Single-center In-hospital Cardiac Arrest Outcomes

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ABSTRACT

Background: This study was designed to evaluate the patient characteristics and outcomes of in-hospital cardiac arrest (IHCA).

Materials and methods: We carried out a single-center, 5-year, retrospective chart review and analysis of resuscitation data for age, gender, body mass index (BMI), length of stay (LOS) until cardiac arrest, survival of initial IHCA, survival to hospital discharge, primary medical service, and determination of the etiology of cardiac arrest.

Results: A total of 500 cases occurred with a mean LOS of 8.5 days until the initial IHCA. Overall, 79.5% survived the initial IHCA and 32.4% survived to discharge. As LOS increased, there was an increase in the proportion of pulmonary and metabolic etiologies. Logistic regression analysis adjusting for BMI, gender, age, LOS, and primary medical service were on a surgical service significant for survival to discharge (p = 0.0007) and LOS <9 days significant for survival of IHCA (p = 0.018).

Conclusion: There are a number of causes of IHCA, and the incidence of death and respiratory related IHCA etiologies increase with LOS. Length of stay carries the highest weight when predicting survival of IHCA. Also, there is a higher rate of survival to discharge when on a primary surgical service.

Keywords: Advanced life support, Cardiac arrest, Cardiopulmonary resuscitation, Causes of cardiac arrest, In-hospital cardiac arrest. *Indian Journal of Critical Care Medicine* (2020): 10.5005/jp-journals-10071-23327

INTRODUCTION

Sudden cardiac arrest is defined by the American College of Cardiology and American Heart Association (AHA) as, "sudden cessation of cardiac activity so that the victim becomes unresponsive, with no normal breathing and no signs of circulation."^{1,2} It is estimated that approximately 292,000 adult IHCAs are treated annually in the United States.³ The AHA identifies hypovolemia, hypoxia, hydrogen ion (acidosis), hypokalemia, hyperkalemia, hypothermia, tension pneumothorax, cardiac tamponade, toxins, pulmonary thrombosis, and coronary thrombosis as reversible etiologies of cardiac arrest to include, which are colloquially known as the H's and T's.⁴ Studies have described the etiology prevalence of in-hospital cardia arrest (IHCA) in the United States; however, there are limited data describing the patient characteristics and patterns in survivability with relation to length of stay (LOS), etiology, and primary service.⁵⁻¹⁰ We aimed to describe the patient characteristics, survivability of IHCA as well as survival to discharge, and the effect different parameters have on predicting survival.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board (201702489) for the University of Florida Health (Gainesville, Florida, USA), which is a tertiary care center with over 950 beds. We carried out a single-center retrospective chart review of patients admitted from January 1, 2012, to December 31, 2017 who had the principal diagnosis of cardiac arrest after presentation to the hospital. Our institutional review board waived the need for written informed consent. The inclusion criteria were both males and females who were between 18 years and 90 years of age who had a cardiac arrest after presentation to the hospital and received full resuscitative measures according to the AHA's advanced cardiac life support (ACLS).⁴ The exclusion criteria were patients undergoing cardiopulmonary resuscitation at the time of arrival

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or before arrival to the hospital or did not receive full resuscitative measures according to ACLS.⁴ In cases where a patient experienced more than one IHCA during a hospitalization, only the initial IHCA event was evaluated.

All clinical data were extracted from the patient's records, including age, gender, body mass index (BMI), primary admitting service, admission etiology, IHCA etiology, and LOS until IHCA, survival of IHCA, and survival to hospital discharge. In-hospital cardiac arrest etiology was categorized into eight groups, such as pulmonary, cardiac, exsanguination, aortic injury, metabolic, cerebral, adverse drug reaction, or unknown¹¹ (Table 1). Patients were designated to one of these groups by identifying documentation of the etiology by the primary healthcare team or upon autopsy. If an autopsy and the primary healthcare team did not identify an etiology, then the IHCA etiology was assigned as unknown. No autopsies or tests were performed for the sole purpose of this study.

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Demographic	n	%
Female	190	38
Male	310	62
Age mean \pm SD (years)	60.9 <u>+</u> 16.0	
BMI mean \pm SD (kg/m ²)	28.6 <u>+</u> 8.5	
Length mean \pm SD (days)	8.5 <u>+</u> 19.5	
Survived IHCA (yes)	398	79.6
Survived IHCA (no)	102	20.4
Survived to discharge (yes)	162	32.4
Survived to discharge (no)	338	67.6
Unknown etiology	249	49.8
Pulmonary etiology	119	23.8
Cardiovascular etiology	68	13.6
Exsanguination etiology	22	4.4
Aortic injury etiology	15	3.0
Metabolic etiology	14	2.8
Cerebral etiology	6	1.2
Adverse drug reaction etiology	6	1.2

Table 1: Patient demographics

STATISTICAL ANALYSIS

Demographic and clinical characteristics of patients were evaluated with between-group differences. We used paired *t* test to analyze the effects of sex, age, BMI, LOS, and admitting service over survival of IHCA and survival to discharge. To examine the association between survival of the arrest and survival to discharge and known cofounders, multivariable logistic regression analysis was used with survival as the exposure variable. The model included important cofounders, including age, sex, BMI, hospital service, and days of hospitalization before the arrest. All *p* values represent 2-sided hypothesis test. The significance level for all test was alpha <0.05. Analysis were performed with GraphPad Prism, version 7.0 (GraphPad Software Inc., La Jolla, California).

RESULTS

Patients

In total, 500 IHCA events were identified and all 500 patients' charts were reviewed. Patient characteristics are shown in Table 1. The study included 310 men (62%) and 190 women (38%) with a mean age of 60.9 ± 16.0 years. The mean BMI was 28.6 ± 8.5 kg/m². The mean LOS until the initial IHCA was 8.5 ± 19.5 days. Of the 500 patients, 398 (79.6%) survived the initial IHCA and 162 (32.4%) survived to hospital discharge (Table 1). A logistic plot model demonstrates the probability.

There were 25 different services listed as primary providers for these patients (Table 2). The three services with the most IHCA were the medical intensive care unit (MICU) with 109 cases (21.8%), thoracic/cardiovascular surgery with 70 cases (14.0%), and internal medicine with 67 cases (13.4%) (Table 2).

Etiologies and Causes

The etiology and examples of the IHCA were categorized as pulmonary (119 cases), cardiovascular (68 cases), exsanguination (22 cases), aortic injury (15 cases), metabolic (14 cases), cerebral (6 cases), adverse drug reaction (6 cases), or unknown (249 cases)¹¹ (Table 1). Hypoxia was identified to be the most common cause with 102 cases (20.4%) followed by arrhythmia in 31 cases (6.2%),

Table 2: Ten primary medical services with the most in-hospital cardiac arrest (IHCA)

Services	n (%)	Average LOS until IHCA (days)	Survived to discharge n (%)
Medical intensive care unit	109 (21.8)	8.0	22 (20.2)
Thoracic/ cardiovascular surgery	70 (14.0)	5.5	33 (47.1)
Internal medicine	67 (13.4)	12.8	17 (25.4)
Vascular	63 (12.6)	8.4	16 (25.4)
Cardiology	51 (10.2)	5.9	18 (35.3)
Trauma	33 (6.6)	3.5	16 (48.5)
Neurosurgery	22 (4.4)	15.0	9 (40.9)
Neurology	17 (3.4)	7.0	8 (47.1)
Pancreaticobiliary	10 (2.0)	24.1	5 (50.0)
surgery			
Kidney, liver, pancreas transplant	10 (2.0)	14.7	3 (30.0)



Fig. 1: Proportion of etiology of in-hospital cardiac arrest grouped by length of stay <9 days or ≥ 9 days

myocardial infarction in 20 cases (4%), hypovolemia in 20 cases (4%), and pulmonary embolism in 13 cases (2.6%).

When the etiology of IHCA are grouped by LOS <9 days or \geq 9 days, there is an upward trend in the proportion of IHCA due to pulmonary (21.8% vs 29.0%) and metabolic (2.3% vs 4.1%), whereas all other etiologies decreased in proportion (Fig. 1).

Subgroup Analysis

Age

Age was divided into two groups, $\leq 60 \text{ or } > 60 \text{ years}$. Of the patients $\leq 60 \text{ years}$ old, 183 survived and 41 died following the initial IHCA, whereas 215 survived and 61 died among patients > 60 years old (p = 0.026) (Table 3). When evaluated for survival to discharge, 77 survived and 147 died among patients $\leq 60 \text{ years}$ old and 85 survived and 191 died among patients > 60 years old (p = 0.128) (Table 3).

Surgical or Nonsurgical Service

Patients were also divided by primary service as surgical or nonsurgical. The mean LOS for IHCA on the surgical service was 8.3 ± 15.0 days, and the mean LOS on the medical service until

Table 3: Survival of initial in-hospita	I cardiac arrest and to discharge
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	Survived (%)	Died (%)	Total	p value	
Survival of initial IHCA					
Age ≤60 years	183 (81.7)	41 (18.3)	224	0.026	
Age >60 years	215 (77.9)	61 (22.1)	276		
Male	252 (81.3)	58 (18.7)	310	0.192	
Female	146 (76.8)	44 (23.2)	190		
Surgical	190 (82.6)	38 (16.5)	230	0.022	
Nonsurgical	206 (76.3)	64 (23.7)	270		
BMI <30	254 (79.6)	65 (20.4)	319	0.172	
BMI ≥30	139 (81.3)	32 (18.7)	171		
Length of stay <9 days	272 (76.6)	83 (23.4)	355	0.172	
Length of stay \geq 9 days	126 (86.9)	19 (13.1)	145		
Survival to discharge after IHCA					
Age ≤60 years	77 (34.4)	147 (65.6)	224	0.128	
Age >60 years	85 (30.8)	191 (69.2)	276		
Male	106 (34.2)	204 (65.8)	310	0.072	
Female	26 (29.5)	134 (70.5)	190		
Surgical	69 (30.0)	161 (70.0)	230	0.029	
Nonsurgical	93 (34.4)	177 (65.6)	270		
BMI <30	102 (32.0)	217 (68.0)	319	0.234	
BMI ≥30	60 (35.1)	111 (64.9)	171		
Length of stay <9 days	117 (33.0)	238 (67.0)	355	0.228	
Length of stay \geq 9 days	45 (31.0)	100 (69.0)	145		

IHCA was 8.9 ± 22.6 days. Of the patients on a surgical service, 192 survived and 38 died following the initial IHCA; 206 survived and 64 died on nonsurgical services (p = 0.022) (Table 3). When evaluated for survival to discharge, 69 survived and 161 died on surgical services and 93 survived and 177 died on nonsurgical services (p = 0.029) (Table 3). The three most frequent etiologies of IHCA for patients on a surgical service was unknown (43.9%), pulmonary (25.7%), and cardiovascular (12.2%). Nonsurgical services had the same three most common IHCA etiology; however, the frequency was different, with unknown (54.6%), pulmonary (22.1%), and cardiovascular (14.8%).

Gender

The patients were comprised of 310 males (62%) and 190 females (38%). Two-hundred and fifty-two (81.3%) male patients survived, and 58 (18.7%) died following the initial IHCA, while 146 (76.8%) female patients survived and 44 (23.2%) died (p = 0.192) (Table 3). When evaluated for survival to discharge, 106 (34.2%) survived and 204 (65.8%) died among males and 56 (29.5%) survived and 134 (70.5%) died among females (p = 0.072) (Table 3).

Length of Stay

Length of stay groups were defined as <9 days (355 patients) or \geq 9 days (145 patients) prior to the IHCA. Of the patients with LOS <9 days, 272 (76.6%) survived and 83 (23.4%) died following the initial IHCA, whereas 126 (86.9%) survived and 19 (13.1%) died with a LOS of \geq 9 days (p = 0.172) (Table 3). When evaluated for survival to discharge, 117 (33.0%) survived and 238 (67.0%) died with a LOS of <9 days and 45 (31.0%) survived and 100 (69.0%) died with a LOS of \geq 9 days (p = 0.228) (Table 3).

Body Mass Index

Body mass index groups were defined as those with either $<30 \text{ kg/m}^2$ (319 patients) or $\geq 30 \text{ kg/m}^2$ (171 patients) prior to the IHCA.

Of the patients with BMI <30 kg/m², 254 (79.6%) survived and 65 (20.4%) died following the initial IHCA, whereas 139 (81.3%) survived and 32 (18.7%) died with a BMI \geq 30 kg/m² (p = 0.17) (Table 3). When evaluated for survival to discharge, 102 (32.0%) survived and 217 (68.0%) died with a BMI <30 kg/m² and 60 (35.1%) survived and 111 (64.9%) died with a BMI \geq 30 kg/m² (p = 0.23) (Table 3).

Logistic Regression Model

A logistic regression was performed to evaluate the effect of hospital service, age, sex, BMI, and LOS before the arrest over survival of the arrest and survival to discharge. When we examined the survival to discharge, the model was able to predict a better survival in patients on surgical service even after adjusted by age, sex, BMI, and days in the hospital before the arrest, p = 0.009 (Fig. 2).

When we examine the survival of the cardiac arrest, the model was able to predict survival of the cardiac arrest with a *p* value of 0.04. The model explains 15% of the variance in survival and correctly classified 80% of the cases with a sensitivity 80%. The interesting finding is that most of the weight was determine by the LOS before the arrest (p = 0.01) and not the service where the patient was admitted (Fig. 2). A logistic probability plot model depicts the probability of surviving to discharge by LOS (Fig. 3).

DISCUSSION

This study demonstrated the frequency and outcomes of IHCA analyzed by BMI, age, LOS, gender, etiology of IHCA, and whether patients were admitted to a surgical or nonsurgical service. As described in previous studies, the occurrence of an IHCA portends a poor prognosis with 79.5% of patients surviving the initial IHCA and ultimately only 32.4% of all patients surviving to discharge in our study.^{5,6,11-13} When our population was evaluated by gender, BMI (<30 kg/m² or \geq 30 kg/m²), age (\leq 60 or >60 years), and LOS until IHCA (<9 days or \geq 9 days), there was no difference in outcomes at discharge. Persons aged \leq 60 years were more likely to survive the initial IHCA; however, there was only a trend for improved survival to discharge.

Individuals with the initial IHCA occurring in the MICU had the poorest outcomes compared with all other groups with only 20.2% surviving to discharge, which is similar to the rates published previously.⁹ Expectedly, patients admitted to the MICU have more comorbidities, acute organ failure, history of cancer, presence of mechanical ventilation, and/or use of vasoactive medications, which are established associations with not surviving to discharge after IHCA.⁹

There was an improved outcome for survival to discharge for patients admitted to surgical compared with medical services. We postulate the etiology of IHCA, average LOS, and level of acuity may contribute to this. Our model was able to confirm that shorter LOS has the highest weight predicting who will survive the arrest regardless of any other variable. Unknown causes of IHCA led to 148 cases (54.6%) on nonsurgical services compared with 101 cases (43.9%) on surgical services, with a between-group percent difference of 10.7%. This discrepancy is a direct reflection of the lack of identifying a cause and possibly a lack of identifiable treatment. We also suspect that there may have been a difference in the level of acuity, complexity of comorbidity, and mortality risk for surgical vs nonsurgical patients. If the data was available to evaluate each patient for Acute Physiology and Chronic Health Evaluation II or Sequential Organ Failure Assessment score, we may have been able to investigate this further.





Figs 2A to D: Logistic regression analysis adjusted for gender, age, body mass index, surgical service, and length of stay; (A) Actual and predicted survival to discharge; (B) Survival to discharge on surgical service; (C) Actual and predicted survival of in-hospital cardiac arrest; (D) Survival of in-hospital cardiac arrest by length of stay



Fig. 3: Logistic probability plot of survival to discharge by length of stay. As length of stay increases, the probability of mortality increases (line)

Length of stay also contributed to patient outcomes. As LOS increased, there was a larger proportion of IHCA attributed to pulmonary and metabolic etiologies; conversely there was

a downward trend in the percentage of cardiac and cerebral etiologies. This is similar to previous data describing the increased proportion of pulmonary etiologies as LOS increased.¹⁰ After adjusting for BMI, age, gender, and whether the patient was on a surgical or nonsurgical service, there was a significant increase in mortality following the initial IHCA as LOS increased. An international review of over four million admissions also found a correlation between increased LOS and mortality.¹⁴ We postulate these factors may be related to patient comorbidities, hospital-acquired aspiration, adverse in-hospital events, and hospital-acquired infections. With these data, healthcare providers should consider these pulmonary and metabolic etiologies more frequently in IHCA occurring in patients with a LOS \geq 9 days. Although monitoring in itself does not reduce the number of IHCA, the upward trend in the number of pulmonary etiologies identified in our population highlights the importance of monitoring oxygenation with the hope to more quickly identify and intervene on a pulmonary etiology for IHCA.

Our study used a similar approach to grouping the IHCA etiology to previous studies; however, there is variation in the literature of how this is categorized.^{4,10-12} When an identifiable etiology for IHCA was determined by the primary healthcare team, it was most commonly a pulmonary or cardiovascular cause

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consistent with prior investigations.^{10–12} We offer that a multisociety approved definition of different categories of causes and etiology will allow for more structured investigation and reporting, and potentially practice changing.

This study has multiple limitations, including a single-center academic institution with unique locoregional pathology. It has been established that regional differences, race, vasoactive medications, mechanical ventilation, age \geq 65 years old, timing (night and weekend), trauma centers, and teaching hospitals are associated with different cardiac arrest incidence and case survival.^{5,6,9} Witnessing the cardiac arrest and ratio of nurses to patients impact survival, which may play a role in our outcomes, but we were unable to identify what proportion of the IHCA occurred in and out of an intensive care setting to investigate this further.⁵ Also, some subgroups have lower sample size and are at risk for type II errors. Our study relied on direct documentation by the primary team or autopsy interpretation to decide the etiology of IHCA, which may be incorrect or incomplete and subsequently leading to confounding results. This raises the guestion again, if standardized documentation following a IHCA may provide more data and guide further studies.^{15,16}

CONCLUSION

In-hospital cardiac arrest portends a poor prognosis with only 32.4% of our patients surviving to discharge. There was a significant difference in the outcome to discharge in favor of patients admitted to a surgical service compared with nonsurgical service. These findings are hypothesis-generating and further clinical trials should evaluate this further.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The need for approval to participate was waived by our institutional review board.

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REFERENCES

- 1. American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (ACC/AHA/HRS Writing Committee to Develop Data Standards on Electrophysiology), Buxton AE, Calkins H, Callans JD, DiMarco JP, Fisher JD, et al. ACC/AHA/HRS 2006 key data elements and definitions for electrophysiological studies and procedures. a report of the american college of cardiology/american heart association task force on clinical data standards (acc/aha/hrs writing committee to develop data standards on electrophysiology). 2006;114(23):2534–2570. DOI: 10.1161/CIRCULATIONAHA.106.180199.
- 2. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS guideline for management of

patients with ventricular arrhythmias and the prevention of sudden cardiac death: executive summary. J Am Coll Cardi 2017;138(13): e201–e217.

- 3. Holmberg MJ, Ross CE, Fitzmaurice GM, Chan PS, Duval-Arnould J, Grossestreuer AV, et al. Annual incidence of adult and pediatric in-hospital cardiac arrest in the United states. Cir Cardiovasc Qual Outcomes 2019;12(7):e005580. DOI: 10.1161/ CIRCOUTCOMES.119.005580.
- Link MS, Berkow LC, Kudenchuk PJ, Halperin HR, Hess EP, Moitra VK, et al. Part 7: adult advanced cardiovascular life support. 2015 american heart association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2015;132(18suppl 2):S444–S464. DOI: 10.1161/CIR.000000000000261.
- Chen LM, Nallamothu BK, Spertus JA, Li Y, Chan PS. Association between a hospital's rate of cardiac arrest incidence and cardiac arrest survival. JAMA Intern Med 2013;173(13):1186–1195. DOI: 10.1001/ jamainternmed.2013.1026.
- Ehlenbach WJ, Barnato AE, Curtis JR, Kreuter W, Koepsell TD, Deyo RA, et al. Epidemiologic study of in-hospital cardiopulmonary resuscitation in the elderly. N Engl J Med 2009;361(1):22–31. DOI: 10.1056/NEJMoa0810245.
- Merchant RM, Yang L, Becker LB, Berg RA, Nadkarni V, Nichol G, et al. Incidence of treated cardiac arrest in hospitalized patients in the United states. Crit Care Med 2011;39(11):2401–2406. DOI: 10.1097/ CCM.0b013e3182257459.
- Schultz SC, Cullinane DC, Pasquale MD, Magnant C, Evans SRT. Predicting in-hospital mortality during cardiopulmonary resuscitation. Resuscitation 1996;33(1):13–17. DOI: 10.1016/S0300-9572(96)00986-0.
- Tian J, Kaufman DA, Zarich S, Chan PS, Ong P, Amoateng-Adjepong Y, et al. Outcomes of critically III patients who received cardiopulmonary resuscitation. Am J Respir Crit Care Med 2010;182(4):501–506. DOI: 10.1164/rccm.200910-1639OC.
- 10. Tran S, Deacon N, Minokadeh A, Malhotra A, Davis DP, Villanueva S, et al. Frequency and survival pattern of in-hospital cardiac arrests: the impacts of etiology and timing. Resuscitation 2016;107:13–18. DOI: 10.1016/j.resuscitation.2016.07.006.
- 11. Wallmuller C, Meron G, Kurkciyan I, Schober A, Stratil P, Sterz F. Causes of in-hospital cardiac arrest and influence on outcome. Resuscitation 2012;83(10):1206–1211. DOI: 10.1016/j.resuscitation.2012.05.001.
- Bergum D, Nordseth T, Mjølstad OC, Skogvoll E, Haugen BO. Causes of in-hospital cardiac arrest – incidences and rate of recognition. Resuscitation 2015;87:63–68. DOI: 10.1016/j.resuscitation.2014.11.007.
- Bergum D, Haugen BO, Nordseth T, Mjølstad OC, Skogvoll E. Recognizing the causes of in-hospital cardiac arrest–a survival benefit. Resuscitation 2015;97:91–96. DOI: 10.1016/j.resuscitation.2015.09.395.
- 14. Lingsma HF, Bottle A, Middleton S, Kievit J, Steyerberg EW, Marang-van de Mheen PJ. Evaluation of hospital outcomes: the relation between length-of-stay, readmission, and mortality in a large international administrative database. BMC Health Serv Res 2018;18(1):116. DOI: 10.1186/s12913-018-2916-1.
- Sukul D, Kamphuis LA, Iwashyna TJ, Bradley SM, Chan PS, Sinha SS, et al. Clinical documentation of in-hospital cardiac arrest in a large national health system. Resuscitation 2017;112:e9–e10. DOI: 10.1016/ j.resuscitation.2016.12.022.
- Allan N, Bell D, Pittard A. Resuscitation of the written word: meeting the standard for cardiac arrest documentation. Clinl Med (Lond) 2011;11(4):348–352. DOI: 10.7861/clinmedicine.11-4-348.