < 0.001**
Brain Death (%)	16/227 (7.0%)	12/65 (18%)	4/162 (2.5%)	**P < 0.001**

	Total Arrests (N=327)	Substance Related (N=86)	Non-Substance Related (N=241)	P-Value
Cardiac Death (%)	9/227 (4.0%)	2/65 (3.1%)	7/162 (4.3%)	P = 1.0
WLST (%)	202/227 (89%)	51/65 (78%)	151/162 (93%)	**P = 0.004**
Time to death, days median [IQR]	5 [3-8] (N=227)	5 [3-7] (N=65)	5 [3-8] (N=162)	P = 0.57

GCS = Glasgow Coma Scale, NR = Not Reported, ROSC = Return of Spontaneous Circulation, TTM = Targeted Temperature Management, WLST = Withdrawal of Life Sustaining Treatment.

Table 2:

Comparison of SRCA patients due to opioids/sedatives versus other substance-related cardiac arrests.

	Opioid/Sedative Related (N=69)	Not Opioid/Sedative Related (N=17)	P-Value
Age, years	42 ± 13	40 ± 16	P = 0.52
Sex, female (%)	21/69 (30%)	4/17 (24%)	P = 0.77
Non-Shockable rhythm, yes (%)	62/69 (90%)	15/17 (88%)	P = 1.0
TTM, yes (%)	57/69 (83%)	15/17 (88%)	P = 0.73
Witnessed, yes (%)	24/69 (35%)	8/17 (47%)	P = 0.41
Hospital Transfer, yes (%)	17/69 (25%)	8/17 (47%)	P = 0.08
Post-ROSC GCS, median [IQR]	3 [3-3] (N=66)	3 [3-3] (N=15)	P = 0.77
Pupillary Light Reflex, present (%)	21/63 (33%)	8/13 (62%)	P = 0.07
Corneal Reflex, present (%)	8/60 (13%)	0/13 (0%)	P = 0.34
Cough reflex, present (%)	11/50 (22%)	4/13 (31%)	P = 0.49
Gag reflex, present (%)	17/58 (29%)	3/11 (27%)	P = 1.00
Imaging			
Time-to-first scan, days median [IQR]	0 [0-1]	0 [0-1]	P = 0.45
Multiple scans, yes (%)	51/69 (74%)	13/17 (76%)	P = 1.00
Severe Cerebral Edema, yes (%)	31/69 (45%)	5/17 (29%)	P = 0.28
Time-to-Severe edema, days median [IQR]	2 [0-3] (N=31)	2 [0-3] (N=5)	P = 1.00
Early Severe Cerebral Edema, yes (%)	15/69 (22%)	2/17 (12%)	P = 0.50
Cortical injury, yes (%)	51/69 (74%)	11/17 (65%)	P = 0.55
Time-to-Cortical Injury, days median [IQR]	2 [0-3] (N=51)	3 [1-4.5] (N=11)	P = 0.24
Early Cortical Injury yes (%)	23/69 (33%)	4/17 (24%)	P = 0.56
Outcomes			
Poor outcome, yes (%)	57/69 (83%)	10/17 (59%)	**P = 0.0497**
In-hospital death, yes (%)	55/69 (80%)	10/17 (59%)	P = 0.11
Cause of Death:			
Brain Death (%)	11/55 (20%)	1/10 (10%)	P = 0.67
Cardiac Death (%)	2/55 (3.6%)	0/10 (0%)	P = 1.0
WLST (%)	42/55 (76%)	9/10 (90%)	P = 0.68
Time to death, days median [IQR]	5 [3-7] (N=55)	5 [4-6] (N=10)	P = 0.79

GCS = Glasgow Coma Scale, NA = Not Applicable, NS = Not selected variable, ROSC = Return of Spontaneous Circulation, TTM = Targeted Temperature Management, WLST = Withdrawal of Life Sustaining Treatment.

Table 3:

Comparison of Patients with and without severe cerebral edema neuroimaging findings. 72 patients had severe cerebral edema with 49 identified on CT, 7 on MRI and 16 on both modalities. The odds ratios are provided for variables included in the final multivariable model predicting severe cerebral edema. * Not included in final multivariable model.

	Severe Cerebral Edema (N=72)	No Severe Cerebral Edema (N=255)	P-Value	Multivariable OR	P-value
Age, years	45±17	58±17	**P < 0.001**	0.97 [0.95-0.98]	**P<0.001**
Sex, female (%)	31/72 (43%)	64/255 (25%)	**P = 0.005**	2.26 [1.24-4.12]	**P = 0.008**
Non-Shockable rhythm, yes (%)	60/72 (83%)	150/255 (59%)	**P < 0.001**	2.58 [1.24-5.38]	**P = 0.01**
TTM, yes (%)	59/72 (82%)	213/255 (84%)	P = 0.72	NS*	NS*
Witnessed, yes (%)	40/72 (56%)	168/255 (66%)	P = 0.13	NS*	NS*
Substance-related cardiac arrest, yes (%)	36/72 (50%)	50/255 (20%)	**P < 0.001**	1.94 [1.00-3.76]	**P = 0.0496**
Hospital Transfer, yes (%)	31/72 (43%)	93/255 (36%)	P = 0.34	NA*	NA*
Post-ROSC GCS, median [IQR]	3 [3-3] (N=66)	3 [3-5] (N=229)	**P < 0.001**	NA*	NA*
Pupillary Light Reflex, present (%)	15/61 (25%)	146/225 (65%)	**P < 0.001**	NA*	NA*
Corneal Reflex, present (%)	6/58 (10%)	54/208 (26%)	**P = 0.01**	NA*	NA*
Cough reflex, present (%)	10/45 (22%)	70/172 (41%)	**P = 0.02**	NA*	NA*
Gag reflex, present (%)	13/49 (27%)	84/192 (44%)	**P = 0.03**	NA*	NA*
Imaging					
Time-to-first scan, days, median [IQR]	0 [0-1]	0 [0-1]	P = 0.75	NA*	NA*
Multiple scans, yes (%)	56/72 (78%)	154/255 (60%)	**P = 0.008**	NA*	NA*
Outcomes					
Poor outcome, yes (%)	71/72 (99%)	167/255 (65%)	**P < 0.001**	NA*	NA*
In-hospital Death, yes (%)	67/72 (93%)	160/255 (63%)	**P < 0.001**	NA*	NA*
Cause of Death					
Brain Death	14/67 (21%)	2/160 (1.3%)	**P < 0.001**	NA*	NA*
Cardiac Death	3/67 (4.5%)	6/160 (3.8%)	P = 0.73	NA*	NA*
WLST	50/67 (75%)	152/160 (95%)	**P < 0.001**	NA*	NA*
Time-to-death (N=227), days, median [IQR]	4 [3-6] (N=67)	5 [3-9.25] (N=160)	**P = 0.03**	NA*	NA*

GCS = Glasgow Coma Scale, NA = Not Applicable, NS = Not Selected variable, ROSC = Return of Spontaneous Circulation, TTM = Targeted Temperature Management, WLST = Withdrawal of Life Sustaining Treatment.

Table 4:

Comparison of Patients with and without widespread cortical injury findings. 163 patients had widespread cortical injury with 64 identified on CT, 60 on MRI and 39 on both. The odds ratios are provided for variables included in the final multivariable model predicting widespread cortical injury. * Not included in final multivariable model.

	Widespread Cortical Injury (N=163)	No Widespread Cortical Injury (N=164)	P-Value	Multivariable OR	P-Value
Age, years	50±16	61±17	**P < 0.001**	0.96 [0.95-0.98]	**P < 0.001**
Sex, female (%)	54/163 (33%)	41/164 (25%)	P = 0.11	NS*	NS*
Non-Shockable rhythm, yes (%)	119/163 (73%)	91/164 (55%)	**P = 0.001**	2.0 [1.23-3.27]	**P = 0.005**
TTM, yes (%)	133/163 (82%)	139/164 (85%)	P = 0.46	NS*	NS*
Witnessed, yes (%)	88/163 (54%)	120/164 (73%)	**P < 0.001**	0.53 [0.32-0.86]	**P = 0.01**
Substance-related cardiac arrest, yes (%)	62/163 (38%)	24/164 (15%)	**P < 0.001**	NS*	NS*
Hospital transfer, yes (%)	77/163 (47%)	47/164 (29%)	**P < 0.001**	NA*	NA*
Post-ROSC GCS (N=295), median [IQR]	3 [3-3] (N=144)	3 [3-5] (N=151)	**P < 0.001**	NA*	NA*
Pupillary Light Reflex, present (%)	54/135 (40%)	107/151 (71%)	**P < 0.001**	NA*	NA*
Corneal Reflex, present (%)	21/125 (17%)	39/141 (28%)	**P = 0.04**	NA*	NA*
Cough reflex, present (%)	28/100 (28%)	52/117 (44%)	**P = 0.02**	NA*	NA*
Gag reflex, present (%)	34/113 (30%)	63/128 (49%)	**P = 0.004**	NA*	NA*
Imaging					
Time-to-first scan, days, median [IQR]	0 [0-1]	0 [0-1]	P = 0.08	NA*	NA*
Multiple scans, yes (%)	131/163 (80%)	79/164 (48%)	**P < 0.001**	NA*	NA*
Outcomes					
Poor outcome, yes (%)	152/163 (93%)	86/164 (52%)	**P < 0.001**	NA*	NA*
In-hospital death, yes (%)	144/163 (88%)	83/164 (51%)	**P < 0.001**	NA*	NA*
Cause of Death					
Brain Death	16/144 (11%)	0/83 (0%)	**P < 0.001**	NA*	NA*
Cardiac Death	5/144 (3.5%)	4/83 (4.8%)	P = 0.73	NA*	NA*
WLST	123/144 (85%)	79/83 (95%)	P = 0.03	NA*	NA*
Time to death (N=227), days median [IQR]	5 [3-7] (N=144)	5 [2-9.5] (N=83)	P = 0.40	NA*	NA*

GCS = Glasgow Coma Scale, NA = Not Applicable, NS = Not Selected variable, ROSC = Return of Spontaneous Circulation, WLST = Withdrawal of Life Sustaining Treatment.

Table 5:

Comparison of patients with favorable (CPC<=3) versus poor (CPC>3) outcomes. The odds ratios are provided for variables included in the final multivariable model predicting poor outcome. *Not included in final multivariable model.

	CPC Good (N=89)	CPC Poor (N=238)	P-Value	Multivariable OR	P-Value
Age, years	52±17	56±18	P = 0.09	1.04 [1.02-1.06]	**P < 0.001**
Sex, female (%)	20/89 (22%)	75/238 (32%)	P = 0.13	NS*	NS*
Non-Shockable rhythm, yes (%)	39/89 (44%)	171/238 (72%)	**P < 0.001**	2.10 [1.14-3.84]	**P = 0.02**
TTM, yes (%)	80/89 (90%)	192/238 (81%)	**P = 0.048**	NS*	NS*
Witnessed, yes (%)	64/89 (72%)	144/238 (61%)	P = 0.07	0.61 [0.32-1.20]	P = 0.15*
Substance-related cardiac arrest, yes (%)	19/89 (21%)	67/238 (28%)	P = 0.26	NS*	NS*
Hospital Transfer, yes	25/89 (28%)	99/238 (42%)	**P = 0.03**	NA*	NA*
Post-ROSC GCS (N=295), median [IQR]	3 [3-6] (N=81)	3 [3-3] (N=214)	**P < 0.001**	NS*	**NS***
Pupillary Light Reflex, present (%)	65/82 (79%)	96/204 (47%)	**P < 0.001**	0.37 [0.19-0.72]	**P = 0.004**
Corneal Reflex, present (%)	19/77 (25%)	41/189 (22%)	P = 0.63	NA*	NA*
Cough reflex, present (%)	35/67 (52%)	45/150 (30%)	**P = 0.002**	NS*	NS*
Gag reflex, present (%)	32/66 (48%)	65/175 (37%)	P = 0.14	NA*	NA*
Imaging					
Time-to-first scan, days median [IQR]	0 [0-1]	0 [0-1]	P = 0.83	NA*	NA*
Severe Cerebral Edema, yes (%)	1/89 (1.1%)	71/238 (30%)	**P < 0.001**	35.7 [4.60–276.67]	**P < 0.001**
Cortical Injury, yes (%)	11/89 (12%)	152/238 (64%)	**P < 0.001**	NA*	NA*

GCS= Glasgow Coma Scale, NA=Not applicable, NS=Not selected variable, ROSC= Return of Spontaneous Circulation, TTM=Targeted Temperature Management