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Factors Influencing Survival and Neurological Outcomes Following Cardiac Arrest

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Abstract

Factors Influencing Survival and Neurological Outcomes Following Cardiac Arrest
By Antoine Raynard Trammell

Survival to discharge rates following cardiac arrest have not improved over 60 years despite research. The post-cardiac arrest period has been considered treatable since 1966, however, the primary focus of cardiac arrest research has been the return of spontaneous circulation. The greatest reduction in survivorship following cardiac arrest occurs in the period following return of spontaneous circulation during the post-cardiac arrest syndrome, characterized by neurological and cardiac dysfunction. Cardiac arrest outcomes also present public health challenges as neurological deterioration increases long-term care costs and decreases quality of life. Survival disparities per ethnic background have also been reported. As the efficacy of interventions after cardiac arrest period to improve outcomes have been shown, the purpose of this investigation is to identify factors during post-cardiac arrest care that impacts outcomes.

Methods: An investigation of 271 cardiopulmonary arrest events over a two-year period at a single center. Code documentation and post-arrest course at 6, 12, 24, and 48 hours was reviewed.

Results: Baseline characteristics among patients are similar. Among the patients 172 (66.7%) survived the event of which 52 (19.2%) survived to discharge. The Cerebral Performance Category score of patients surviving to discharge differs from patients not surviving to discharge (2 vs 5, $p < 0.0001$). In multivariate analyses, neurological status (9.30, 3.51-24.65, $p < 0.0002$) and mean arterial pressure at 24-hours (OR 1.03, 1.02-1.04, $p < 0.0001$) are associated with survival to discharge. Mean arterial pressure at 6-hours (OR 1.27, 1.01-1.03, $p = 0.004$) and 24-hours (OR 1.02, 1.01-1.02, $p < 0.0001$) are associated with neurological preservation. Survival analyses demonstrate increased survival to 48-hours with neurological preservation ($p < 0.0001$), higher pH ($p < 0.001$), and higher mean arterial pressure ($p = 0.002$). Survivors with neurological deterioration have a greater risk of not surviving to discharge (HR 2.73, 1.83-4.08, $p < 0.001$).

Summary: Patients with neurological preservation following cardiac arrest have better survival outcomes. Factors favoring neurological preservation include systemic perfusion and systemic ischemia. Further investigation and development of post-cardiac care strategies have the potential to address disparate outcomes and healthcare costs.

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1. Introduction

Rates of survival to discharge following cardiac arrest have not improved in 60 years [1-3]. Historically, the focus of cardiac arrest research has been the return of spontaneous circulation with less emphasis on post-cardiac arrest care[4]. However, the greatest reduction in number of survivors occurs during the post-cardiac arrest period, between return of spontaneous circulation and hospital discharge[1,5-7]. Cardiac arrest is also associated with challenges to public health due to disparate outcomes and increased long-term care expenditures for survivors with neurological dysfunction [8]. Each year, in the United States, 424,000 people experience non-traumatic, out-of-hospital cardiac arrest and 209,000 people experience in-hospital cardiac arrest [9]. The average annual cost of care and quality adjusted life year for neurologically intact cardiac arrest survivors is $200,182 and 4.19, whereas survivors with neurological dysfunction have an average annual cost of $336,090 and quality adjusted life year of 0.39 [10]. Furthermore, rates of survival to discharge among Blacks is nearly two-fold less than Whites and even lower among Hispanics and has been attributed to variations in post-cardiac arrest care and hospital racial composition [11-13].

Despite the reduction in number of survivors, interventions during the post-cardiac arrest period have been shown to be efficacious, cost-effective, and capable of sustaining quality of life at lower long-term costs [10,14]. The purpose of this investigation is to explore the post-cardiac arrest period for factors that impact neurological and survival outcomes.

2. Literature Review

A review of related literature was performed by query of the National Library of Medicine MEDLINE database under the MeSH term, “predictors of survival after in-hospital cardiac arrest”. The search results included 368 articles of which the abstracts were

reviewed for relevance to the subject (Figure 1). Articles discussing post-cardiac arrest care, targeted temperature management, and survival to hospital discharge after cardiac arrest were further reviewed. Sixty-one articles met the inclusion criteria. References of the included articles were reviewed additional related citations. An additional twenty-five article were identified and included in the review. A summary of the 86 articles, organized by primary topics (post-cardiac arrest syndrome, targeted temperature management, survival to hospital discharge, post-cardiac arrest care, and post-cardiac arrest laboratory markers) is presented below.

2.1. Post-cardiac arrest syndrome

Thirty-three articles discussing the post-cardiac arrest syndrome were reviewed. A recurrent theme among the papers is the recognition of systemic disease following cardiac arrest limits survival and neurological recovery. Cardiac arrest is a maximal stress that persists following return of spontaneous circulation as a constellation of pathophysiological processes limiting neurologically intact survival [15]. The syndrome, termed "post-resuscitation disease" in 1972 and implied completion of cardiac arrest, consists of pathological processes resulting from whole-body ischemia includes brain injury and cardiac dysfunction [16,17]. The period has been considered treatable since 1966 per inclusion in a consensus statement on cardiac arrest management [18]. Despite being considered treatable for 50 years, return of spontaneous circulation has been the primary focus of cardiac arrest research followng the introduction of closed cardiac massage in 1960 [16,19,20]. Interestingly, rates of survival to discharge have remained at approximately 20% since the introduction of closed cardiac massage [3,21].

Neurological dysfunction is a major manifestation of the post-cardiac arrest syndrome and has varied presentation including altered consciousness, seizures, and post-anoxic myoclonus. Estimates of neurological deterioration following out-of–hospital cardiac arrest range from 43 to 88% [22]. Estimates for the prevalence of neurological injury following in-hospital cardiac arrest are undetermined. Neurological dysfunction is recognized as a key factor of decreased survival. However, there are no measures to prognosticate neurological outcomes [23]. In response, the American Heart Association recommends electroencephalogram monitoring as it yields clinically relevant information [23,24]. Examination findings that suggest neurological dysfunction among comatose survivors not treated by targeted temperature management include myoclonus, absent pupillary reflexes, and low voltage on electroencephalogram between 24 and 72 hours [25]. An investigation of neurosurgical patients noted infection, comatose state, and lack of spontaneous respiration as predictors of decreased survival. The study further notes that code duration exceeding 30 minutes and initial rhythm of asystole predict neurological deterioration [26]. Cerebral oxygenation levels have also been found to predict return of spontaneous circulation and subsequent neurological outcomes [27,28].

Neurological preservation after cardiac arrest is correlated with beneficial long-term effects, which emphasizes the importance of investigating predictors and developing treatment strategies that impact early and long-term outcomes [29,30]. Moreover, as cardiac arrest survivors with neurological dysfunction account for increased intensive care unit resources, elucidation mechanisms that preserve neurological function remains an important focus.

In addition to neurological deterioration, cardiac dysfunction is a major manifestation of the post-cardiac arrest syndrome that contributes to reduced survivorship. Beyond myocardial stunning, a physiological state similar to adrenal insufficiency is thought to limit survival, however, there is limited data demonstrating a survival effect from corticosteroid therapy [14,16,31-33]. An in-hospital investigation of hypotension following cardiac arrest found low blood pressure to predict death prior to discharge as well as neurological disability among survivors. Although hypotension after return of spontaneous circulation is potentially treatable, interventions have not been developed [34]. Garcia-Tejada et al reported prolonged code duration, hypotension, and the use of vasopressors to be associated with poor outcomes following in-hospital cardiac arrest [35]. An out-of-hospital investigation of early goal-directed hemodynamic optimization found decreased mortality with the use of vasopressors and crystalloid fluids by maintaining mean arterial pressure above 80 mm Hg [36]. The American Heart Association also recommends target ranges for mean arterial pressure following cardiac arrest, however, supporting evidence is lacking [23]. A recent investigation indicates the superiority of intravenous fluids and targeted temperature management to vasopressor therapy. The study analyzed mean arterial pressure and vasopressor use at one, six, 12, and 24 hours after return of spontaneous circulation in patients undergoing targeted temperature management. Improved outcomes are observed in patients with higher mean arterial pressures while receiving intravenous fluids compared to those who require vasopressor treatment [37]. Besides vasopressor therapy reflecting illness severity, another possible explanation for this result is capillary leakage after cardiac arrest resulting in the extravasation of fluid with commensurate decrease in cardiac index that has been found to be responsive to crystalloid fluid infusion [38]. Targeted temperature management improves cardiac contractility by increasing myocardial calcium sensitivity; yet, ideal the determination of ideal temperature ranges

requires further investigation [39]. A promising investigation is currently underway that explores the role of nitrite infusion during post-cardiac arrest care on cardiac and neurological sequelae [40].

2.2. Targeted temperature management

Ten articles discussing benefits and limitations of targeted temperature management following cardiac arrest were reviewed. Prior to this intervention, fever among cardiac arrest survivors has been shown to be associated with increased mortality. The occurrence of temperatures exceeding 36.5C has been associated with greater rates of neurological dysfunction and 30-day mortality [41]. While, targeted temperature management has been demonstrated to work regardless of cooling method, conditions associated with optimal outcomes remain unclear as validated tools offering guidance are lacking [42]. Despite the demonstration of improved neurological dysfunction following targeted temperature management after out-of-hospital arrest, the assessment of outcomes associated with the intervention are complicated by inconsistent implementation. Decisions to perform cooling after cardiac arrest are the discretion of treating physicians. Furthermore, factors associated with decisions to cool include witnessed arrest, bystander chest compressions, and a shockable initial rhythm. In contrast, factors associated with decisions to not cool that may yield worsened survival outcomes include older age and female gender [43]. Thus, inconsistent implementation and imprecise treatment parameters contributes to poor rates of neurologically intact survival. Additional limitations to targeted temperature management include insufficient guidance on duration of cooling and management of complications. One complication, rebound pyrexia with temperatures exceeding 38.7C, is associated with neurological dysfunction [44]. The impact of the cooling rate and initial body temperature on outcomes remains to be more fully characterized as well [45].

Overall, investigations discussing targeted temperature management that were reviewed for this writing reveal conflicting outcomes. One study reported no difference between the intervention and standard therapy [46]. Another reported improved survival and neurological outcomes among survivors treated with cooling within four hours of return of spontaneous circulation [47]. These differences in outcomes may relate to the aforementioned inconsistent and individualized implementation. The use of targeted temperature management is also characterized by decisions to delay therapy as well as commonplace premature withdrawal of care due to suspected poor prognosis [48,49]. These factors contribute to a limitation of targeted temperature management on long-term survival by increasing the number of patients who would have not otherwise survived and by extending the life of survivors with neurological dysfunction and poor quality of life at high cost [10].

2.3. Survival to hospital discharge

Four papers discussing the impact of post-cardiac arrest care on survival to discharge were reviewed. Variance in hospital care after cardiac arrest has been recognized to impact survival up to one month after discharge [50]. Uniform post-cardiac arrest care across hospitals may decrease disparate outcomes while improving long-term survival rates and associated expenditures. Neurological preservation after cardiac arrest positively impacts survival to discharge [51]. Moreover, age does not significantly impact long-term survival [52]. Therefore, factors more specific to the post-cardiac arrest care period must be determined as elderly patients have outcomes similar to younger patients [53].

2.4. Post-cardiac arrest care

Twenty articles discussing post-cardiac arrest care were identified in the literature search. One out-of-hospital investigation discusses the importance of active, post-cardiac arrest care to improve outcomes [54]. Another investigation, citing the success of interventions following return of spontaneous circulation explores the feasibility of other interventions including cardiac catheterization to improve survival outcomes [55]. Wang et al discuss differences in post-cardiac arrest care following out-of-hospital arrest between early and late survival at 10 regional hospitals. They report disparate outcomes and varied post cardiac arrest care measures across the hospitals [56]. The need for conducting a multicenter investigations to coordinate post-cardiac arrest care has been recognized since the 1990s [57].

The primary aim of cardiopulmonary resuscitation is the restoration of cardiac mechanical activity with minimal neurological dysfunction [58]. And, among survivors with minimal neurological dysfunction, a functional status similar to pre-arrest has been demonstrated [59]. Merchant et al demonstrate that post-cardiac arrest intervention is cost effective, preserves quality of life, and associated with decreased long-term spending [10]. In an investigation that included octogenarians, the beneficial effects of favorable quality of life has been established to hold for older survivors [60]. Gage et al, report that resource utilization following in-hospital arrest is greater for patients who do not survive to discharge compared to patients who survive to discharge. A principle area of increased resource allocation following in-hospital cardiac arrest is code duration [61]. While it is not able to address code duration, uniform care following return of spontaneous circulation and training strategies may increase survivorship and reduce associated costs of prolonged post-cardiac arrest care**.** A recent six-year investigation of factors influencing post cardiac

arrest syndrome outcomes at a single center reports the duration of no pulse; number of organs with dysfunction; and physiological scores (APACHE II) are significant during post cardiac arrest care [62].

The feasibility of training healthcare workers for care following return of spontaneous circulation has been demonstrated. Rittenberger et al report a program of provider feedback; on-call consultants for patient care and hypothermia induction; and order protocols to favorably impact outcomes among comatose survivors of out-of-hospital and in-hospital cardiac arrest [63]. In an earlier investigation of uniform care following out-of-hospital cardiac arrest, Sunde et al established its utility in improving survival to discharge, neurological dysfunction, and 1-year survival. They describe hospital care during the post-cardiac arrest care period as the most critical predictor of survival [64]. In an investigation of dedicated cardiac resuscitation centers Roberts et al report promising results as comatose survivors experienced improved neurological outcomes [65]. This report supports the importance of uniform post-cardiac arrest care as well as the creation of dedicated care units. Dedicated units may prove advantageous in Emergency Departments with critical care capabilities by decreasing time to intervention and intensive care unit admission following out-of-hospital arrest [66]. Earlier intervention in Emergency Departments may also yield cost savings compared to utilizing intensive care unit resources. Despite scant evidence supporting uniform post-cardiac arrest care, one investigation establishes decreased time to intervention as a benefit that may improve outcomes [67]. Prompt implementation of interventions with well-defined post-cardiac arrest care has the potential to decrease disparate outcomes [68].

Community involvement through education programs may increase rates of bystander cardiopulmonary resuscitation [69]. In addition to clinician training, education initiatives incorporating survivor stories have been reported to increase the impact of training and dissemination [70]. Within healthcare centers, multidisciplinary initiatives with focused short and long-term goals are associated with greater success in implementing changes in post-cardiac arrest care [71].

Varied post-cardiac arrest care also impacts post-hospital discharge quality of life as heterogeneous outcomes are reported [72]. Uniformity among post-cardiac arrest care may promote homogeneity in quality of life among survivors.

2.5. Laboratory markers

Among the included articles, 10 discuss laboratory and physiological targets during post-cardiac arrest care. While evidence that in-hospital multidisciplinary systems such as Rapid Response teams impact mortality among survivors remains lacking [73], physiological and laboratory parameters associated with mortality have been identified. Takaki et al report initial heart rate and pH to be associated with neurological outcomes that impact cardiac arrest outcomes [74]. Kim et al identified respiratory infection and Simplified Acute Physiology Score II; hypokalemia and tachycardia at one hour after admission; low mean arterial pressure, serum bicarbonate concentration, and venous oxygen saturation at 24-hours after admission to be associated with increased mortality [73]. Starodub et al reported that low initial serum lactate levels correlate with improved survival outcomes. Specifically, a low serum lactate level at 12 and 24-hours after arrest is positively associated with survival to discharge [75]. Further, increasing serum lactate after return of spontaneous circulation is associated with higher mortality [76]. An in-hospital investigation of 100

patients further supports the role of lactate measurement after cardiac arrest as a significant relationship between the percentage lactate decrease, survival, and neurological outcomes was found at baseline, 12-hours, and 24-hours [77]. Measurement of serum lactate thus offers prognostic information during post-cardiac arrest care[62]. In addition to elevated serum lactate level, vasopressor therapy; a higher arterial minus end-tidal carbon dioxide ratio; and higher alveolar dead space ventilation ratio are associated with increasing mortality [78].

In addition to surrogates of poor perfusion, elevated markers of systemic inflammation, macrophage migration inhibitory factor, have been detected following return of spontaneous circulation and hold promise of clinical utility [79]. Clarification of the significance of this finding in the management of cardiac arrest requires further exploration and may serve as a target for early post-cardiac arrest care. Moreover, it is not clear whether the degree of elevation reflects the extent of the inflammatory state or how it impacts neurological and survival outcomes. Additional investigation of therapies that decrease macrophage migration inhibitory factor level are warranted. Complement activation has also been shown to correlate with survival outcomes as they are higher in non-survivors compared to survivors after cardiac arrest [80].

In summary, prior cardiac arrest investigations offer guidance on post-cardiac arrest management as well as recommendations to improve hospital and provider factors. The review of prior literature supports the feasibility of investigating post-cardiac arrest factors to increase rates of neurologically intact survival to discharge.

3. Design and Methodology

3.1. Design

An observational, retrospective investigation of cardiac arrest outcomes at a single hospital center to explore whether factors during post-cardiac arrest care impact neurologically intact survival to discharge. Patients experiencing cardiac arrest are divided into two cohorts based on survival to discharge (survive to discharge and non-survivors to discharge). Observational data offers the advantage of minimal impact from bias. An additional strength of the study design is inclusion of data from a single center eliminates confounding effects associated with variations in care at multiple-centers. Retrospective data may also be quickly obtained and less costly to generate in comparison to prospective studies while offering the possibility of studying multiple outcomes. A key limitation of the retrospective design relates to data quality in approaching research questions given absent control over data collection. An addition limitation of the design is utilizing a sample of hospitalized patients that is not reflective of the source population.

3.2. Methods

3.2.1. Code Team

The hospital code team that responds to all in-hospital cardiac arrest events consists of the Rapid Response nurse team, the on-duty clinical pharmacist, a respiratory therapist, on-call Anesthesiology house staff, the Internal Medicine house staff admitting team, and the on-call medical intensive care unit house staff. The Rapid Response Team, clinical pharmacy staff, respiratory therapy staff, on-call Anesthesiology house staff, and Emergency Medicine house staff respond to codes occurring on admitted patients in the Emergency Department. The code team provides coverage 24-hours per day.

3.2.2. Chart Review

In-hospital cardiopulmonary events for patients over the age of 18 years occurring between 1 January 2010 and 31 December 2011 were reviewed. Events were identified from copies of code documentation provided by the Rapid Response Team supervisor. The code sheets were reviewed for completion and identification of code variables (Table 1). Pulseless cardiopulmonary arrest events, unstable tachycardia, and unstable bradycardia were included in the study. Admitted patients waiting for transfer to a hospital care unit who experienced cardiac arrest were considered to be in-hospital events. Study events were limited to the first code for patients who experienced multiple episodes of cardiac arrest within a 24-hour period. Patient variables were identified by retrospective review of the hospital electronic medical record (Table 1). Admission cerebral performance category and Charlson comorbidity scores were determined from review of clinical notes. Code survivors, defined as patients experiencing return of spontaneous circulation and initiation of post-cardiac arrest care, were grouped into two cohorts based on survival to hospital discharge. The electronic medical record was reviewed for post-code variables at 6-hours, 12-hours, 24-hours, and 48-hours unless death or discharge occurred prior to the 48-hour mark (Table 1). Hemodynamic and laboratory measurements collected one hour before or after the time-points were accepted. Selected patient variables, code variables, and post-code variables were based on results of the literature review, part nine of the 2010 American Heart Association Advanced Cardiac Life Support guidelines (Post-Cardiac Arrest Care) and part eight of the 2015 American Heart Association Advanced Cardiac Life Support guidelines on (Post-Cardiac Arrest Care). Patients surviving to discharge were further grouped by neurological status at discharge. Survivors with Final CPC scores between 1 and 2 were deemed to have “neurological preservation” while survivors with scores ranging 3 to 5 deemed to have “neurological deterioration” (Table 2). The author reviewed code

documentation and electronic health records. The Emory University Institutional Review Board (Atlanta, Georgia) and Grady Memorial Hospital Research Oversight Committee (Atlanta, Georgia) approved data collection.

3.3. Research site

Grady Memorial Hospital is a 916 bed, academic medical center providing medical and surgical care to an indigent population in Atlanta, Georgia. The hospital reported 110,403 emergency department patient encounters and a total of 26,840 admissions for 2014 [81]. During the study period, the research site treated 495 episodes of out-of-hospital and in-hospital cardiopulmonary arrest of which 79 people (16%), survived to hospital.

4. Data Collection, Analysis, and Results

4.1. Data sources

Retrospective data on cardiopulmonary arrest events was collected from two sources: 1) paper in-hospital cardiac arrest records and 2) an electronic medical record for post-cardiac arrest information. Given the limited control over initial data collection paper cardiac arrest records and post-cardiac arrest information was reviewed twice.

4.2. Statistical analyses

Patients were divided into groups based on survival to discharge: survivors and non-survivors. Summary statistics and baseline characteristics are reported by the survival to discharge outcome. Differences between groups were analyzed by chi-square for categorical data, t tests for interval data, and equivalent non-parametric tests for median data. The strength of relationships between outcome variables, and post-arrest variables were measured by correlation analyses. Multivariate logistic regression was used to explain

relationships between neurological and survival outcomes with post-cardiac arrest variables. Product-moment survival estimates were calculated with the Kaplan-Meier. A Cox regression model estimated the hazard ratio for Final CPC to predict mortality. All statistics were calculated with SAS version 9.4 (SAS Institute Inc., Cary, NC).

4.3. Results

4.3.1. **Code and baseline patient characteristics**

There were 287 episodes of in-hospital cardiopulmonary arrest identified during the two-year study period. However, 16 events (5.6%) had insufficient code documentation to permit study inclusion. Therefore, 271 (94.4%) events were reviewed. Among the reviewed events, 172 (63.5%) patients survived the resuscitation effort from which 52 (19.2%) survived to hospital discharge (Figure 2). Resuscitation outcomes are reported per the simplified Utstein template [82].

Within the sample, patients had a mean age of 56 ± 15 years, 173 (63.8%) were male, and 222 (84.1%) were Black. Patients had a median Charlson score of 4 (2,6) and median admission CPC score of 1 (1,2) (Table 3). The median code duration was 16 (IQR 9,25) minutes. The most frequent initial management algorithm followed was for pulseless electrical activity and nearly half of all codes occurred in the intensive care unit. A majority of the events were witnessed by hospital staff on patients with cardiac monitoring. Chest compressions were initiated and the first dose of epinephrine was administered within two minutes (Table 4).

4.3.2. **Post-cardiac arrest course by time points**

At 6-hours survivors to discharge have a higher arterial pH level ($p = 0.013$), higher systolic blood pressure ($p = 0.0014$), and lower lactic acid level ($p = 0.0017$) in comparison to non-survivors. Survivors to discharge also have higher systolic blood pressure ($p = 0.038$) at 12-hours. The trend of higher systemic perfusion with less systemic ischemia among patients surviving to discharge remains at 24-hours and 48-hours (Table 7).

4.3.3. **Neurological outcomes**

A majority of code survivors received care in the intensive care unit (Table 6), but patients surviving to discharge have Final CPC score of 2(IQR 2,3) compared to a Final CPC score of 5 (IQR 5,5) among non-survivors ($p < 0.001$) (Table 5). Among non-survivors, 117 (97.5%) patients had neurological deterioration compared to 27 (51.9%) patients surviving to discharge with neurological preservation ($p < 0.001$). Correlation analyses reveal significant positive relationships between the Final CPC score and mean arterial pressure at each time point during post-cardiac arrest care (Table 13). In multivariate analyses, the mean arterial pressure at 6-hours (OR 1.02 [95% CI 1.01 – 1.03], $p = 0.004$) and 24-hours (OR 1.02 [95% CI 1.01 – 1.02], $p < 0.0001$) are significant predictors of the Final CPC sore.

4.3.4. **Survival to Discharge**

There are no significant differences in code characteristics for survivors to discharge compared to non-survivors (Table 8). However, survivors to discharge were more likely to be conscious before arrest ($p = 0.004$), have a pulse at onset of arrest ($p = 0.003$), and receive prompt defibrillation ($p = 0.043$) (Table 9).

Within the post-cardiac arrest course, survivors to discharge had significantly higher arterial pH and mean arterial pressures at each time point (Table 7). At 6-hours, survivors to discharge have lower lactate levels than non- survivors (3.8 versus 7.5, $p = 0.0017$) and at 24-hours survivors to discharge have lower respiratory rates than non-survivors (19 versus 22, $p = 0.002$) (Table 7). Correlation analyses demonstrate significant positive relationships between survival to discharge and mean arterial pressure at 6-hours, 12-hours, and 48-hours. There is also a significant positive relationship between survival to discharge and arterial pH at all post-cardiac arrest time points. Significant negative relationships are present for survival to discharge and the respiratory rate at 24-hours and lactate level at 48-hours (Table 14). In multivariate analyses, the Final CPC score (OR 9.30 [95% CI 3.51-24.65], $p < 0.0002$) and mean arterial pressure at 24-hours (1.03, [95% CI 1.02 – 1.04], $p < 0.0001$) are significant predictors of survival to discharge.

Survival analyses (Figure 3) reveal increased probability of survival to 48-hours with neurological preservation ($p < 0.0001$), higher arterial pH ($p < 0.0001$), higher mean arterial pressure ($p = 0.002$), lower WBC count ($p = 0.002$), and lower blood glucose levels ($p = 0.02$) (Table 11). The Final CPC score is demonstrated to be a significant predictor of 48-hour mortality (HR 2.73, [95% CI 1.83 – 4.08], $p < 0.001$) (Table 12).

5. Discussion

Results of this investigation demonstrates that factors during the post-cardiac arrest period impact outcomes. The study results are consistent with prior investigations and has two main findings. First, neurological preservation is associated with higher rates of surviving to discharge. Second, systemic dysfunction related to perfusion and ischemia during the post-cardiac arrest period impact neurological outcomes and survival to discharge. Patients with a clinical state comparable to shock following cardiac arrest are

less likely to survive to discharge. Patients who did not survive to discharge had higher lactic acid levels consistent with outcomes of sepsis [83-85]. Further, patients who did not survive to discharge had lesser systemic perfusion capable of creating systemic dysfunction and decreased cardiac index. The impact of factors during post-cardiac arrest period on survival and neurological outcomes establishes the importance of active cardiac arrest management beyond the return of spontaneous circulation. This is consistent with literature reports of the greatest reduction in survivor number occurring in the post-cardiac arrest period and represents an opportunity to improve stagnant rates of survival to discharge [1,6,86].

Furthermore, the majority of patients who survived to discharge were Black and at a rate consistent with literature reports. This is relevant to the existence of disparate outcomes and post-cardiac arrest care across hospitals [56]. Investigation of post-cardiac arrest care differences may lead to treatment strategies of target parameters from which disparate outcomes, inequitable spending, and differences in quality of life among survivors could be addressed.

There are several limitations to the findings. The sample is comprised of hospitalized patients at a single center thus not representative of the source population. The data utilized in the investigation does not have an original research purpose as well as a retrospective design precluding control over data collection. Cardiac arrest documentation is not always completed real-time therefore subject to recall bias. Further, as clinical information was obtained by chart review instead of actual examination it is not possible to verify CPC scores. Given the findings of the investigation, however, it is likely that the CPC scores were accurate.

In closing, factors during the post-cardiac arrest period significantly impact neurological and survival outcomes. Given the proven efficacy of intervention during this period to improve outcomes, further investigation of care differences has the potential to improve disparate outcomes, preserve quality of life, and reduce healthcare spending. Bundled educational and clinical interventions has been demonstrated to be effective [87], and when inclusive of organizational and individual factors capable of promoting process change in healthcare fields [88]. This investigation demonstrates the effect of hemodynamic optimization during post-cardiac arrest care on outcomes and emphasizes the need for prospective investigations of strategies that promote favorable outcomes. Developing evidence-based, uniform post-cardiac arrest care has the potential to improve neurologically intact survival to discharge, long-term survival, and reduce associated disparities.

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7. Appendix

Table 1. Study variables

Outcome		
	Final CPC	Post-cardiac arrest CPC score
	Survive	Code survival
	DC	Survival to discharge
Independent		
Patient Variables		
	Sex	Gender
	Age	Age
	Race	Ethnicity
	Charlson	Comorbidity score
	Admit CPC	Admission CPC score
Code Variables		
	InitRhy	Initial cardiac rhythm
	IntCPR	Time to initiation of chest compressions
	IntEpi	Time to first dose of epinephrine
	IntShock	Time to defibrillation
	IntBicarb	Time to first dose of sodium bicarbonate
	ROSC	Time to return of spontaneous circulation
Post-code Variables		
	pH	Arterial pH from blood gas
	CO_2	Arterial carbon dioxide concentration from blood gas
	O_2	Arterial oxygen concentration from blood gas
	Temp	Temperature (Celsius)
	SBP	Systolic blood pressure
	DBP	Diastolic blood pressure
	MAP	Mean arterial pressure
	Pulse	Heart rate
	RR	Respiratory rate
	WBC	White blood cell count
	BG	Serum blood glucose
	Lactate	Serum lactic acid

Table 2. Cerebral Performance Category

1 = Conscious and alert with normal function or only slight disability
2 = Conscious and alert with moderate disability
3 = Conscious with severe disability
4 = Comatose or persistent vegetative state
5 = Brain dead or death from other causes

Table 3. Patient characteristics by survival to discharge (n = 271)

	Survivor n(%), median (IQR), mean (±SD)	Non-survivor n(%), median (IQR), mean (±SD)	
Age (years)	55 (±15)	56 (±15)	p = 0.64
Gender			p = 0.95
Female	19 (7.01)	79 (29.2)	
Male	33 (12.2)	140 (51.7)	
Ethnicity			p = 0.53
Black	42 (15.9)	180 (68.2)	
White	8 (3.03)	20 (7.58)	
Asian	0	3 (1.14)	
Other	2 (0.76)	9 (3.41)	
Missing	0	7 (2.58)	
Charlson Comorbidity score	4(1,6)	4 (2, 7)	p = 0.30
CPC score	1 (1,2)	1 (1,2)	p = 0.14

Table 4. Code characteristics (n = 271)

	n(%), median (IQR), mean (±SD)
Code Duration (minutes)	16 (9,25)
Code survival	
Yes	172 (66.7)
No	86 (33.3)
Discharge survival	
Yes	52 (19.2)
No	120 (44.2)
Initial Rhythm	
Ventricular fibrillation/pulseless ventricular tachycardia	26 (9.96)
Pulseless electrical activity	122(46.74)
Asystole	56 (21.46)
Ventricular tachycardia	3(1.15)
Supraventricular tachycardia	11 (4.21)
Bradycardia	43 (16.48)
Code Location	
Floor	90 (33.21)
ICU	129 (47.60)
Step Down	41 (15.13)
Other	10 (3.69)
ED	1 (0.37)
Arrest Type	
Cardiac	198 (73.3)
Respiratory	13 (4.81)
Both	59 (21.85)
Unknown	1 (0.3)
Code Announced	
Yes	220 (81.3)
No	49 (18.3)
Witnessed Arrest	
Yes	200 (81.3)
No	49 (18.3)
Monitored at Arrest	
Yes	181 (87.4)
No	26 (12.6)
Conscious at Arrest	
Yes	43 (16.8)
No	213 (83.2)
Pulse at Arrest	
Yes	61 (23.3)
No	201 (76.7)
Drug doses	
Amiodarone	1 (1,1)
Atropine	1 (1,3)
Epinephrine	1 (1,2)
Sodium bicarbonate	1 (1.28)
Time to intervention (minutes)	
Epinephrine	2 (0, 5)
Chest compressions	0 (0,1)
Sodium bicarbonate	8 (4,12)
Defibrillation	7 (3, 13)

Table 5. Comparison of CPC scores by survival to discharge (n = 52)

	median (IQR)	
CPC		
Survivor	Non-survivor	
2 (2,3)	5 (5,5)	$p < 0.0001$

Table 6. Locations of post-cardiac arrest care (n = 172)

	n(%)
ICU	136 (79.02)
Intermediate	14(8.02)
Ward	22 (12.8)

Table 7. Comparison of post-cardiac arrest variables by survival to discharge (n = 172)

		Non-survivor median (IQR)	Survivor median (IQR)	
6 hours				
	pH	7.29 (7.06, 7.39)	7.33 (7.28, 7.40)	p = 0.013
	CO_2	35 (28, 44)	36.5 (29.5, 46)	p = 0.70
	O_2	142 (97, 210)	141 (90, 229)	p = 0.54
	Temperature	36 (35, 37)	37(36, 37)	p = 0.29
	Systolic blood pressure	105 (82, 134)	128 (112, 148)	p = 0.0014
	Diastolic blood pressure	60 (45, 70)	69 (59, 77)	p = 0.097
	Mean arterial pressure	0 (0, 53)	84 (0, 94)	p = 0.94
	Pulse	100 (80, 118)	94 (74, 108)	p = 0.078
	Respiratory rate	22 (18, 30)	19 (15, 22)	p = 0.43
	WBC	12 (8, 16)	11 (9, 18)	p = 0.25
	Glucose	136 (93, 212)	200 (135, 263)	p = 0.097
	Lactate	7.5 (3.5, 10)	3.8 (2.2, 4.1)	p = 0.0017
12 hours				
	pH	7.31 (7.14, 7.41)	7.39 (7.33, 7.46)	p = 0.16
	CO_2	35 (27, 54)	33 (27, 38)	p = 0.33
	O_2	126 (78, 183)	112 (75, 159)	p = 0.80
	Temperature	36 (35, 37)	37 (36, 37)	p = 0.80
	Systolic blood pressure	112 (97, 140)	126 (111, 146)	p = 0.038
	Diastolic blood pressure	62 (51, 75)	68 (60, 78)	p = 0.21
	Mean arterial pressure	0 (0,0)	79 (0, 96)	p < 0.0001
	Pulse	96 (82, 119)	91 (74, 107)	p = 0.93
	Respiratory rate	20 (15, 25)	20 (16, 22)	p = 0.14
	WBC	12 (9, 16)	11 (8, 16)	p = 0.37
	Glucose	137 (89, 196)	140 (104, 226)	p = 0.50
	Lactate	6 (1.9, 10)	2.15 (1.5, 2.90)	p = 0.088
24 hours				
	pH	7.35 (7.19, 7.43)	7.43 (7.39, 7.48)	p = 0.0008
	CO_2	33 (26, 46)	32 (29, 39)	p = 0.5
	O_2	124 (88, 189(	112 (79, 164)	p = 0.88
	Temperature	36 (35, 37)	37 (36, 37)	p = 0.88
	Systolic blood pressure	112 (91, 132)	124 (114, 147)	p = 0.0018
	Diastolic blood pressure	60 (47, 74)	72 (61, 77)	p = 0.044
	Mean arterial pressure	0 (0,0)	87 (27, 93)	p < 0.0001
	Pulse	97 (77, 114)	85 (76, 101)	p = 0.36
	Respiratory rate	22 (18, 32)	19 (16, 23)	p – 0.002
	WBC	12 (8, 16)	11 (7, 13)	p = 0.18
	Glucose	149 (106, 178)	132 (113, 180)	p = 0.25
	Lactate	4.8 (3.4, 8.3)	1.3 (1.05, 1.80)	p = 0.046
48 hours				
	pH	7.4 (7.28, 7.47)	7.45 (7.41, 7.51)	p = 0.006
	CO_2	29 (23, 44)	32 (29, 37)	p = 0.70
	O_2	114 (88, 153)	119 (89, 142)	p = 0.96
	Temperature	37 (36, 38)	36.8 (36.5, 37.6)	p = 0.94
	Systolic blood pressure	116 (110, 129)	130 (119, 148)	p = 0.025
	Diastolic blood pressure	65 (57, 83)	67 (58, 75)	p = 0.74
	Mean arterial pressure	0 (0,0)	81 (9, 91)	p < 0.0001
	Pulse	108 (88, 116)	86 (71, 101)	p = 0.065
	Respiratory rate	20 (14, 26)	18 (14, 25)	p = 0.90
	WBC	12 (8, 18)	10 (8, 15)	p = 0.58
	Glucose	131 (91, 155)	124 (105, 201)	p = 0.22
	Lactate	5 (2, 9)	1.3 (0.8, 2.0)	p = 0.12

Table 8. Comparison of survival to discharge by code characteristics (n = 271)

	Discharge status		
	Non-survivor	Survivor	
Admission CPC	1 (1,2)	2 (1,2)	p = 0.14
Charlson score	7 (4,8)	6 (4,8)	p = 0.29
Duration	25 (15, 35)	21 (13,27)	p = 0.052
Interval to epinephrine	2(1,5)	3 (0,6)	p = 0.39
Interval to bicarbonate	8 (4,12)	8 (4,15)	p = 0.75
Interval to shock	7 (4,14)	9 (4, 12)	p = 0.065

Table 9. Survival to discharge by patient characteristics (n = 172)

Conscious at arrest	p = 0.004
Pulse at arrest	p = 0.003
Initial cardiac rhythm	p = 0.011

Table 10. Survival to discharge by initial cardiac rhythm (n = 52)

	n(%)
Ventricular fibrillation/pulseless ventricular tachycardia	9 (17.3)
Pulseless electrical activity	16 (30.8)
Asystole	6 (11.5)
Unstable ventricular tachycardia	0 (0)
Unstable supraventricular tachycardia	4 (7.7)
Unstable bradycardia	12 (23.1)
Missing	5 (9.6)

Table 11. Probability of survival to 48-hours by post-cardiac arrest variables (n = 172)

Final CPC	p < 0.0001
pH	p < 0.0001
CO_2	p = 0.01
O_2	p = 0.001
Temperature	p = 0.82
Systolic blood pressure	p = 0.27
Diastolic blood pressure	p = 0.06
Mean arterial pressure	p = 0.002
Heart rate	p = 0.68
Respiratory rate	p = 0.94
Oxygen saturation	p = 0.04
WBC	p = 0.002
Glucose	p = 0.02
Lactate	p = 0.001

Table 12. Neurological outcome (Final CPC) as a predictor of mortality at 48-hours (n = 172)

	HR	**95% CI**	
Final CPC	2.73	1.83, 4.08	p < 0.001

Table 13. Correlation analyses of Final CPC by post-cardiac arrest variables (n = 172)

	Final CPC	6-hour MAP	12-hour MAP	24-hour MAP	48-hour MAP
Final CPC	1	0.21 p = 0.0003	0.26 p < 0.0001	0.33 p < 0.0001	0.32 p < 0.0001

Table 14. Correlation analyses of survival to discharge by post-cardiac arrest variables (n = 172)

	DC survival	Final CPC	6-hour pH	12-hour pH	24-hour pH	48-hour pH	6-hour MAP	12-hour MAP	48-hour MAP	24-hour Respiratory rate	48-hour Lactate
DC survival	1	0.500 p < 0.0001	0.19 p = 0.04	0.34 p = 0.002	0.37 p = 0.0008	0.08 p = 0.01	0.41 p < 0.0001	0.50 p < 0.0001	0.54 p < 0.0001	-0.34 p = 0.0022	-0.53 p = 0.02

Figure 1. Literature search

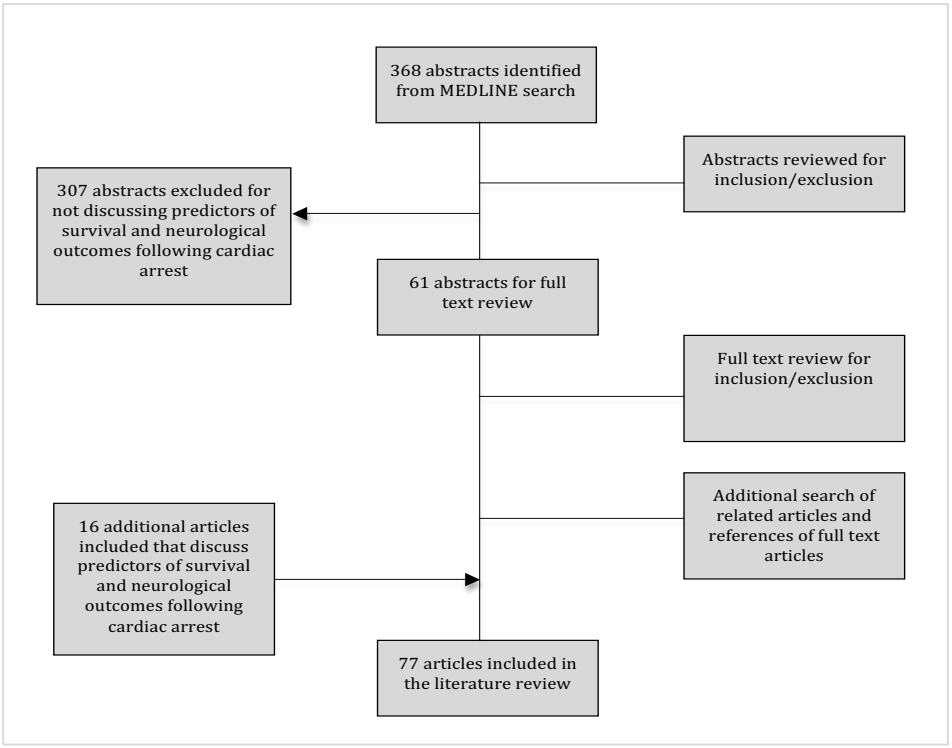

Figure 2. Results per Simplified Utstein Template

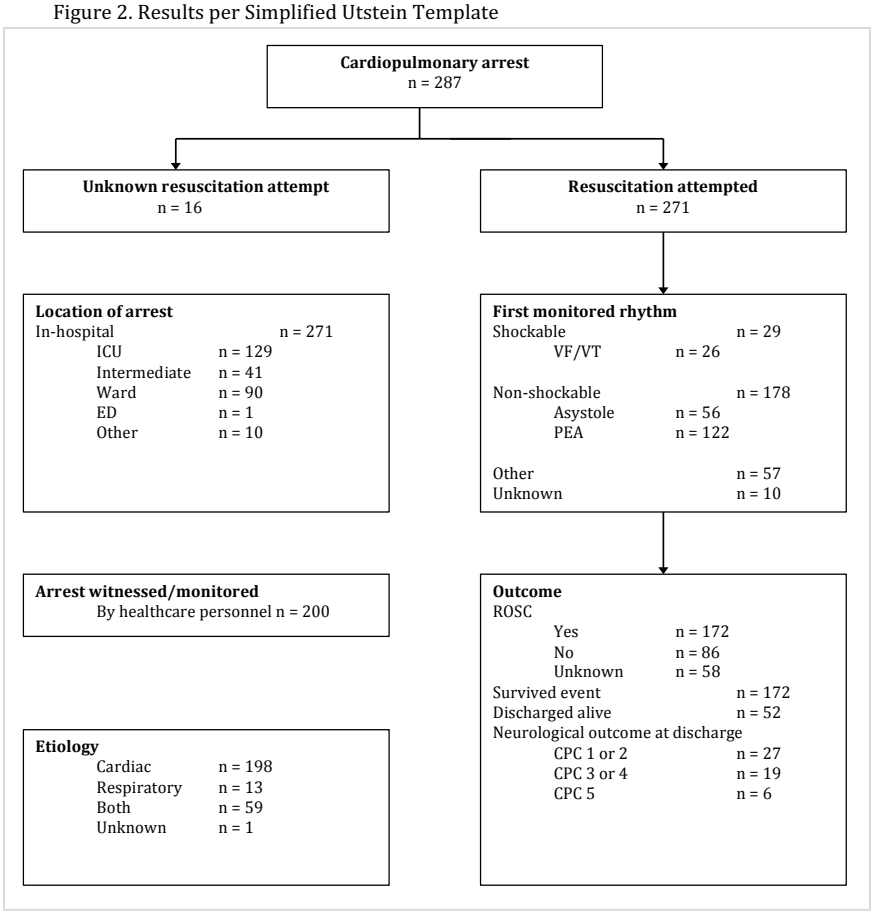

Figure 3. Kaplan-Meier Plots of survival to 48-hours post-cardiac arrest by post-cardiac arrest variables