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Predicting in-Hospital Mortality After an in-Hospital Cardiac Arrest: A Multivariate Analysis

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Clincal paper

Predicting in-hospital mortality after an in-hospital cardiac arrest: A multivariate analysis

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Abstract

Aim of the study: Most survivors of an in-hospital cardiac arrest do not leave the hospital alive, and there is a need for a more patient-centered, holistic approach to the assessment of prognosis after an arrest. We sought to identify pre-, peri-, and post-arrest variables associated with in-hospital mortality amongst survivors of an in-hospital cardiac arrest.

Methods: This was a retrospective cohort study of patients ≥18 years of age who were resuscitated from an in-hospital arrest at our University Medical Center from January 1, 2013 to September 31, 2016. In-hospital mortality was chosen as a primary outcome and unfavorable discharge disposition (discharge disposition other than home or skilled nursing facility) as a secondary outcome.

Results: 925 patients comprised the in-hospital arrest cohort with 305 patients failing to survive the arrest and a further 349 patients surviving the initial arrest but dying prior to hospital discharge, resulting in an overall survival of 29%. 620 patients with a ROSC of greater than 20 min following the in-hospital arrest were included in the final analysis. In a stepwise multivariable regression analysis, recurrent cardiac arrest, increasing age, time to ROSC, higher serum creatinine levels, and a history of cancer were predictors of in-hospital mortality. A history of hypertension was found to exert a protective effect on outcomes. In the regression model including serum lactate, increasing lactate levels were associated with lower odds of survival.

Conclusion: Amongst survivors of in-hospital cardiac arrest, recurrent cardiac arrest was the strongest predictor of poor outcomes with age, time to ROSC, pre-existing malignancy, and serum creatinine levels linked with increased odds of in-hospital mortality.

Keywords: Cardiac arrest, Prognosis, In-hospital

Introduction

Approximately 292,000 adults suffer an in-hospital cardiac arrest (IHCA) in the United States each year.[1] The burden and mortality of IHCA are high, and it requires ample attention to understand the complexities of providing care to patients who have just suffered an arrest. Multiple risk scores predicting survival of an IHCA have been developed but had suboptimal predictive accuracy or employ only baseline patient characteristics and, thus, are limited to patients who have yet to suffer an arrest.[2–4] Most of these models are designed to predict outcomes prior to a cardiac arrest (and therefore do not include data from the cardiac arrest itself) to inform code status and clinical decision-making. However, the cardiac arrest is in itself a prognostic

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marker and informs the conversation, and there is a need for more robust research and clinical data from post-IHCA patients so as to better risk stratify.

For those who initially survive an IHCA, prognosis is very poor, with 12–25% surviving to hospital discharge.[5] More recent studies have tried to look at individual variables associated with survival with meta-analysis aggregating these variables.[4] The challenge with this approach is that the interdependence of variables is lost. They also do not include more recent data looking at factors such as recurrent cardiac arrest.[6] However, there is a need for a more patient-specific, holistic approach to the assessment of prognosis, using variables gathered from the both the peri- and post-arrest period.

Although tempting to use a predictive score to guide the care of an individual patient, the score is derived from a population, and should be cautiously applied to an individual patient. At best, it can be used to more precisely inform family and caregivers about the likelihood of survival and good functional outcome. In doing so, these patients can experience a more timely and efficient transition to comfort measures over prolonged and possibly deleterious continued resuscitative measures that may provide minimal to no benefit. Our aim therefore, is to identify pre-, peri- and post-arrest variables associated with in-hospital mortality amongst initial survivors of an IHCA.

Methods

This was a retrospective cohort study of patients ≥18 years of age who had an IHCA at our University Medical Center from January 1, 2013 to September 31, 2016. January 2013 was used as a starting point due to a standardized protocol instituted at our institution around therapeutic hypothermia. September 2016 was used as an ending time period for this cohort due to the transition between ICD9 to ICD10 at our institution. The local Institutional Review Board approved the protocol for the study (*approval number:* 47166).

Patient population

Patients were initially screened using a multi-faceted approach to identify all cardiac arrests. This included a review of all of the code sheets in our hospital system, ICD9 codes for cardiac arrest, VT and VF arrest, therapeutic hypothermia database, and cardiac catheterization lab records. These were then manually reviewed for appropriateness of inclusion. An arrest was defined as "cessation of cardiac activity, confirmed by the absence of a detectable pulse, unresponsiveness and apnea".[7] Duplicate patient entries were excluded as well as patients who had an out of hospital cardiac arrest (OHCA), had a cardiac arrest as a terminal event (either did not survive the code or not resuscitated due to goals of care), or when code data was not available or incomplete (brief arrests occurring in the catheterization lab or during surgery for instance).

Definitions

The definitions and parameters used during this document comply with the "in-hospital Utstein style" consensus guidelines published by the AHA.[8] Pulseless ventricular tachycardia and ventricular fibrillation were classified as shockable rhythms. Pulseless electrical activity and asystole were classified as non-shockable rhythms. Re-arrest was defined as a recurrent arrest after sustained ROSC for >20 min. All relevant clinical variables, including demographic data, history of cardiovascular disease, cardiovascular risk factors and laboratory values, were obtained from review of the electronic medical record. Laboratory values of interest were the closest values recorded after ROSC was achieved.

Code response team

The code team at our institution consists of a senior medicine resident, two to three junior medical residents, registered nurses, a senior anesthesia or emergency medicine resident, a respiratory therapist and a pharmacist. All participants are certified in advanced cardiac life support (ACLS). All the information about the arrest is documented on a "code sheet" containing information such as: location of the code, time and date, patient demographics, medications administered, duration of the code, shocks delivered, and whether ROSC was achieved. Following ROSC, standard post resuscitation measures are carried out including obtaining laboratory investigations as well as transfer to a higher level of care if needed. The code leader then reviews the "code sheet" and confirms the documented information. Given the focus on IHCA, the majority of patients had code sheets that were reviewed. For scenarios where code sheets were not available, the pertinent variables were identified through chart review or charts were excluded if data was missing.

Outcomes

Patient charts were reviewed to assess for pre-specified outcomes. Since the cerebral performance category (CPC) score was inconsistently documented, we chose in-hospital mortality as a primary outcome and unfavorable discharge disposition as a secondary outcome. An unfavorable disposition was recorded if the patient died during the hospitalization, was discharged to a long-term acute care facility (requiring prolonged hospitalization or mechanical ventilatory support) or hospice. A favorable discharge disposition was determined if the patient was discharged to a skilled nursing facility (for rehabilitation purposes) or home. An exploratory analysis looking at rates and predictors of 30-day readmission was also done.

Statistical analysis

Patient characteristics were compared by outcome status. For categorical variables, frequencies and column percentages (%) were reported and p-values were calculated using χ^2 and Fisher's exact tests, as appropriate. Continuous variables were tested for normality using the Shapiro-Wilk normality test along with histograms. Normally distributed continuous variables were reported using means and standard deviations (SD) and p-values were calculated using two-sample t-tests and one-way ANOVAs. Non-normally distributed variables were reported as medians and first/third quartiles, with p-values calculated using Mann–Whitney U and Kruskal–Wallis tests. Stepwise regression procedures were used to identify the binary logistic regression models most predictive of each outcome variable by selecting the groups of predictor variables that minimize each model's AIC. Variables were excluded from consideration as predictor variables if there was too much missingness or too little variation. Nineteen variables were included in the multi-variable analysis; age, female sex, race, minutes to ROSC, re-arrest, un-shockable initial rhythm, pH, creatinine, glucose, GCS, lactate, as well as history of coronary artery disease, chronic obstructive pulmonary disease, cerebrovascular disease, diabetes mellitus, hypertension, cancer, tobacco use (past or present), and seizures. A series of stepwise regressions were then performed to isolate those variables that were most predictive of the primary outcome of survival to hospital discharge. Statistical significance was set at $p \leq 0.05$ and all tests were two-sided. Missing observations were excluded on an analysis-by-analysis basis. All analyses were done in R programming language, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). All graphics were produced using the R package ggplot2, version 3.1.1 (Hadley Wickham).

Results

A total of 1069 IHCA were recorded in our database during the study period. After excluding duplicate entries (75 patients) and entries with missing variables about the code (69 patients), 925 patients comprised the overall IHCA cohort. 305 patients did not survive the arrest and a further 349 patients died prior to hospital discharge, resulting in an overall survival of 29% (271 survived out of 925). The cohort included in the stepwise regression analyses to identify predictors of outcomes was the 620 patients who initially survived the IHCA (Fig. 1).

Univariable associations with in-hospital mortality of initial survivors of IHCA

Our cohort of 620 patients were predominantly Caucasian (86.6%), with 61.1% being male and an average age of 59.3 (SD+/−15.8). The

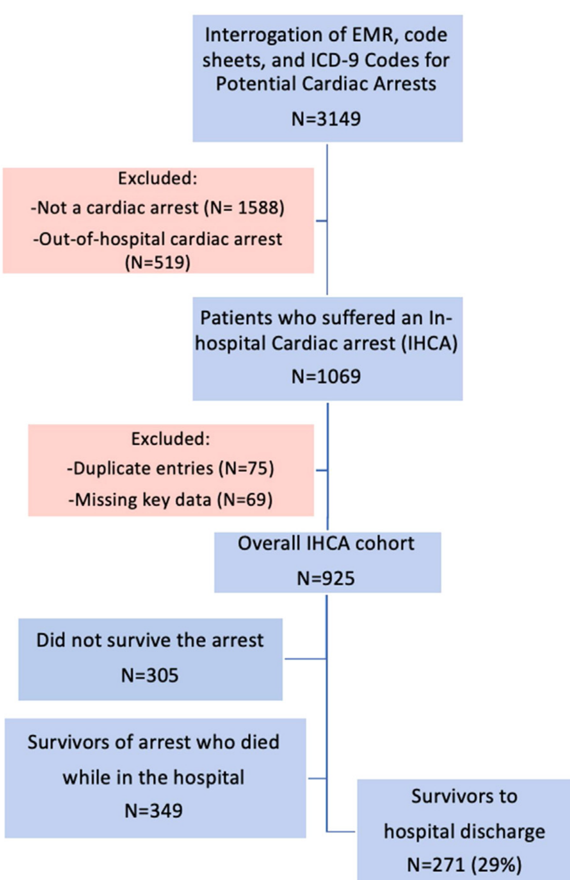

Fig. 1 – STROBE flowchart of patients.

majority of patients (81.1%) had suffered a PEA or asystolic arrest. Table 1 lists the baseline characteristics of the patient group and highlights the variables that were found to have statistically significant differences between the survivor and non-survivor groups. Of the 271 patients who survived to hospital discharge, 249 were found to have had a favorable discharge, while the other 22 were sent to hospice or long-term acute care facilities. Amongst the 271 patients who survived to hospital discharge, 67 patients (25%) were readmitted to our facility within 30 days.

Independent variables within multiple variable models

Nineteen independent variables were included in the multivariable modeling. A regression model (Model 1) utilizing the most complete data (n=593) was created for both the primary and secondary outcomes. Serum lactate level was missing in 15% of patient records but was a strong predictor of outcomes in the univariate analysis. Therefore, a second regression model (Model 2) was created with the subgroup of patients that also had lactate data available (n=504).

Primary outcome

For predicting the primary outcome of in-hospital mortality, Model 1 had an AUC of 0.735 (95% CI, 0.696−0.775) while model 2 had an AUC of 0.772 (95% CI, 0.732−0.812) [Fig. 2]. In both models, recurrent cardiac arrest was the strongest predictor of in-hospital mortality, with increasing age, increasing time to ROSC, higher serum creatinine levels, and a history of cancer being consistent predictors of mortality. In Model 2, increasing lactate levels were also predictors of in-hospital mortality. With the subsequent introduction of recurrent arrest and lactate, the prognostic value of initial non-shockable rhythm became progressively less important in the models. Female gender was also associated with higher in-hospital mortality, and improved the performance of the models, but did not reach statistical significance as an independent variable in either Model 1 (OR: 1.374, CI [0.951,1.994], p=0.091) or Model 2 (OR: 1.477, CI (0.978,2.239], p=0.065). Hypertension was found to be protective in Model 2. The results for Model 1 are displayed in Table 2 and the results for Model 2 are displayed in Table 3.

Secondary outcomes

For predicting the secondary outcome of unfavorable discharge disposition, Model 1 had an AUC of 0.719 (95% CI, 0.678−0.759) while model 2 had an AUC of 0.754 (95% CI, 0.712−0.796) [Fig. 3]. Similar to the primary outcome, recurrent cardiac arrest was the strongest predictor of an unfavorable discharge disposition with increasing age, increasing time to ROSC, increasing creatinine, and a history of cancer also being predictors in both models. An initial non-shockable rhythm and a history of seizures were predictors of unfavorable discharge disposition in both models, while they were not significant predictors in models of in-hospital mortality. In Model 2, increasing lactate was also a predictor of unfavorable discharge disposition. Similar to in-hospital mortality, there was a trend for female gender to be predictive of an unfavorable discharge disposition that did not reach statistical significance in both Model 1 (OR: 1.355, CI [0.939, 1.964], p=0.105) and Model 2 (OR: 1.391, 95% CI [0.925, 2.102], p=0.115). Finally, a history of hypertension was found to be protective of the secondary outcome in both models. Full details of

Table 1 – Patient demographics of entire cohort stratified by survival to hospital discharge.

	All patients	Survived to hospital discharge		*p*-value
		Yes	No	
Number of patients	620	271	349	
Age, years (SD)	59.3 (15.2)	58.9 (15.1)	59.6 (15.3)	0.562
Female, N (%)	239 (38.9)	96 (36.2)	143 (41.0)	0.398
Race,				0.067
White	537 (86.6)	234 (86.3)	303 (86.8)	
African American	67 (10.8)	28 (10.3)	39 (11.2)	
Other	16 (2.6)	9 (3.4)	7 (2.0)	
Medical History, N (%)				
Coronary artery disease	256 (41.7)	112 (42.3)	144 (41.3)	0.867
Chronic kidney disease	208 (33.9)	89 (33.6)	119 (34.1)	0.963
Cancer	150 (24.4)	55 (20.8)	95 (27.2)	0.080
Chronic obstructive pulmonary disease	185 (30.1)	86 (32.5)	99 (28.4)	0.315
Cerebrovascular disease	80 (13.0)	36 (13.6)	44 (12.6)	0.814
Diabetes Mellitus	227 (37.0)	100 (37.7)	127 (36.4)	0.797
Hypertension	452 (73.6)	202 (76.2)	250 (71.6)	0.235
Tobacco use, past or present	304 (49.0)	134 (49.4)	170 (48.7)	0.920
Arrest parameters, N (%)				
Non-shockable initial Rhythm	501 (81.1)	209 (77.4)	292 (83.9)	0.052
Re-arrest	153 (24.7)	24 (8.9)	129 (37.0)	<0.001
Minutes to ROSC, Median [Q1,Q3]	5.0 [3.0, 10.0]	4.0 [2.0, 8.0]	7.0 [4.0, 12.0]	<0.001
Laboratory results, median [Q1, Q3]				
Creatinine (mg/dL)	1.3 [0.9, 2.5]	1.2 [0.8, 2.2]	1.6 [1.0, 2.8]	<0.001
Glucose (mg/dL)	137.0 [108.2, 194.5]	139.0 [108.0, 195.0]	136.0 [109.0, 192.0]	0.690
Lactate (mmol/L)	3.3 [1.6, 7.6]	1.9 [1.2, 4.4]	5.2 [2.4, 9.1]	<0.001
PH	7.3 [7.2, 7.4]	7.3 [7.2, 7.4]	7.3 [7.1, 7.4]	<0.001
Troponin (ng/mL)	0.1 [0.0, 0.4]	0.1 [0.0, 0.3]	0.1 [0.1, 0.6]	0.022

ROSC: return of spontaneous circulation.

these multivariable models are available in Supplementary Table 1 and 2.

Discussion

Summary of major findings

Our study is one of the largest single-center series in recent years on the outcomes of patients resuscitated after IHCA. We report several important findings; (1) age, time to ROSC, serum creatinine level, pre-existing malignancy, serum lactate level, and re-arrest were the variables most strongly associated with in-hospital mortality, (2) recurrent arrest is the strongest predictor of outcomes and associated with a 5-fold lower survival chances after an IHCA, (3) hypertension appears to exert a protective effect on survival outcomes after an IHCA.

Comparison with previous studies

In the United States, approximately half of IHCA occur on wards with most survivors then transferred to an ICU.[9,10] This implies that ICU care providers often assume care of post IHCA patients after an arrest and then have to make decisions on their prognosis and code status. The prior published IHCA scores primarily incorporated pre-arrest patient risk factors.[11],[12] Our approach differs from what has previously been published as we incorporated peri-arrest parameters as well as included only patients who survived the index arrest event. This creates a set of parameters that are relevant to ICU providers who encounter patients after their index event which is akin to patients who suffer an OHCA, where both peri-arrest and pre-arrest factors predict survival.[13],[14]

Results of our analysis reveal the following variables to be predictive of in-hospital mortality after controlling for confounders: age, time to ROSC, re-arrest, serum creatinine level, serum lactate level, and pre-existing malignancy. Interestingly, these variables represent pre-, intra-, and post-arrest variables, most of which should be present at time of evaluation. While many of these variables have been found to be predictive in other studies, they are often done so in isolation. The multivariable regression models are better able to account for potential confounding, though collinearity may still exist.

The variable most strongly associated with the odds of in-hospital mortality was re-arrest. Although it may seem intuitive that recurrent arrest is associated with poorer survival to hospital discharge, this association only recently came to light after data from Get With The Guidelines (GWTG) registry.[6] Another notable finding from the registry analysis was the lower rates of DNR and withdrawal of care orders in patients with a recurrent arrest despite their worse prognosis.[6] Given the frequency of a recurrent arrest that we report and the poor prognosis (5-times higher odds of death), it is prudent that care providers take this into account when discussing goals of care and code status with patients and their families. Early involvement of a

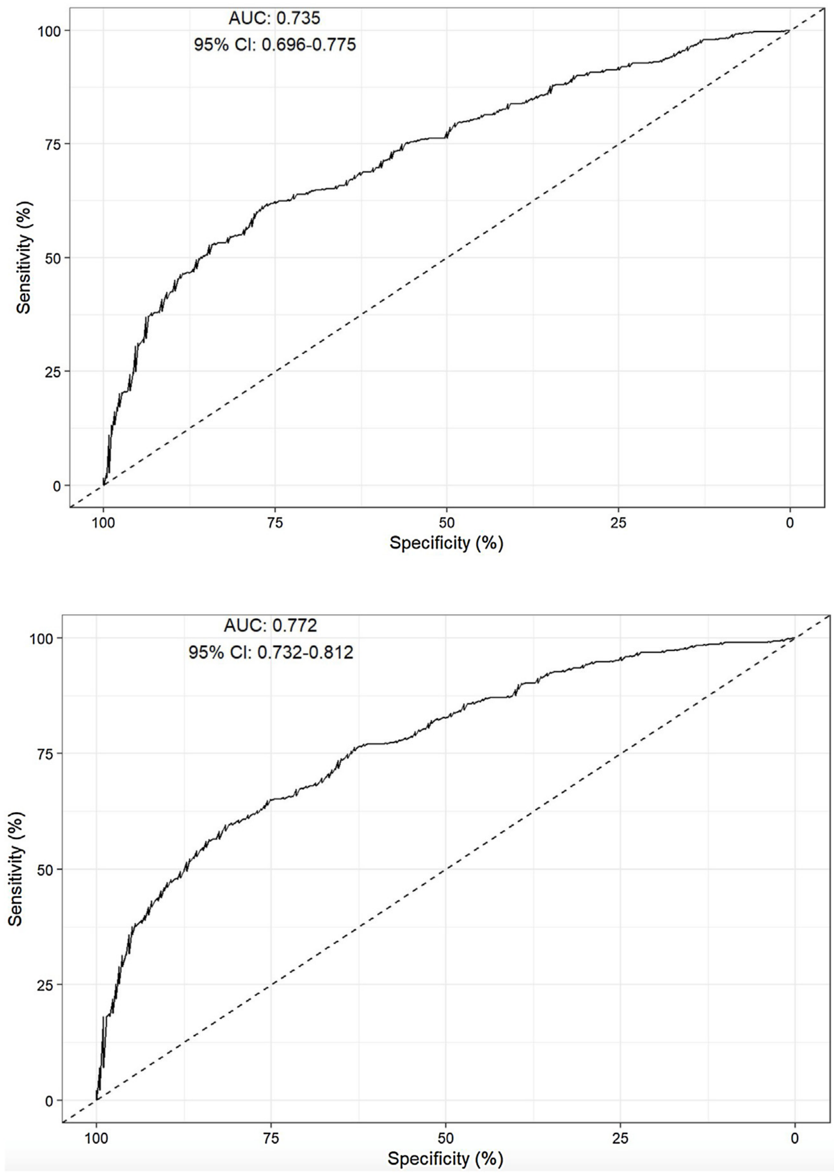

Fig. 2 – ROC plots for regression models to predict in-hospital mortality excluding lactate (top panel) and including lactate (bottom panel).

Table 2 – Regression results for predicting in-hospital mortality (total cohort).

Parameter	Failure to survive discharge (OR, 95% CI)	*p*-value
Patient age (1-year increase)	1.013 (1, 1.026)	0.057
Female (vs. male)	1.374 (0.951, 1.994)	0.091
Minutes to ROSC (1-min increase)	1.057 (1.028, 1.089)	<0.001
Re-arrest	5.871 (3.586, 9.994)	<0.001
Non-shockable initial Rhythm	1.455 (0.923, 2.305)	0.107
pH	0.359 (0.116, 1.09)	0.072
Creatinine (1-unit increase)	1.129 (1.02, 1.215)	0.020
GCS (1-point increase)	0.969 (0.93, 1.01)	0.135
Hypertension	0.642 (0.405, 1.013)	0.058
Cancer	1.655 (1.084, 2.547)	0.020

ROSC: return of spontaneous circulation.
GCS: Glasgow coma scale.

Table 3 – Regression results for predicting in-hospital mortality — lactate included.

Parameter	Unfavorable disposition at discharge (OR, 95% CI)	*p*-value
Age (1-year increase)	1.018 (1.003, 1.034)	0.017
Female (vs. male)	1.477 (0.978, 2.239)	0.065
Minutes to ROSC (1-min increase)	1.05 (1.019, 1.082)	0.001
Re-arrest	5.557 (3.206, 10.095)	<0.001
Creatinine (1-unit increase)	1.183 (1.061, 1.324)	0.003
Lactate	1.132 (1.08, 1.19)	<0.001
Hypertension	0.502 (0.297, 0.839)	0.009
Cancer	1.902 (1.188, 3.08)	0.008

ROSC: return of spontaneous circulation.

palliative care team may help align the care delivery with the patient's prognosis.

Serum lactate level has never been previously reported as a predictor of outcomes in patients with an IHCA. Notwithstanding, a previous report and a recent meta-analysis in patients after an OHCA did reveal worse outcomes in patients with higher serum lactate levels.[15,16] The finding should not be surprising as elevated lactate levels usually signal critical illness or prolonged periods of hypoperfusion, both of which are markers of poor prognosis.[17,18] Similarly, time to achieve ROSC has been previously established as a

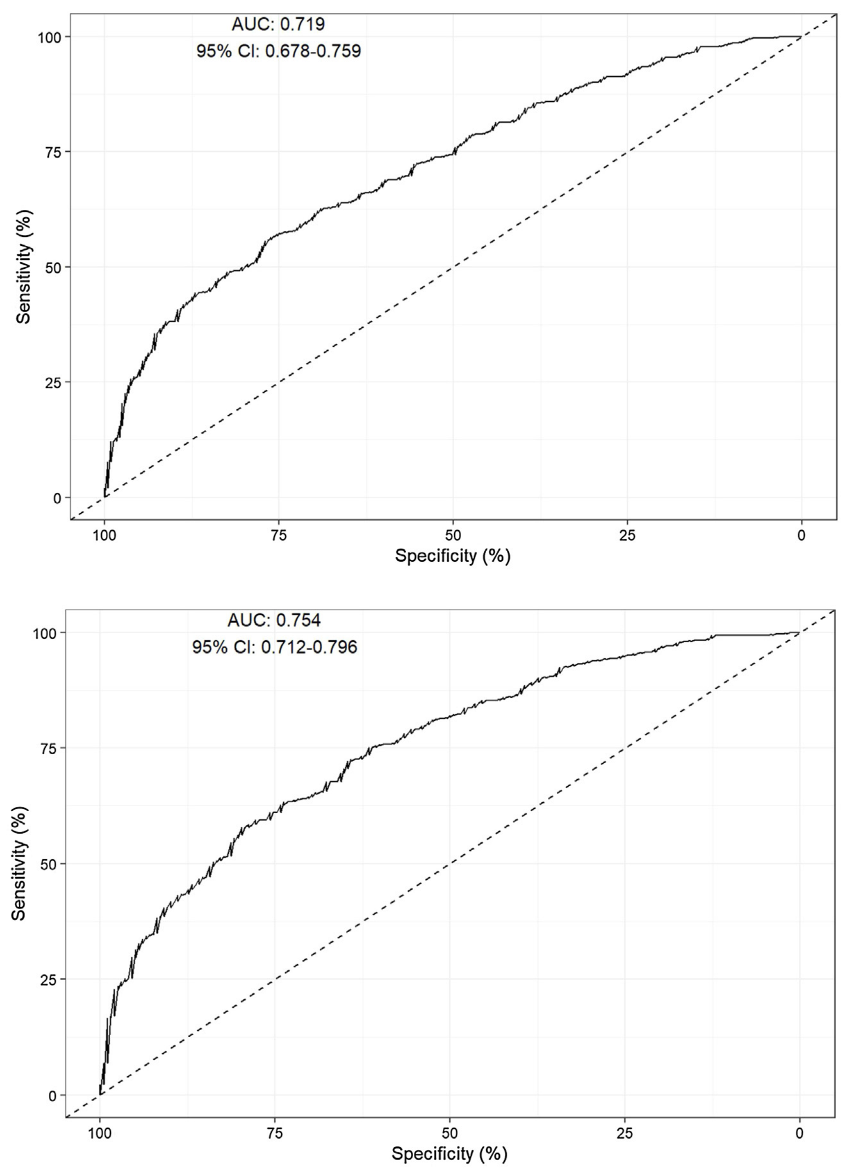

Fig. 3 – ROC plots for regression models to predict unfavorable discharge disposition excluding lactate (top panel) and including lactate (bottom panel).

determinant of survival to hospital discharge.[5,19–21] Our study reports the significance of time to ROSC even as a continuous variable with every additional minute reducing the odds of survival by 5%. We also confirm that malignancy and elevated serum creatinine levels are associated with in-hospital mortality after an IHCA as has been previously reported.[5,22] While older reports yielded conflicting data about the impact of age on outcomes after an IHCA, our results are in-line with the more contemporary data which show worse outcomes after an IHCA amongst the elderly.[5,21,23,24]

One interesting finding is the limited role of the initial rhythm in predicting in-hospital mortality when controlling for recurrent cardiac arrest and lactate levels. A potential explanation is the implication that an initial shockable rhythm is more likely to be correctable in etiology or more likely to occur in otherwise healthier patients. However, recurrent cardiac arrest is likely a more reliable marker of recurrence risk or the ability to correct the underlying etiology. Likewise, lactate levels may be a better marker of underlying patient health, as does age, end-organ function, and pre-existing conditions. Lactate levels (and potentially creatinine) indicate the level of hypoperfusion, which may influence mortality more than etiology. It is worth noting however, that patients who suffered brief arrests during invasive procedures (coronary angiography for instance) were excluded from our analysis. These patients are typically defibrillated and resuscitated rapidly and thus our findings do not extend to this population.

Hypertension, on the other hand, appeared to have a protective effect on survival to hospital discharge, a finding which has never been previously reported. It is well established that heart disease, with hypertension being one of its prominent risk factors, is strongly associated with the incidence of cardiac arrest.[25] Recently, data from OHCA survivors revealed that a history of hypertension was linked to higher likelihood of survival to hospital discharge.[26] Any potential explanations for our findings remain speculative. Certain anti-hypertensive medication may exert a protective effect; angiotensin converting enzyme inhibitors and preserved ischemic preconditioning.[27] Another hypothesis includes worse outcomes among patients with early post ROSC hypotension suggesting that higher blood pressure may be associated with better outcomes.[28] However, there is no data to support that hypertensive patients attain a higher blood pressure post ROSC, so this association is difficult to confirm. Although the findings of our study suggest a link between hypertension and favorable prognosis after IHCA, more research must be conducted to better understand the underlying causal mechanism and to confirm our findings.

Strengths and limitations

As one of the largest single-center experiences of outcomes in patients who survived an initial IHCA, we report on important associations (re-arrest and serum lactate levels) that have not been previously well reported in the IHCA literature. Given the large cohort of patients included and the limited exclusion criteria for our study, our results should be generalizable to many other centers who wish to explore the outcomes of IHCA survivors.

As a retrospective, single-center study consisting of a select patient population, our report has limitations. It is subject to the inherent limitations of a retrospective study including accuracy of documented information within the electronic medical record and the tracking of follow up data. While we had no data on CPC or other objective scores to define outcomes on discharge, we used discharge from hospital as a surrogate outcome since it has been shown that these patients have decent long-term survival rates.[22] We did not have detailed information on arrest aspects such as chest compression interruptions or intubations. Similarly, we did not record post-arrest treatments such as hypothermia or cardiac catheterizations, but those are used infrequently in IHCA survivors.[29] Patients who may have sustained brief cardiac arrests during invasive procedures (invasive angiography for instance) typically have favorable outcomes as they are quickly defibrillated. These patients were excluded from our analysis as they are difficult to capture (sub-optimal coding or charting) and this represents a selection bias. Finally, the variables identified in our study are dynamic and available at different times during the patient's course and thus may not be translatable into a risk score.

Conclusion

We report on several pre-, peri-, and post-arrest variables associated with in-hospital mortality amongst IHCA survivors. We were able to confirm that age, time to ROSC, pre-existing malignancy, serum creatinine levels, and re-arrest are associated with increased odds of in-hospital mortality. Re-arrest was found to be the strongest predictor of poor outcomes. For the first time, we demonstrated an association between serum lactate levels and worse outcomes in patients with an IHCA. Finally, our results suggest a protective effect of hypertension on outcomes which represents an intriguing area for future research.

Financial disclosure/relationship with industry

None.

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Conflict of interest

All authors have no financial support and protentional conflicts of interest for this work.

CRediT authorship contribution statement

Talal Alnabelsi: Investigation, Writing - original draft, Writing - review & editing, Visualization, Data curation. **Rahul Annabathula:** Writing - original draft, Visualization. **Julie Shelton:** Investigation, Validation, Data curation. **Marc Paranzino:** Investigation, Validation, Data curation. **Sarah Price Faulkner:** Investigation, Data curation. **Matthew Cook:** Investigation, Data curation. **Adam J. Dugan:** Formal analysis, Visualization, Data curation. **Sethabhisha Nerusu:** Formal analysis, Data curation. **Susan S. Smyth:** Conceptualization, Writing - review & editing, Supervision. **Vedant A. Gupta:** Conceptualization, Methodology, Writing - review & editing, Supervision, Data curation.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resplu.2020.100039.

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