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Arrest etiology among patients resuscitated from cardiac arrest

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Abstract

Introduction: Cardiac arrest etiology is often assigned according to the Utstein template, which differentiates medical (formerly “presumed cardiac”) from other causes. These categories are poorly defined, contain within them many clinically distinct etiologies, and are rarely based on diagnostic testing. Optimal clinical care and research require more rigorous characterization of arrest etiology.

Methods: We developed a novel system to classify arrest etiology using a structured chart review of consecutive patients treated at a single center after in- or out-of-hospital cardiac arrest over four years. Two reviewers independently reviewed a random subset of 20% of cases to calculate interrater reliability. We used χ^2 and Kruskal-Wallis tests to compare baseline clinical characteristics and outcomes across etiologies.

Results: We identified 14 principal arrest etiologies, and developed objective diagnostic criteria for each. Inter-rater reliability was high ($\kappa = 0.80$). Median age of 986 included patients was 60 years, 43% were female and 71% arrested out-of-hospital. The most common etiology was respiratory failure (148 (15%)). A minority (255 (26%)) arrested due to cardiac causes. Only nine (1%) underwent a diagnostic workup that was unrevealing of etiology. Rates of awakening and survival to hospital discharge both differed across arrest etiologies, with survival ranging from 6% to 60% (both $P < 0.001$), and rates of favorable outcome ranging from 0% to 40% ($P < 0.001$). Timing and mechanism of death (e.g. multisystem organ failure or brain death) also differed significantly across etiologies.

Conclusions: Arrest etiology was identifiable in the majority cases via systematic chart review. “Cardiac” etiologies may be less common than previously thought. Substantial clinical

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heterogeneity exists across etiologies, suggesting previous classification systems may be insufficient.

Keywords

Cardiac arrest; post-arrest; etiology; epidemiology; outcomes

Introduction

Cardiac arrest is defined by cessation of circulation, and can result from many different disease processes, injuries or circumstances. Much of the literature sorts cardiac arrest into medical and non-medical causes,[1] previously referred to as “presumed cardiac” and “noncardiac” causes.[2] These categories are poorly defined, contain within them many different etiologies, and are usually assigned based on prehospital data without the benefit of diagnostic testing. A default value of medical (or presumed cardiac) is typically assigned if no readily apparent cause of arrest is identified. Medical treatment of patients who are resuscitated from cardiac arrest should be adapted to the particular disease process or etiology that led to cardiac arrest. Different interventions may be beneficial for cardiac arrest from one medical etiology (e.g. anticoagulation for thromboembolic disease) and inert or harmful in another (e.g. sepsis or gastrointestinal bleeding). Similarly chances of awakening from coma, survival, functionally favorable recovery or other important patient-centered outcomes such as coma duration or hospital length of stay may differ substantially depending on the cause of arrest. From the perspective of clinical research, unmeasured heterogeneity may increase the chance of neutral results. For example, a trial of cardiac catheterization after arrest from “presumed cardiac” causes might maximize its effect size by enrollment of patients with acute coronary syndrome, whereas enrolling patients with congenital heart disease might reduce the effect size. Titrating clinical care, public health efforts, and selection of appropriate subjects for clinical trials requires more rigorous characterization of cardiac arrest etiology.

To address this need for patients hospitalized after cardiac arrest, we sought to develop a method to define cardiac arrest etiology using available clinical information in a structured and reproducible manner that could be used by other investigators or sites, thus allowing between-center comparisons of similar patients. We hypothesized that most patients could be assigned to well-defined categories that were meaningful to clinicians who care for these patients and clinical researchers. We secondarily aimed to report the frequency of different etiologies among a large cohort of patients, and compare clinical characteristics and patient outcomes across etiologies.

Methods

Study design and setting

We used a modified Delphi process to develop a novel arrest etiology classification system (see below). After finalizing our classification rubric, we performed a structured chart review of consecutive patients treated at a single academic medical center after resuscitation from in- or out- of-hospital cardiac arrest from February 15, 2012 to February 15, 2016. This

center is a tertiary care referral center with an organized Post-Cardiac Arrest Service involved in clinical care, resuscitation research and ongoing quality improvement, as has been previously described in detail.[3, 4] We defined “cardiac arrest” as a patient who received chest compressions or defibrillation from a medical provider or a rescue shock from an automated external defibrillator, and included patients with return of spontaneous circulation (ROSC) for at least 20 minutes. Our Institutional Review Board approved all aspects of this study with a waiver of informed consent.

Classification system development

Our first step was to perform a literature review and 1 on 1 interview with sixteen content experts to develop an exhaustive list of potential arrest etiologies and potential working definitions of each. Participants included members of the Pittsburgh Post-Cardiac Arrest Service trained in emergency medicine and/or critical care medicine, interventional cardiologists, cardiac intensivists, neuro-intensivists and intensive care unit (ICU) nurses in the cardiac and neuroscience ICUs. Our initial list of potential arrest etiologies included 34 potential etiologies of cardiac arrest. We then used a modified Delphi process in which we asked participants to rank the importance of each category, propose revisions and group similar etiologies together when clinical heterogeneity was thought to be unimportant. We iteratively held a total of 6 meetings until consensus on a final list of arrest etiologies and broad definitions was reached. Finally, we developed precise criteria to rule in, rule out, or suggest each etiology, and a framework for structured chart review, both of which we presented at a final meeting for approval of the entire working group. Ultimately, this process resulted in 14 well-defined etiologies of cardiac arrest (Table 1, Figure 1) with associated objective diagnostic criteria (Supplemental Appendix 1) and a reproducible workflow for structured chart review (Figure 2). Arrest was only considered secondary to respiratory failure when primary pulmonary pathology (e.g. hypoxia or hypercarbia due to exacerbation of asthma, chronic obstructive pulmonary disease or multifocal pneumonia) led to respiratory failure. In arrests where respiratory failure occurred secondary to an extrinsic cause (e.g. left ventricular failure causing pulmonary edema, pulmonary embolism, or opioid overdose), the inciting cause was considered the etiology of arrest (in those examples, left ventricular failure, right ventricular failure or toxicological etiology, respectively).

Etiology measurement

We performed a structured chart review to extract results of: chest imaging (roentgenogram, computerized tomography (CT) and bronchoscopy); electrocardiograms; cardiac catheterization; echocardiography; cardiac magnetic resonance imaging (MRI); CT angiography for pulmonary embolism; CT or MRI of the brain; electrophysiology studies; vascular duplex ultrasound; urine drug screens; serum glucose, troponin, magnesium, and potassium levels; and attending physician impression as documented in daily progress notes during the index admission. We collected data for each patient in a standardized template built in REDCap. If multiple providers from different specialties provided differing accounts of the pre-arrest history, these details were not used in the categorization of etiology. We classified patients as having a given arrest etiology if they met rule-in criteria for only that single etiology. Patients who had findings suggestive of multiple etiologies were categorized as unknown.

Clinical covariates and outcomes

We used our prospective registry to abstract patient demographics including age, gender, arrest location, initial arrest rhythm and Pittsburgh Cardiac Arrest Category (PCAC). PCAC is a validated 4-level ordinal scale modeling post-arrest illness severity that is strongly predictive of outcomes at hospital discharge.[5, 6] Outcomes were survival to hospital discharge, discharge disposition (home, acute rehabilitation, skilled nursing facility, long-term acute care facility, hospice or death) and time to awakening. We considered patients to have a favorable functional outcome at hospital discharge if they were discharged to home or acute rehabilitation. Among nonsurvivors, we also abstracted the mode of death, which we categorized as withdrawal based on perceived poor neurological prognosis; progression to brain death; rearrest, intractable shock or other non-survivable extra-cerebral organ failure; or, withdrawal based on non-neurological factors (e.g. preexisting advanced directives or advanced pre-arrest comorbidities).

Statistical methods

We used descriptive statistics to summarize baseline population characteristics and outcomes. We used Chi2 tests to compare categorical variables across arrest etiologies and Kruskal-Wallis tests to compare continuous variables across etiologies, and report Bonferroni-corrected P values to correct for account comparisons. Next, we compared clinical characteristics and outcomes restricted to arrest etiologies that would be considered medical (or presumed cardiac) under the Utstein template to test for heterogeneity across these etiologies. Two reviewers independently abstracted data and assigned arrest etiology on a random subset of 20% of cases and we calculated inter-rater reliability within this subset. Cases of disagreement were reclassified as having multiple possible etiologies. We used Stata Version 14.2 (StataCorp, College Station, TX) for all analyses.

Results

Cohort characteristics

Overall, there were 1006 patients who presented during the 4-year study period. Of these, 24 patients were determined on chart review not to have suffered a true cardiac arrest or did not have ROSC, and were therefore excluded, leaving 982 patients in our final cohort. Median age was 60 years [interquartile range (IQR) 49 – 71] and 418 (43%) were female (Table 2). Only 291 patients (30%) had an initial shockable rhythm, with 397 (40%) pulseless electrical activity, 217 (22%) asystole, and the remaining 77 (8%) unknown. Most subjects 694 (71%) arrested out of hospital. When graded on initial illness severity, 210 (21%) were PCAC I (awake in the first 6 hours after ROSC), 154 (16%) were PCAC II (light coma without severe cardiopulmonary dysfunction), 93 (7%) were PCAC III (light coma with severe cardiopulmonary dysfunction), 444 (45%) were PCAC IV (deep coma with loss of some brainstem reflexes) and in 81 (8%) PCAC could not be determined because of uncorrectable confounders or delayed presentation.

Of the 771 patients that were initially comatose, 204 (26%) awakened from coma to follow verbal commands. Survival to hospital discharge was 39%, and 236 (24% overall, 62% of survivors) were discharged with functionally favorable outcomes. Among non-survivors, 268

(45%) had life-sustaining therapy withdrawn for perceived poor neurological prognosis, 50 (8%) progressed to brain death, 72 (12%) had withdrawal of life-sustaining therapy for non-neurological reasons, and 212 (35%) succumbed to multisystem organ failure, intractable shock or rearrest.

Arrest etiologies

The most common single etiology of arrest was respiratory failure (148 (15%)), with an additional 54 (6%) of arrests due to focal upper airway obstruction (Table 1). A minority of subjects (255 (26%)) had an arrest etiology attribute to cardiac causes, of which most (135/255 (53%); 12% of overall patients) were acute coronary syndrome. Only nine subjects (1%) underwent a diagnostic workup for arrest etiology that was unrevealing, while 74 (7%) did not undergo a diagnostic workup (Table 1). Of these 83 subjects with unknown arrest etiologies, most (58%) rearrested, progressed to brain death or had limitations of care because of pre-existing advanced directives within 24 hours of admission. The incidence of unknown arrest etiologies did not differ by arrest location ($P=0.11$). There were 169 subjects (17%) that met diagnostic criteria for more than one arrest etiology (Table 1, Supplemental Appendix 2). Among those meeting criteria for two arrest etiologies, the most common combinations were acute coronary syndrome with arrhythmia secondary to cardiomyopathy, and respiratory failure with other well-defined etiology, each accounting for 9% of these 116 cases (Supplemental Appendix 2). Inter-rater reliability was high ($\kappa = 0.80$). In cases of disagreement, most (65%) occurred when one adjudicator judged there to be two potential arrest etiologies while the other adjudicator felt only one of these etiologies was likely.

Clinical characteristics and outcomes across etiologies

Nearly all baseline clinical characteristics and outcomes differed significantly across arrest etiologies (Table 3). Among etiologies with at least 10 subjects, rates of awakening from coma and survival to hospital discharge both ranged from 6% to 60% (both $P < 0.001$), and rates of favorable outcome at discharge ranged from 0% to 40% ($P < 0.001$). Nearly one third of decedents with a toxicological or neurological etiology of arrest progressed to brain death, while only 2% of patients with respiratory failure and no patients with acute coronary syndrome progressed to brain death ($P < 0.001$). By contrast, the majority of decedents who arrested secondary to left ventricular failure, exsanguination, or other well-defined etiologies of arrest not included in other categories succumbed to rearrest, intractable shock or multisystem organ failure ($P < 0.001$).

Among the 338 patients with etiologies likely to have been classified as medical under the Utstein template (acute coronary syndrome, intrinsic arrhythmia, arrhythmia secondary to cardiomyopathy, structural heart disease, left ventricular failure, right ventricular failure and unknown), 236 (70%) were initially comatose, and of these rates of awakening from coma differed significantly across etiologies (range 13% to 100%, $P < 0.001$). Of these 338 subjects, survival to discharge differed (range 16% to 60%, $P < 0.001$), as did functionally favorable survival (range 9% to 100%, $P < 0.001$). Clinical outcomes also differed across etiologies when restricted to the subset of patients with non-medical (not “presumed cardiac”) etiologies under the Utstein template. Survival to discharge ranged from 6% to 50% ($P = 0.01$) while functionally favorable survival ranged from 0% to 28% ($P = 0.01$).

Discussion

We present a novel system to classify cardiac arrest etiology in the cohort of patients surviving to hospital care after resuscitation from cardiac arrest. Using our rubric, most patients had a well-defined etiology of arrest. Our system includes seven etiologies that historically have been grouped together as medical (or presumed cardiac) etiologies, as well as seven other etiologies deemed to be clinically important. We observed a 10-fold difference in the rates of awakening and survival to discharge across etiologies, and even greater differences in incidence of rearrest and brain death. The National Academies of Medicine has highlighted post-arrest care and personalized medicine as research priorities. [7] Our classification method builds towards these priorities by capturing an important source of between patient heterogeneity that has frequently been overlooked. We believe this methodology has immediate relevance to clinical practice, epidemiological research and the design and conduct of resuscitation trials.

The Utstein style of reporting has largely defined standard terminology and reporting in resuscitation. This influential consensus recommendation initially dichotomized arrest etiology as “presumed cardiac” or “non-cardiac,” specifying that cases in which the arrest etiology is not readily apparent classified as presumed cardiac.[2] In subsequent updates, “presumed cardiac” etiologies were reclassified as “medical,” while “non-cardiac” etiologies were further stratified as trauma, drowning, overdose, electrocution and asphyxial.[1] The template is optimized for performance in the prehospital setting, where many diagnostic modalities are unavailable and a minority of patients achieves ROSC. As such, under this system most cases are classified as medical (or presumed cardiac) arrests.[8–10] At the same time, the incidence of cardiac arrest acute coronary syndrome and structural heart disease continues to decrease, while arrests due to opioid overdose and IHCA are increasing.[7, 11] Classifying OHCA without an extrinsic cause obvious to prehospital providers as “medical” does not capture an between-patient heterogeneity in terms of post-arrest pathophysiology, treatment responsiveness and outcomes.

Other strategies have been previously used to more precisely define the underlying etiology of cardiac arrest. In non-survivors of OHCA, autopsy may elucidate the cause of arrest in a substantial proportion of subjects.[9] For those surviving to hospital arrival after OHCA with no obvious cause of arrest, systematic coronary angiography and CT identifies more than half of arrest etiologies.[10] These methods have limitations as well. Autopsy studies cannot be used to inform research or care of those successfully resuscitated, and routine use of coronary angiography may have a lower diagnostic yield in populations where acute coronary syndrome is less common, such as the cohort we present.

Our classification system may be a useful framework to guide clinicians’ initial diagnostic workup and early resuscitative interventions, thereby improving the quality of post-arrest care. Most of the tests used to determine arrest etiology can be rapidly obtained at most medical centers within hours of hospital arrival. A rapid, directed diagnostic workup to define arrest etiology may be useful insofar as many causes of arrest benefit from time sensitive interventions like coronary revascularization,[12] thrombolysis,[13] surgical intervention, antidotes, or rapid correction of other inciting causes.[14] Equally importantly,

among survivors to hospital discharge, accurate identification of arrest etiology can guide efforts in secondary prevention such as implantable defibrillator placement,[15] initiation of new medications,[16] post-acute psychiatric care and addiction counseling,[17] or other etiology-specific post-acute care. It can also serve to inform clinicians and families about the anticipated clinical course and outcomes in this population, both in terms of prospects for survival and favorable recovery at discharge as well as potentially unavoidable mechanisms of in-hospital mortality such as early rearrest or progression to brain death.

Our findings have potential epidemiological and public health significance as well. We note that in our cohort, etiologies historically grouped as medical (or presumed cardiac) represent a minority of overall cases, with only 14% due to acute coronary syndrome and 7% due to various arrhythmias. This may be due in part to our inclusion of IHCA patients and the fact that our cohort is restricted to those surviving to hospital care. As these patient populations grow, they are priorities for future research.[7] The distribution of etiologies we identified likely also reflects the changing demographics of cardiac arrest. Over time, the incidence of shockable rhythms has fallen with improved secondary prevention,[7] the population of the United States has aged and become more chronically ill,[18] and new medical conditions like opioid dependence and overdose are becoming more prevalent.[19] Important secular trends in the epidemiology of cardiac arrest etiology can only be measured by a granular classification system.

The inability of prior classification systems to measure clinically significant heterogeneity may in part explain the preponderance of neutral results from cardiac arrest trials.[20] Many postarrest interventions that may be lifesaving after a particular cause of cardiac arrest (e.g. coronary angiography for acute coronary syndrome) may be inert in other populations (e.g. coronary angiography for a congenital arrhythmia). Inclusion and randomization of patients in whom an intervention is inert reduces a study's effect size and may result in inadequate power. Worse, lifesaving interventions for one group (e.g. thrombolysis after massive pulmonary embolism) may be frankly harmful in others (e.g. thrombolysis after arrest from hemorrhage). Reasonable investigators may speculate that distinct patterns of injury, clinical phenotypes or individual patient need resulting from specific arrest etiologies may benefit from different depths or durations of hypothermia (various comparisons have been equivalent at population levels [21, 22]), pharmacological neuroprotective strategies (all phase III trials to date have been neutral [23]), or other general aspects of post-arrest critical care.

Our work has several important limitations. First, to date our methodology lacks external validation. As a high volume cardiac arrest receiving center with organized systems of care, the population we included not be generalizable to other settings due to survival bias, selection bias on the part of the referring physicians and indication bias with respect to patients who are transferred by nature of their need for specialized care. This may have enriched our population for specific arrest etiologies while decreasing the apparent incidence of others. Outside the center effect, the incidence of each etiology reflects regional data that may not translate to other parts of the world. For example, the incidence of toxicological arrests, most of which were attributed to accidental opioid overdose, would not be expected to reflect the incidence in countries where opioid dependence and recreational drug overdose

are rare. Additionally, determination of a final arrest etiology is dependent on clinician-driven diagnostic testing. Although most of these tests are standard of care (electrocardiography, chest roentgenography, blood chemistries, etc), some tests such as cardiac MRI or genetic testing may only be available or preferentially obtained in a tertiary care setting. Together, these factors may alter the frequency of given etiologies within our system or increase the frequency of unknown etiologies in systems with fewer resources. By contrast, were diagnostic tests to be acquired systematically in all patients regardless of clinical suspicion (e.g. routine cardiac catheterization or chest CT), the proportion of patients with unknown arrest etiology would be expected to decline.

In conclusion, we present a novel classification system for arrest etiology in patients resuscitated from cardiac arrest with clinical, epidemiological and research significance. Arrest etiology was identifiable in the large majority of cases through systematic chart review and clinician-directed diagnostic testing. A minority of patients, even those arresting out-of-hospital, arrested due to etiologies historically described as medical (or presumed cardiac), and even within this subgroup we found significant heterogeneity in clinical characteristics and outcomes. Previous classification systems likely underestimate the diversity of cardiac arrest etiology, supporting the need for validated classification schema to inform post-arrest care and future study designs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:

Cardiac arrest etiologies, stratified by etiologies likely to be considered “presumed cardiac” under the classic Utstein template; non-cardiac etiologies; and other unclassified, multiple and unknown etiologies.

Figure 2:
Flowchart for determination of cardiac arrest etiology

Table 1 –

Final cardiac arrest etiologies and their relative incidence among patients resuscitated from cardiac arrest, stratified by arrest location

Cardiac arrest etiology	Overall cohort (n = 982)	Out-of-hospital arrests (n = 694)	In-hospital arrests (n = 288)
Acute coronary syndrome	135 (14)	112 (16)	23 (8)
Congenital arrhythmia	5 (1)	5 (1)	0 (0)
Arrhythmia secondary to cardiomyopathy	60 (6)	44 (6)	16 (6)
Structural heart disease	7 (1)	5 (1)	2 (1)
Left ventricular failure	12 (1)	5 (1)	7 (2)
Right ventricular failure	36 (4)	20 (3)	16 (6)
Toxicological	87 (9)	78 (11)	9 (3)
Upper airway obstruction	54 (6)	34 (5)	20 (7)
Respiratory failure	148 (15)	85 (12)	63 (22)
Neurological catastrophe	16 (2)	16 (2)	0 (0)
Trauma	24 (2)	19 (2)	5 (2)
Non-traumatic exsanguination	25 (3)	13 (2)	12 (4)
Distributive shock	33 (3)	19 (3)	14 (5)
Metabolic derangement	46 (5)	31 (4)	15 (5)
Other identifiable etiology*	42 (4)	21 (3)	21 (7)
Multiple likely etiologies#			
Two likely etiologies	116 (12)	89 (13)	27 (9)
Three likely etiologies	36 (4)	24 (3)	12 (4)
Four or more possible etiologies	17 (2)	9 (1)	8 (3)
Unknown etiology			
Did not undergo diagnostic workup	74 (7)	57 (8)	17 (6)
Extensive testing unrevealing	9 (1)	8 (1)	1 (0)

* Other identifiable arrest etiologies were (number - etiology): 5 - Arrest during PCI, EP ablation or failure to terminate VT in EP lab; 5 - Long QT that could not be delineated as secondary to medications, metabolic disarray, congenital long QT or multifactorial; 3 - Peri-intubation; 3 - Smoke inhalation/CO burning; 3 - Hypothermia from exposure; 3 - Vasovagal; 2 - Seizure followed by cardiac arrest; 2 - Pacemaker failure; 2 - LVAD failure; 2 - Adverse reaction to chemotherapy infusion; 1 - Large bowel perforation; 1 - Electrocution; 1 - Autopsy: Physical stress of surgery complicating severe underlying heart disease; 1 - Autopsy: Ischemic bowel and cardiogenic shock due to severe CAD; 1 - Autopsy: suspected arrhythmia from severe LVH; 1 - Amiodarone toxicity; 1 - Aortic dissection leading to tamponade; 1 - Cyanide poisoning; 1 - Heart allograft rejection; 1 - Autopsy: Cardiomyopathy of pregnancy with acute MI; 1 - Severe hemolytic anemia; 1 - Spontaneous tension pneumothorax

Table 2:

Overall cohort clinical characteristics and outcomes

Characteristic	Overall cohort (n = 982)
Age, years	60 [49 – 71]
Female sex	418 (43)
Arrest out-of-hospital	694 (71)
PCAC	
I	210 (21)
II	154 (16)
III	93 (9)
IV	444 (45)
Unknown	81 (8)
Arrest rhythm	
VT/VF	291 (30)
PEA	397 (40)
Asystole	217(22)
Unknown	77 (8)
Survival to discharge	380 (39)
Responsive at discharge *	335 (88)
Ever responsive	390 (40)
Good outcome	236 (24)
Days to awakening	1 [0 – 3]
Discharge disposition *	
Home	147 (39)
Acute rehab	89 (23)
SNF	85(22)
LTAC	35 (9)
Hospice	17 (4)
Other	7 (2)
Mode of death [#]	
Unstable	212 (35)
Brain death	40 (8)
WLST - non-neurological reasons	72 (12)
WLST - neurological prognosis	268 (45)
Length of stay, days	
Survivors	14 [8 – 22]
Non-survivors	2 [1 – 4]

Data are presented as median [interquartile range] for continuous variables and raw number with corresponding percentages for categorical variables.

Abbreviations: PCAC - Pittsburgh Cardiac Arrest Category; VT/VF - Ventricular tachycardia or fibrillation; PEA - Pulseless electrical activity; SNF - Skilled nursing facility; LTAC - Long-term acute care facility; WLST - Withdrawal of life-sustaining therapy

* Data are presented as the proportion of survivors to discharge. # Data are presented as the proportion of non-survivors

Table 3:

Comparisons of baseline characteristics and outcomes across arrest etiologies. Etiologies likely to be classified as “medical” under the Utstein template are denoted with gray shading.

Characteristic	Arrest etiology																	P value ^a
	1 n = 135 ^b	2 n = 5	3 n = 60	4 n = 7	5 n = 12	6 n = 36	7 n = 87	8 n = 54	9 n = 148	10 n = 16	11 n = 24	12 n = 25	13 n = 33	14 n = 46	15 n = 42	16 n = 166	17 n = 83	
Age, years	61 [53–69]	31 [19–41]	63 [53–71]	22 [19–42]	58 [45–77]	60 [49–65]	37 [28–50]	54 [40–68]	63 [53–73]	56 [47–64]	59 [34–67]	60 [53–69]	62 [55–70]	61.5 [49–74]	60 [36–67]	64 [54–74]	67 [55–80]	<0.001
Female sex	50 (37)	2 (40)	18 (30)	5 (71)	5 (42)	23 (64)	35 (40)	12 (22)	71 (48)	11 (69)	10 (42)	11 (44)	24 (73)	23 (50)	18 (43)	68 (40)	32 (39)	<0.001
Arrest out-of-hospital	112 (83)	5 (100)	44 (73)	5 (71)	5 (42)	20 (56)	78 (90)	34 (63)	85 (57)	16 (100)	19 (79)	13 (52)	19 (58)	31 (67)	21 (50)	122 (72)	65 (78)	<0.001
PCAC																		<0.001
I	55 (41)	1 (20)	21 (35)	2 (29)	4 (33)	12 (33)	9 (10)	2 (4)	31 (21)	0 (0)	2 (8)	5 (20)	12 (36)	11 (24)	12 (29)	24 (14)	7 (8)	
II	28 (21)	4 (80)	13 (22)	2 (29)	0 (0)	5 (14)	12 (14)	15 (28)	20 (14)	1 (6)	2 (8)	1 (4)	2 (6)	9 (20)	5 (12)	25 (15)	10 (12)	
III	11 (8)	0 (0)	8 (13)	2 (29)	2 (17)	4 (11)	3 (3)	2 (4)	18 (12)	1 (6)	0 (0)	4 (16)	1 (3)	2 (4)	4 (10)	26 (15)	5 (6)	
IV	34 (25)	0 (0)	15 (25)	1 (14)	4 (33)	14 (39)	54 (62)	31 (57)	68 (46)	10 (63)	16 (67)	8 (32)	13 (39)	18 (39)	17 (40)	87 (51)	54 (65)	
Unknown	7 (5)	0 (0)	3 (5)	0 (0)	2 (17)	1 (3)	9 (10)	4 (7)	11 (7)	4 (25)	4 (17)	7 (28)	5 (15)	6 (13)	4 (10)	7 (4)	7 (8)	
Arrest rhythm																		<0.001
VT/VF	106 (79)	5 (100)	52 (87)	2 (29)	3 (25)	1 (3)	6 (7)	3 (6)	6 (4)	1 (6)	0 (0)	4 (16)	2 (6)	22 (48)	15 (36)	43 (25)	20 (24)	
PEA	9 (7)	0 (0)	3 (5)	3 (43)	6 (50)	28 (78)	42 (48)	24 (44)	85 (57)	8 (50)	14 (58)	19 (76)	23 (70)	13 (28)	12 (29)	72 (43)	36 (43)	
Asystole	17 (13)	0 (0)	4 (7)	1 (14)	3 (25)	6 (17)	28 (32)	19 (35)	43 (29)	4 (25)	6 (25)	1 (4)	6 (18)	7 (15)	11 (26)	41 (24)	20 (24)	
Unknown	3 (2)	0 (0)	1 (2)	1 (14)	0 (0)	1 (3)	11 (13)	8 (15)	14 (9)	3 (19)	4 (17)	1 (4)	2 (6)	4 (9)	4 (10)	13 (8)	7 (8)	
Survival to discharge	81 (60)	5 (100)	32 (53)	6 (86)	5 (42)	17 (47)	32 (37)	18 (33)	53 (36)	1 (6)	7 (29)	6 (24)	9 (27)	23 (50)	21 (50)	48 (28)	16 (19)	<0.001
Responsive at discharge [*]	75 (93)	5 (100)	30 (94)	5 (83)	5 (100)	17 (100)	25 (78)	13 (72)	46 (87)	1 (100)	6 (86)	6 (100)	9 (100)	23 (100)	20 (95)	35 (73)	15 (94)	0.02
Ever responsive	81 (60)	5 (100)	35 (58)	5 (71)	5 (42)	19 (53)	26 (30)	16 (30)	59 (40)	1 (6)	7 (29)	9 (36)	12 (38)	26 (57)	22 (52)	45 (27)	17 (20)	<0.001
Good outcome	54 (40)	5 (100)	20 (33)	5 (71)	2 (17)	10 (28)	22 (25)	12 (22)	22 (15)	0 (0)	6 (25)	4 (16)	6 (18)	13 (28)	16 (38)	29 (17)	10 (12)	<0.001
Days to awakening	1 [0–2]	3 [2–3]	1 [0–3]	1 [1–1]	2 [1–2]	1 [0–2]	2 [1–6]	2 [1–5]	1 [0–3]	2 [2–2]	1 [1–2]	1 [1–3]	0.5 [0–1]	1.5 [1–3]	1 [0–3]	1 [0–3]	1 [1–2]	0.31
Discharge disposition [*]																		0.10
Home	43 (53)	3 (60)	13 (41)	3 (50)	0 (0)	7 (41)	10 (31)	7 (39)	13 (25)	0 (0)	1 (14)	3 (50)	3 (33)	9 (39)	11 (52)	18 (38)	3 (19)	
Acute rehab	11 (14)	2 (40)	7 (22)	2 (33)	2 (40)	3 (18)	12 (38)	5 (28)	9 (17)	0 (0)	5 (71)	1 (17)	3 (33)	4 (17)	5 (24)	11 (23)	7 (44)	
SNF	20 (25)	0 (0)	7 (22)	0 (0)	3 (60)	4 (24)	4 (13)	1 (6)	17 (32)	1 (0)	0 (0)	1 (17)	1 (11)	9 (39)	3 (14)	9 (19)	5 (31)	
LTAC	3 (4)	0 (0)	1 (3)	1 (17)	0 (0)	2 (12)	2 (6)	2 (11)	10 (19)	0 (0)	0 (0)	1 (17)	1 (11)	1 (4)	2 (10)	8 (17)	1 (6)	
Hospice	4 (5)	0 (0)	3 (9)	0 (0)	0 (0)	1 (6)	1 (3)	2 (11)	3 (6)	0 (0)	0 (0)	0 (0)	1 (11)	0 (0)	0 (0)	2 (4)	0 (0)	
Other	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	3 (9)	1 (6)	1 (2)	0 (0)	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Mode of death [#]																		<0.001
Unstable	21 (39)	--	13 (46)	0 (0)	5 (71)	9 (47)	10 (18)	5 (14)	28 (29)	0 (0)	3 (18)	11 (58)	17 (71)	8 (35)	11 (52)	42 (35)	29 (43)	
Brain death	0 (0)	--	0 (0)	0 (0)	0 (0)	2 (11)	16 (29)	3 (8)	2 (2)	5 (33)	3 (18)	0 (0)	1 (4)	0 (0)	3 (14)	7 (6)	8 (12)	
WLST - non-neurological reasons	4 (7)	--	2 (7)	0 (0)	1 (14)	1 (5)	3 (5)	5 (14)	19 (20)	0 (0)	1 (6)	2 (11)	4 (17)	3 (13)	1 (5)	15 (12)	11 (16)	
WLST - neurological prognosis	29 (54)	--	13 (46)	1 (100)	1 (14)	7 (37)	26 (47)	23 (64)	46 (48)	10 (67)	10 (59)	6 (32)	2 (8)	12 (52)	6 (29)	57 (47)	19 (28)	
Length of stay, days																		

Characteristic	Arrest etiology																	P value ⁺
	1 n = 135	2 n = 5	3 n = 60	4 n = 7	5 n = 12	6 n = 36	7 n = 87	8 n = 54	9 n = 148	10 n = 16	11 n = 24	12 n = 25	13 n = 33	14 n = 46	15 n = 42	16 n = 166	17 n = 83	
Survivors	10 [6–16]	12 [7–18]	14 [8–18]	15 [9–21]	22 [18–28]	15 [11–21]	18 [8–27]	12.5 [6–19]	16 [11–24]	44 [44–44]	14 [8–41]	16 [12–16]	14 [7–25]	16 [10–20]	10 [4–15]	15 [8–25]	19 [9–29]	0.04
Non-survivors	3 [1–6]	--	4 [1–5]	3 [3–3]	2 [1–4]	1 [0–2]	2 [1–4]	3 [1–5]	3 [1–5]	1 [1–2]	1 [1–3]	1 [0–5]	1 [0–3]	4 [1–5]	2 [1–4]	2 [1–4]	1 [0–2]	<0.001

Data are presented as median [interquartile range] for continuous variables and raw number with corresponding percentages for categorical variables.

Etiology abbreviations: 1 - Acute coronary syndrome; 2 - Intrinsic arrhythmia; 3 - Arrhythmia secondary to cardiomyopathy; 4 - Structural heart disease; 5 - Left ventricular failure; 6 - Right ventricular failure; 7 - Toxicological; 8 - Upper airway obstruction; 9 - Respiratory failure; 10 - Neurological catastrophe; 11 - Trauma; 12 - Non-traumatic exsanguination; 13 - Distributive shock; 14 - Metabolic derangement; 15 - Other identifiable etiology; 16 - Multiple likely etiologies; 17 - Unknown

Abbreviations: PCAC - Pittsburgh Cardiac Arrest Category; VT/VF - Ventricular tachycardia or fibrillation; PEA -Pulseless electrical activity; SNF - Skilled nursing facility; LTAC - Long-term acute care facility; WLST - Withdrawal of life-sustaining therapy

^{*}Data are presented as the proportion of survivors to discharge. # Data are presented as the proportion of non-survivors

[‡]P values are Bonferroni-corrected for multiple comparisons.