1-1-2016

Sudden Cardiac Arrest: Novel Uses of Risk Standardization and Post-Arrest Body Temperature to Improve Outcomes

Anne Victoria Grossestreuer
University of Pennsylvania, agrossestreuer@gmail.com

Sudden Cardiac Arrest: Novel Uses of Risk Standardization and Post-Arrest Body Temperature to Improve Outcomes

Abstract
Sudden cardiac arrest is a leading cause of death and disability in the US, with over 500,000 events annually and <20% surviving to hospital discharge. Half of survivors suffer some degree of neurologic disability from massive ischemic injury and subsequent reperfusion processes. It therefore is vital to evaluate cardiac arrest at both population and clinical levels to improve outcomes. In response, this dissertation had three objectives. First, we examined whether hospital performance could be benchmarked using administrative data, which is more common than registry data. Two risk standardization models were developed using logistic regression involving 2453 patients treated from 2000-2015 at University of Pennsylvania Health System hospitals. Registry and administrative data were accessed for all patients and used to develop separate risk standardization models with survival to hospital discharge as the outcome and the registry model considered the "gold standard." The administrative model had a receiver operating characteristic (ROC) area of 0.891 (95% CI: 0.876-0.905) compared to a registry area of 0.907 (95% CI: 0.895-0.919), indicating that risk standardization can be performed using administrative data. Second, serial temperatures were collected during the 72 hours following targeted temperature management (TTM) and rewarming on 465 TTM-treated patients from the Penn Alliance for Therapeutic Hypothermia (PATH) registry, of whom 179 (38.5%) had at least one pyrexic temperature (≥38oC). Higher maximum temperature was associated with worse neurologic outcome and lower survival in pyrexic patients. Pyrexia duration and outcomes were not related, unless duration was calculated as hours at or above 38.8oC; at those elevated temperatures, longer duration was associated with worse neurologic and survival outcomes. Third, serial temperatures were collected during the 72 hours post-arrest on 578 PATH patients not treated with TTM; 228 (39.5%) had at least one pyrexic temperature. Worse neurologic and survival outcomes were associated with increasing maximum temperature, the combination of higher maximum temperatures and longer durations at an elevated temperature, and timing of onset of pyrexia between 10.2-24.5 hours post-arrest. This work establishes the potential for using administrative data to create new opportunities to compare hospital performance regarding cardiac arrest and extends knowledge on clinical implications of post-arrest temperature on outcomes.

Degree Type
Dissertation

Degree Name
Doctor of Philosophy (PhD)

Graduate Group
Epidemiology & Biostatistics

First Advisor
Benjamin S. Abellla

Second Advisor
Douglas J. Wiebe

SUDDEN CARDIAC ARREST: NOVEL USES OF RISK STANDARDIZATION AND POST-ARREST BODY TEMPERATURE TO IMPROVE OUTCOMES

Anne V. Grossestreuer

A DISSERTATION

in

Epidemiology and Biostatistics

Presented to the Faculties of the University of Pennsylvania

in

Partial Fulfillment of the Requirements for the

Degree of Doctor of Philosophy

2016

Supervisor of Dissertation

_____

Benjamin S. Abella, Associate Professor of Emergency Medicine

Graduate Group Chairperson

_____

John H. Holmes, Professor of Medical Informatics in Epidemiology

Dissertation Committee

Douglas J. Wiebe, Associate Professor of Epidemiology

David F. Gaieski, Associate Professor of Emergency Medicine

Michael W. Donnino, Associate Professor of Emergency Medicine; Pulmonary/Critical Care Medicine

This dissertation is dedicated to my family, whose support and unwavering confidence were integral in all stages of my education.

ACKNOWLEDGEMENT

I would like to acknowledge my dissertation committee for providing invaluable feedback and guidance. I especially would like to acknowledge my dissertation committee chair, Dr. Douglas Wiebe, for his support and creativity in exploring sources of funding to ensure that I would be able to finish coursework and my dissertation, and Dr. David Gaieski, for the encouragement that led to the pursuit of a doctorate, as well as direction over the last six years. Also, thanks to Drs. Joshua Nelson and Eric Mutter for serving as resuscitation experts and evaluating thousands of diagnoses, procedures, and orders associated with cardiac arrest patient hospitalization.

Additionally, I would like to acknowledge my colleagues at the Center for Resuscitation Science and the Center for Clinical Epidemiology and Biostatistics, particularly Dr. Sarah Perman, Gail Delfin, Kelsey Sheak, Marisa Cinousis, David Buckler, Daniel Ikeda, and Dr. Alison Culyba, who served as sounding boards, collaborators, study partners, voices of reason, and, most importantly, friends. Finally, thanks to Brian William Gish, for his patience reading manuscripts, editing graphs, and listening to presentations, and his steadfast belief in my ability to achieve any goals.

ABSTRACT

SUDDEN CARDIAC ARREST: NOVEL USES OF RISK STANDARDIZATION AND POST-ARREST BODY TEMPERATURE TO IMPROVE OUTCOMES

Anne V. Grossestreuer, M.S.

Benjamin S. Abella, M.D., M.Phil.

Sudden cardiac arrest is a leading cause of death and disability in the US, with over 500,000 events annually and <20% surviving to hospital discharge. Half of survivors suffer some degree of neurologic disability from massive ischemic injury and subsequent reperfusion processes. It therefore is vital to evaluate cardiac arrest at both population and clinical levels to improve outcomes. In response, this dissertation had three objectives. First, we examined whether hospital performance could be benchmarked using administrative data, which is more common than registry data. Two risk standardization models were developed using logistic regression involving 2453 patients treated from 2000-2015 at University of Pennsylvania Health System hospitals. Registry and administrative data were accessed for all patients and used to develop separate risk standardization models with death prior to hospital discharge as the outcome. The registry model considered the "gold standard." The administrative model had a receiver operating characteristic (ROC) area of 0.891 (95% CI: 0.876-0.905) compared to a registry area of 0.907 (95% CI: 0.895-0.919), indicating that risk standardization can be performed using administrative data. Second, serial temperatures were collected during 72 hours following targeted temperature management (TTM) and rewarming on 465 TTM-treated patients from the Penn Alliance for Therapeutic Hypothermia (PATH)

registry, of whom 179 (38.5%) had at least one pyrexic temperature (≥38°C). Higher maximum temperature was associated with worse neurologic outcome and lower survival in pyrexic patients. Pyrexia duration and outcomes were not related, unless duration was calculated as hours ≥38.8°C; at those elevated temperatures, longer duration was associated with worse neurologic and survival outcomes. Third, serial temperatures were collected during the 72 hours post-arrest on 578 PATH patients not treated with TTM; 228 (39.5%) had at least one pyrexic temperature. Worse neurologic and survival outcomes were associated with increasing maximum temperature, the combination of higher maximum temperatures and longer durations at an elevated temperature, and timing of onset of pyrexia between 10.2-24.5 hours post-arrest. This work establishes the potential for using administrative data to create new opportunities to compare hospital performance regarding cardiac arrest and extends knowledge on clinical implications of post-arrest temperature on outcomes.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ILLUSTRATIONS

CHAPTER 1

Cardiac arrest risk standardization using administrative data compared to registry data

INTRODUCTION

Cardiac arrest is a challenge to prevent, manage, and study as a clinical condition in the real world. Differences in definitions (Nishiyama et al. 2014), termination-of-resuscitation rules (Sasson et al. 2009; Sasson et al. 2010), data collection (Cummins et al. 1991; Jacobs et al. 2004; Nishiyama et al. 2014) and participation in registries (Sasson et al. 2010), as well as patient heterogeneity (Cabanas et al. 2015) make even capturing the incidence of sudden cardiac arrest difficult (Cummins et al. 1991; Grasner et al. 2011; Jacobs et al. 2004; Morrison et al. 2008; Nishiyama et al. 2014). This diversity can lead to differences in outcomes that may be influenced by variations in care (Carr et al. 2009a; Carr et al. 2009b; Chen et al. 2015; Fredriksson, Herlitz, Nichol 2003; Heffner et al. 2012; Hinchey et al. 2010; Kellum, Kennedy, Ewy 2006; Kellum et al. 2008; Lund-Kordahl et al. 2010; Nichol et al. 2008; Nichol and Soar 2010; Spaite et al. 2014; Stub et al. 2015). However, recent initiatives to change both intra- and post-arrest care have led to improved outcomes (Adielsson et al. 2011; Fothergill et al. 2013; Fugate et al. 2012; Hollenberg, Svensson, Rosenqvist 2013; Iwami et al. 2009; Iwami et al. 2012; Japanese Circulation Society Resuscitation Science Study Group 2013; Kitamura et al. 2010; Kitamura et al. 2012; Neumar et al. 2008; Peberdy et al. 2010; Ro et al. 2013; Tagami et al. 2012; Weisfeldt et al. 2010; Wissenberg et al. 2013), highlighting the importance of performing these assessments. Additionally, the Institute of Medicine has recognized as a

priority the need for better cardiac arrest data collection and outcomes improvement (Becker, Aufderheide, Graham 2015).

An important step to better understand the management of cardiac arrest involves comparing hospitals to determine which modalities and clinical protocols are associated with better outcomes (Donnino et al. 2012). Unfortunately, many US hospitals do not participate in a registry that provides such outcomes; contributing can be prohibitive in terms of financial and time costs (Khuri et al. 1998; Render et al. 2003). Additionally, voluntary participation in a registry may lead to selection bias (Ferreira-Gonzalez et al. 2009). As registry data are the only current method for risk adjustment (Chan et al. 2013) in cardiac arrest, there is no way to enable fair comparison of observed mortality relative to expected mortality given patient characteristics across all US hospitals treating cardiac arrest.

To our knowledge, no studies have investigated whether administrative data on cardiac arrest, which have been shown to be effective in sepsis patients (Lagu et al. 2011). Administrative data potentially are available for all hospitals in the U.S., could perform as well as registry data to accomplish risk standardization in order to study variability in cardiac arrest outcomes. If, as we hypothesized, administrative-type data perform as well as registry data in this population, we will have evidence that a tool for risk standardization can be developed and applied to hospitals across the US. Using data from a national cardiac arrest registry at the University of Pennsylvania and administrative data from the University of Pennsylvania Health System on the same cohort of cardiac arrest patients, we aimed to develop a method for risk-standardizing hospital survival after cardiac arrest using administrative data that is validated against one

using registry data.

METHODS

Data source

The registry data were from the Penn Alliance for Therapeutic Hypothermia (PATH) database. PATH is an internet-based registry established by the University of Pennsylvania in 2010. PATH includes cardiac arrest data from pre-hospital, emergency department, and in-hospital settings. Potentially available to any US hospital, PATH supports the tracking of all patients who experience cardiac arrest and receive cardiopulmonary resuscitation. Cardiac arrest is defined in PATH as a loss of pulse with subsequent chest compressions. Each patient record in PATH consists of 30 required data elements based on the Utstein template (Jacobs et al. 2004; Perkins et al. 2014). One hundred additional data elements are required for research participation. Further optional data elements are also available to address specific research questions. Data are entered via a secure website and maintained on a password-protected encrypted server at the University of Pennsylvania. Data are collected retrospectively at each of the participating institutions. Before entering data, data abstractors undergo structured training including mock case entry and case review. All participants are provided with a standardized data dictionary and are subject to a formal auditing process (Leary et al. 2013). PATH currently supports 34 member hospitals from 19 US states and includes data from over 5000 cardiac arrests. Exclusion criteria are age <18 years, traumatic etiology of arrest, active do-not-resuscitate orders prior to arrest, and lack of administrative data. This study was approved by the University of Pennsylvania Institutional Review Board.

Administrative data for this study were from the Penn Data Store, a research initiative at the University of Pennsylvania that integrates clinical data on all University of Pennsylvania Health System (UPHS) patients. All available administrative information on cardiac arrest patients (defined as having an ICD-9 code of 427.5) seen at three UPHS hospitals, the Hospital of the University of Pennsylvania, Penn Presbyterian Medical Center, and Pennsylvania Hospital, was queried, and consisted of demographics, procedure codes, diagnosis codes, and drug and other orders. These data were then matched on medical record number to records from the PATH database. Only the patients who have both registry data in PATH and administrative-type data in Penn Data Store were included in the risk standardization model building.

Model building

Recommended guidelines for conducting risk adjustment for trauma, another time-sensitive critical illness, have been published, allowing comparison of trauma center outcomes (Newgard et al. 2013). Using these methods as guidance, we applied and adapted that approach to develop two risk standardization models.

First, we developed a method for risk-standardization using registry data for in- and out-of-hospital cardiac arrest patients using logistic regression with survival to discharge as the outcome. Cox regression was not used because our interest was not in time to the outcome of interest (death) but in whether death had occurred by hospital discharge. A total of 17 variables (Table 1) were modeled as potential independent, adjustor variables. The variables were selected to match, to the extent possible, the variables in the Utstein template (Jacobs et al. 2004; Perkins et al. 2014). These variables were modeled through a backward stepwise variable selection process (using a $p<0.25$ to

enter the model) (Maldonado and Greenland 1993; Mickey and Greenland 1989) to generate the most parsimonious model and evaluate changes in predictive ability. Variables that did not contribute to prediction were excluded from the final model. The final model included race, whether the arrest was witnessed, initial rhythm, age, if intra-arrest epinephrine was given, cumulative dose of intra-arrest epinephrine, if patient was treated with TTM, year of arrest, and whether the patient regained consciousness shortly post-arrest (defined as ineligibility for TTM due to purposeful following of commands). Significant missing data (more than 5% but no more than 15%) were addressed through multiple imputation, conducted using 20 iterations and then combined using the "mi estimate" Stata command (Cañette and Marchenko 2013; Newgard et al. 2013; StataCorp 2013). A final logistic regression model generated the risk-adjusted predicted probability of death for each patient, ranging from 0 to 1, with higher values indicating a higher predicted probability that a given patient had died by hospital discharge. This final predictive model was assessed using conventional techniques including the Hosmer-Lemeshow goodness-of-fit statistic to assess calibration, calibration curves, c-statistic to assess discrimination, and Akaike information criterion value to compare model fit and composition across multiple models. The resulting model was considered the gold standard for risk adjustment for our study purposes. In order to accommodate for multiple imputation, we used two strategies once arriving at a final model to derive a predicted probability for each patient: the predicted value of each of the imputed data sets averaged per patient using the "mim" suite of commands (Galati, Royston, Carlin 2013) and by using the imputed dataset closest to the median receiver operating characteristic (ROC) curve with the better Hosmer-Lemeshow goodness-of-fit statistic.

To verify that there are not significantly better modeling methods of risk standardization in this population, we repeated this analysis using hierarchical mixed effect models and generalized estimating equations. Bayesian analysis was not explored, due to its incompatibility with multiple imputation, and linear and Poisson regression were not used because of the nature of the outcome and our question of interest (dichotomous survival) (Newgard et al. 2013).

Next, we developed a method for risk-standardizing hospital survival using administrative data. To identify candidate variables for exploration, we queried all available diagnostic codes, procedure codes, demographics, and orders for all patients with an ICD-9 code for cardiac arrest (427.5). We then isolated all unique diagnosis codes, procedure codes, and orders. These were assessed by two physician-fellows in resuscitation science to determine, by consensus, which of these should be explored as candidate variables due to their possible relationship to survival. Each identified candidate variable then was tested in univariate logistic regression against the outcome of interest (death at hospital discharge).

We next employed the same logistic regression methodology to the administrative data as was done with the registry data, developing a logistic regression model using death at hospital discharge as the outcome. The administrative candidate variables were modeled as potential independent, adjustor variables through a manual forward stepwise variable selection process (using a univariate $p<0.25$ to enter the model) (Maldonado and Greenland 1993; Mickey and Greenland 1989). Variables that did not contribute to prediction were excluded from the final model. Variance inflation factors were checked and collinear variables were collapsed or omitted. There was no missing data in the

administrative data set that was greater than 1%. The final logistic regression model generated the risk-adjusted predicted probability of death for each patient; this model was used in comparison to the "gold standard" registry model.

Finally, we assessed the performance of the risk standardization done using administrative data to the performance of the "gold standard" risk standardization done using registry data. The results for both sets of analysis were reported as c-statistics, calibration plots, and Bland-Altman plots. To evaluate the models against each other, we used Bland-Altman plots to assess mean difference in predicted values and the percentage of values outside the limits of agreement, defined as two standard deviations of the mean difference (Giavarina 2015), a Hosmer-Lemeshow plot of the performance of the predicted values from each model compared to the observed values, and tests of the equality of receiver operating characteristic (ROC) areas between models. The last assessment, a test of the equality of ROC areas between models, was chosen a priori as the final determination for model comparison, with significance assessed at $p<0.05$.

In the primary analysis, all patients will be included. However, due to differences in out-of-hospital versus in-hospital cardiac arrest, the same methodology will be applied to those two subgroups to evaluate differences in model performance based on location of arrest.

RESULTS

Patient population

There were 2453 patients who had both administrative and registry data between 1/2000-4/2015. This cohort had a median age of 63 (IQR: 51, 74) years; 57.8% of these

patients were male, 44.1% white, 24.8% had an initial shockable rhythm of ventricular fibrillation or pulseless ventricular tachycardia (VF/VT), 60.6% had a presumed cardiac etiology of arrest, 53.7% had an out-of-hospital cardiac arrest (OHCA), 26.3% of OHCAs received bystander CPR, 74.8% had a witnessed arrest, and 83.5% had intra-arrest epinephrine given, with a median dose of 2 (IQR: 0, 3) mg. The median duration of arrest was 11 (IQR: 5, 25) minutes, 62.5% had return of spontaneous circulation (ROSC), 19.8% of patients received TTM, 17.4% of patients regained arousal shortly post-ROSC, 25.8% of patients survived to hospital discharge, and 20.0% of patients had a favorable neurologic outcome (as defined as a Cerebral Performance Category [CPC] score of 1-2, an outcome measure which is commonly employed in the resuscitation literature (Bernard et al. 2002; Hypothermia after Cardiac Arrest Study Group 2002; Nielsen et al. 2013; Perkins et al. 2014).

Registry risk standardization

There were 2622 cardiac arrests in PATH between 1/2000-4/2015 and 2453 of the arrests matched with administrative data (93.6%). The patients that did not match with administrative data were significantly more likely to have initial shockable rhythms, to be African-American, to have a cardiac etiology of arrest, to have an OHCA, to have a witnessed arrest, to not receive epinephrine intra-arrest and to receive a lower dose if given, to have a longer duration of cardiac arrest, to achieve ROSC, to not receive TTM, to regain consciousness shortly post-arrest, to survive to hospital discharge and to have an CPC score of 1 or 2 at hospital discharge (Appendix Table 1).

The c-statistic in the final model containing nine predictor variables using the average predicted values from each imputation was 0.9119 (95% CI: 0.9003-0.9235) with

a median Hosmer-Lemeshow goodness-of-fit statistic of 0.36 (IQR: 0.19-0.58). The final model using the median imputed dataset had a c-statistic of 0.9078 (95% CI: 0.8959-0.9197) with a Hosmer-Lemeshow goodness-of-fit statistic of 0.38. However, when evaluating the risk standardization with Bland-Altman plots using the model composed of the average predicted values from all imputations, we found a much worse fit in terms of Pitman's test of difference in variance than when using the single imputed dataset. Therefore, we chose to use the values from the median imputed dataset as the "gold standard". The ROC area used for comparison to administrative modeling was slightly different due to a few missing ages in the administrative dataset (<1%).

Use of generalized estimating equations controlling for clustering by year provided identical results (c-statistic: 0.9078 [95% CI: 0. 0.8959-0.9197]). Use of a mixed effects model with year as a random intercept resulted in an ROC area of 0.9147 (95% CI: 0.9028-0.9267), which was not statistically different from either the logistic regression or the generalized estimating equations approach.

Administrative risk standardization

Penn Data Store reported 5424 patients between 1/2000-4/2015 with an ICD-9 code of 427.5. These patients were 57.3% male, 50.1% white, and had a median length of hospital stay of 6 (IQR: 1, 17) days. Forty-five percent of the patients with an ICD-9 code for cardiac arrest were matched with registry data. On these 5424 arrests, there were 1423 unique procedure codes, 2001 unique drugs, 5632 unique orders, and 4723 unique diagnosis codes (13,792 candidate variables including race, sex, and age).

A list of all unique procedure codes, drug orders, other orders, and diagnosis codes was compiled for assessment by two physician-fellows in resuscitation science

involved in this study. Both fellows eliminated any variables assessed as irrelevant for predicting survival outcome in cardiac arrest patients. Any variable eliminated by one fellow but not the other remained eligible for exploration. After the fellows' assessment, 1719 (12.5%) potential variables remained. Each of these was then analyzed in univariate logistic regression with survival to discharge as the outcome. Any variable with a p-value of <0.25 remained eligible for the model, which resulted in 317 variables. Using manual forward selection in order of lowest p-value to highest, variables were then entered into the logistic regression model. Variables remained in the model if they improved the predictive value and were removed if they worsened the predictive value or if it remained the same. After analyzing all 317 variables, 133 remained in the model (Appendix Table 2) with a c-statistic of 0.8905 (95% CI: 0.8757-0.9054) and a Hosmer-Lemeshow goodness of fit of 0.58. To get a c-statistic>0.80, only 15 variables were needed: codes 37.94 (Implantation or replacement of automatic cardioverter/defibrillator, total system), 96.72 (Continuous invasive mechanical ventilation for 96 consecutive hours or more), 96.04 (Insertion of endotracheal tube), 43.11 (Percutaneous [endoscopic] gastrostomy [PEG]), 37.22 (Left heart cardiac catheterization), 414.01 (Coronary atherosclerosis of native coronary artery), 507 (Pneumonitis due to solids and liquids), 599 (Urinary tract infection, site not specified), 39.61 (Extracorporeal circulation auxiliary to open heart surgery), 37.23 (Combined right and left heart cardiac catheterization), 427.41 (Ventricular fibrillation), 88.53 (Angiocardiography of left heart structures), year of arrest, respiratory failure (composite of 518.81, 518.83, 518.84, and 799.1), and presence of a DNR (composite of V49.86 and order for DNR-C [comfort measures]). The ROC curve for this reduced model was 0.8004. To assess the performance of other models, we

used a generalized estimating equation model controlling for clustering by year and a mixed effects model with year as a random intercept. Both of these models provided identical results to the model using logistic regression (c-statistic: 0.8905 [95% CI: 0.8757-0.9054]).

Comparing risk standardization models

Using the "rocgold" Stata command, the registry data ROC area using the imputation with a value closest to the median was 0.9069 (95% CI: 0.8949-0.9189) compared to an administrative ROC area of 0.8905 (95% CI: 0.8755-0.9052). This was an insignificant difference (p=0.075; Figure 1). Controlling for trend with a Bland-Altman plot, we found that the mean difference between the two methods of risk standardization was 0.002 (95% CI: -0.009-0.014) with a non-significant Pitman's test of difference in variance (p=0.437), which we conclude represents good agreement; the line of equality falls within the confidence interval of the mean difference and only 4.97% of the data points lie outside the recommended range of two standard deviations of the mean difference. As seen in Figure 2, there is more agreement in the patients with a predicted poor outcome (Giavarina 2015). Both models had good calibration, as seen in Figures 3 & 4 and by non-significant Hosmer-Lemeshow goodness-of-fit statistics.

Out-of-hospital cardiac arrest

In patients with an out-of-hospital cardiac arrest, 231 of the 1719 candidate variables identified by the two resuscitation science physician-fellows had a univariate relationship with survival of $p<0.25$. Using manual forward selection in order of lowest p-value to highest, variables were entered into the model, remaining in the model if the predictive value was improved and removed if the predictive value worsened or remained

the same. After analyzing all 231 variables, 98 remained in the model (Appendix Table 3) with a c-statistic of 0.9346 (95% CI: 0.9178-0.9515) and a Hosmer-Lemeshow goodness of fit statistic of 0.08. To get a c-statistic>0.80, only 5 variables were needed: codes 96.72 (Continuous invasive mechanical ventilation for 96 consecutive hours or more), 96.04 (Insertion of endotracheal tube), 37.22 (Left heart cardiac catheterization), 414.01 (Coronary atherosclerosis of native coronary artery), and year of arrest. The ROC area for this reduced model was 0.8011.

The best model for the registry data was the model developed for use in both in- and out-of-hospital arrests. This model had an ROC area of 0.9447 (95%CI: 0.9328-0.9567) when limited to OHCAs. Comparing the registry and administrative models, there was no significant difference in the ROC areas (p=0.316; Figure 5). Less than 5% of the data points in the Bland-Altman plot lie outside the recommended range of two standard deviations of the mean difference (Appendix Figure 1).

In-hospital cardiac arrest

Inpatients with an in-hospital cardiac arrest, 172 of the 1719 candidate variables identified by the two resuscitation science physician-fellows had a univariate relationship with survival of $p<0.25$. Using manual forward selection in order of lowest p-value to highest, variables were entered into the model, remaining in the model if the predictive value was improved and removed if the predictive value worsened or remained the same. After analyzing all 172 variables, 100 remained in the model (Appendix Table 4) with a c-statistic of 0.8673 (95% CI: 0.8447-0.8898) and a Hosmer-Lemeshow goodness of fit statistic of 0.065. To attain a c-statistic>0.80, 18 variables were needed: 96.71 (Continuous invasive mechanical ventilation for less than 96 consecutive hours), 96.72

(Continuous invasive mechanical ventilation for 96 consecutive hours or more), 599 (Urinary tract infection, site not specified), 43.11 (Percutaneous [endoscopic] gastrostomy [PEG]), 37.22 (Left heart cardiac catheterization), 37.94 (Implantation or replacement of automatic cardioverter/defibrillator, total system), V49.86 (presence of a DNR), 0.17 (infusion of a vasopressor), 429.83 (Takotsubo syndrome), 995.92 (Severe sepsis), 997.31 (ventilator-associated pneumonia), 8.45 (Intestinal infection due to clostridium difficile), 37.72 (Initial insertion of transvenous leads [electrodes] into atrium and ventricle), 50.59 (liver transplant), 570 (acute necrosis of liver), 38.97 (Central venous catheter placement with guidance), 276.2 (acidosis), and 88.72 (diagnostic ultrasound of heart). The ROC area for this model is 0.8003.

The best model for the registry data was the model developed for use in both in- and out-of-hospital arrests. This model had an ROC area of 0.8629 (95% CI: 0.8412-0.8846) when restricted to in-hospital arrests. Comparing the registry and administrative models, there was no significant difference in the ROC areas (p=0.781; Figure 6). Less than 5% of the data points in the Bland Altman plot lie outside the recommended range of two standard deviations of the mean difference (Appendix Figure 2).

DISCUSSION

In developing two risk standardization models with extremely small differences between their c-statistics (0.0164), we have identified that risk adjustment modeling for cardiac arrest can be performed using administrative data, which are readily available and less costly (Khuri et al. 1998; Render et al. 2003) and less challenging to compile and to access than registry data. We therefore have evidence that a tool developed using

administrative data is feasible and that this model can be optimized for all patients or stratified by location of arrest. This tool could be applied in research to identify variability in the management of cardiac arrest and to learn from effective modalities and protocols to allow hospitals identify opportunities for improvement.

Other studies have used risk standardization in the context of in-hospital cardiac arrest. One, using nine variables in their model of in-hospital cardiac arrest in the United States, found a c-statistic of 0.74, and was successful in risk standardizing hospital survival rates (Chan et al. 2013). Another study of in-hospital cardiac arrest done in the U.K. found a c-statistic of 0.81 (Harrison et al. 2014). In our work, we had a similar c-statistic in both our registry and administrative models when limited to in-hospital arrests.

In the U.S., there has been found to be a 42% difference in the odds of survival in in-hospital arrests even after risk adjusting the patient population for comparison (Merchant et al. 2014). Hospital-level interventions have been shown to be effective (Adielsson et al. 2011; Fothergill et al. 2013; Fugate et al. 2012; Hollenberg, Svensson, Rosenqvist 2013; Iwami et al. 2009; Iwami et al. 2012; Japanese Circulation Society Resuscitation Science Study Group 2013; Kitamura et al. 2010; Kitamura et al. 2012; Neumar et al. 2008; Peberdy et al. 2010; Ro et al. 2013; Tagami et al. 2012; Weisfeldt et al. 2010; Wissenberg et al. 2013), and hospitals that perform well with regard to in-hospital cardiac arrest have also been found to be better at preventing cardiac arrest (Chen et al. 2013). Therefore, adequate comparisons, such as those provided using risk standardization, are vital to improve patient care and outcomes.

A recent study called into question the utility of administrative data for identifying out-of-hospital cardiac arrest (Coppler et al. 2016). Investigators queried ICD-

9 codes for cardiac arrest as well as VF, paroxysmal ventricular tachycardia, ventricular flutter, and respiratory arrest and found that only 40% of patients who had these ICD-9 codes had an out-of-hospital cardiac arrest upon chart review. Similarly, we found that 45% of the patients with an ICD-9 code for cardiac arrest were matched with registry data, although our study only included one ICD-9 code as well as both in- and out-of-hospital cardiac arrests. Although 94% of the cardiac arrests in the registry were able to be matched to administrative data, there were some significant differences between the patients who were matched and those who were not. Interestingly, and in concordance with the above study, all patients who were not matched were able to be successfully resuscitated, leading to the unmatched patients having significantly better neurologic and survival outcomes. Despite our ability to risk standardize in a comparable way to registry data, we do not currently have a way to accurately capture administrative data on the patient population in question. Further work is needed to develop methods to identify this population in administrative datasets as well as to elucidate the scope of the problem.

To properly build a nationally representative tool, clustering by site may be problematic and, although we found similar results using logistic regression compared to generalized estimating equations and hierarchical mixed effects modeling in our study of a single health system, those methods may be warranted in multi-site analysis. However, if the goal is to compare risk-standardized hospital performance, controlling for clustering by hospital may smooth out important differences at the hospital level; in that case, logistic regression would be encouraged.

The data from PATH have the limitations of data from any retrospective registry, including the use of predefined data points and the risk of data entry errors or

inconsistencies. Additionally, while administrative data potentially are available from all institutions and can be a reflection of "real world" situations, the information in these databases are not collected for research purposes, and often key variables are not recorded by administration, which have non-medical and non-research motivations for collecting information; these motivations can lead to documentation that might not match with research documentation. Finally, the data collected by the University of Pennsylvania Health System may differ from that collected at other institutions, despite having many common elements, limiting generalizability.

CONCLUSION

This study serves as evidence that risk standardization using administrative data is comparable to that of registry data in the context of cardiac arrest. The critical gap of only having information on the performance of a subset of hospitals that participate in a registry potentially could be addressed by providing support for a new method that may identify hospital variability. This could lead to the identification of successful strategies at high-performing hospitals and the targeting of low-performing hospitals for intervention. Future investigations into expanding this methodology to include more sites may lead to a new tool for nationwide risk standardization to allow benchmarking and comparison of hospitals in terms of expected to observed mortality to identify high- and low-performing hospitals.

CHAPTER 2

Degree of temperature elevation is associated with neurologic and survival outcomes in resuscitated cardiac arrest patients with post-rewarming pyrexia

INTRODUCTION

Significant morbidity and long-term impairments are common in cardiac arrest survivors (Cronberg et al. 2015; Moulaert et al. 2009; Nichol et al. 2015; Raina et al. 2008; Smith et al. 2015). Approximately half of survivors suffer some degree of neurologic disability (Moulaert et al. 2009), resulting from ischemic injury occurring during no- and low-flow states as well as reperfusion injury occurring after restoration of native circulation. Collectively, this injury pattern is known as post-cardiac arrest syndrome (PCAS) (Adrie et al. 2002; Neumar et al. 2008). The adverse consequences of PCAS are frequent but variable, ranging from memory loss and proprioceptive derangements to persistent vegetative state (Moulaert et al. 2009; Raina et al. 2008), with impact on long-term function, health, and economic cost. Laboratory and clinical studies have suggested that elevated temperatures may exacerbate PCAS and subsequent neurologic injury (Leary et al. 2013; Polderman 2008; Suffoletto et al. 2009; Winters et al. 2013).

Two randomized trials from 2002 demonstrated that post-arrest therapeutic hypothermia, also known as targeted temperature management (TTM), improves neurologic outcomes and survival. In these investigations, patients with out-of-hospital cardiac arrest (OHCA) with initial shockable rhythms were randomized to prompt cooling to 32-34°C for 12-24 hours or to passive temperature management (Bernard et al.

2002; Hypothermia after Cardiac Arrest Study Group 2002). Observational studies have confirmed these findings for OHCA from shockable rhythms and extended these findings to other types of cardiac arrest patients (Arrich and European Resuscitation Council Hypothermia After Cardiac Arrest Registry Study Group 2007; Busch et al. 2006; Lundbye et al. 2012; Oddo et al. 2006; Perman et al. 2015; Sagalyn et al. 2009; Schefold et al. 2009; Sunde et al. 2007). However, in part due to concerns that the control groups in both of the trials trended toward an elevated mean temperature and that a significant percentage of the control patients had pyrexia, a recent multicenter clinical trial (Nielsen et al. 2013) randomized both arms to active TTM, 33°C or 36°C. That study found no significant difference in terms of neurologic outcome or mortality, raising the question of whether reduced temperature is the protective component of TTM treatment or if protection is conferred by avoidance of elevated temperatures (Nielsen et al. 2013; Rittenberger and Callaway 2013).

Development of markedly elevated temperatures (pyrexia), often a response to cellular injury, activation of inflammatory cascades, or infection (Saper and Breder 1994), is frequent after cardiac arrest (Albrecht, Wass, Lanier 1998; Bouwes et al. 2012; Cocchi et al. 2014; Merchant et al. 2006; Pichon et al. 2007; Suffoletto et al. 2009; Takasu et al. 2001; Takino and Okada 1991; Winters et al. 2013; Zeiner et al. 2001). In diverse groups of patients with encephalopathy, markedly elevated temperatures are often a marker of poor outcomes and continued physiologic damage (Madden and DeVon 2015; Niven and Laupland 2013; Sadaka 2013; Wrotek et al. 2011); however, whether this is true in post-arrest patients, particularly those treated with TTM, has yet to be clearly demonstrated. A connection between pyrexia and worse outcomes in TTM-

treated patients has received support in smaller retrospective studies (Bro-Jeppesen et al. 2013; Gebhardt et al. 2013; Leary et al. 2013; Suffoletto et al. 2009; Winters et al. 2013), extending findings from earlier research done prior to the adoption of TTM as standard of care for treatment of anoxic encephalopathy (Albrecht, Wass, Lanier 1998; Langhelle et al. 2003; Zeiner et al. 2001).

We hypothesized that TTM-treated patients with higher maximum temperatures following rewarming will have worse outcomes than those with lower maximum temperatures. We also hypothesized that patients with a longer duration of time at pyrexic temperatures and with earlier onset of pyrexia will have worse outcomes than those with a shorter duration.

MATERIALS AND METHODS

To evaluate how body temperature is related to outcomes after reestablishment of post-TTM normothermia, the Penn Alliance for Therapeutic Hypothermia (PATH) registry was queried. PATH is an internet-based registry established at the University of Pennsylvania in 2010 that includes cardiac arrest data from pre-hospital, emergency department, and in-hospital settings with a focus on post-arrest care. Potentially available to any US hospital, PATH supports tracking patients who experience cardiac arrest and receive cardiopulmonary resuscitation. Each record in PATH consists of 30 data elements required from all participating institutions. One hundred additional data elements are required for institutions interested in using aggregate PATH data for research and further optional data elements are also available, including the capability to collect serial temperature measurements for successfully resuscitated patients. Data are

entered via a secure website and maintained on a password-protected encrypted server. Before entering data, data abstractors undergo structured training including mock case entry and case review. They are provided with a standardized data dictionary and subject to a formal auditing process (Leary et al. 2013). PATH currently supports 34 member hospitals and includes data from >5000 cardiac arrests. This project was approved by the University of Pennsylvania Institutional Review Board.

Serial temperatures in the 72 hours following reestablishment of post-TTM normothermia (defined as reaching ≥36.5°C (Bro-Jeppesen et al. 2013) after a period of TTM treatment at temperature of ≤34.0°C) were evaluated. Only patients who received TTM were included. Exclusion criteria were: age <18 years; traumatic etiology of arrest; death in the first 24 hours post-arrest; and no recorded temperatures during the applicable time period. Patients also were excluded if target temperature (≤34°C) was never achieved or if they did not survive until completion of the rewarming phase of TTM. Both OHCA and in-hospital cardiac arrests (IHCA) were included. Pyrexia was defined as ≥38.0°C, which has been used in other post-cardiac arrest studies on the effects of temperature (Benz-Woerner et al. 2012; Bouwes et al. 2012; Bro-Jeppesen et al. 2013; Gebhardt et al. 2013; Leary et al. 2013; Suffoletto et al. 2009; Winters et al. 2013). The primary outcome was neurologic status (measured by a Cerebral Performance Category (CPC) score dichotomized into "favorable" [CPC 1-2] and "unfavorable" [CPC 3-5]) and the secondary outcome was survival, both measured at hospital discharge. CPC has been used frequently as an outcome measure in prior clinical studies of cardiac arrest (Bernard et al. 2002; Hypothermia after Cardiac Arrest Study Group 2002; Nielsen et al. 2013).

There were three predefined exposures: maximum temperature, duration of pyrexia, and timing of onset of first pyrexic temperature (described below); maximum temperature was the primary analysis for which the study was powered.

Maximum temperature

Maximum temperature was defined as the highest recorded temperature in the 72 hours after completion of TTM and rewarming. Multiple classification approaches were used to account for different possibilities of how maximum temperature related to outcomes: as a continuous variable, as an ordinal variable (by single temperature degree), and as a dichotomous variable (≥38.0°C, yes/no) in separate models. Of note, 118 (25%) of the patients evaluated for maximum temperature were included in previous work analyzing temperature elevation (Leary et al. 2013), although the patients in that study were followed for 48 hours instead of 72 hours and normothermia was defined as 37.0^{o}C instead of 36.5°C. In that project, duration of pyrexia and timing of onset were not analyzed, so the patients were shared only when the effects of maximum temperature were analyzed.

Duration of pyrexia

The duration of time a patient experienced a certain temperature (or above) was calculated by assigning half of the time at a pyrexic temperature and half of the time at a non-pyrexic temperature when the patient transitioned between a pyrexic to a non-pyrexic point (and vice versa). This calculation ended 72 hours post-rewarming and was repeated for every tenth of a degree, beginning with 38.0°C and ending with 42.2°C (the highest recorded temperature), to calculate the duration of time at or above each tenth of a degree. This was to assess whether duration of time at different temperatures (e.g.

38.0°C, 38.1°C, 38.2°C,...42.2°C) had different relationships to outcomes. Due to diversity in maximum temperature cutoffs across studies (Leary et al. 2013; Winters et al. 2013), we analyzed each tenth of a degree to allow for a data-driven temperature threshold, as opposed to one that was predefined. Each measure of time was treated first as a continuous variable (hours at temperature of interest) and then as an ordinal variable (divided by tertile) for each temperature cut point.

Timing of onset of pyrexia

Timing of onset of pyrexia was defined as the time between the patient's return to normothermia and the first recorded pyrexic temperature (≥38°C). Timing of onset of pyrexia was assessed in 4 ways: early (first 36 hours post-normothermia) vs. late (second 36 hours post-normothermia) onset, continuously (time from normothermia to first temperature ≥38°C in hours), in deciles, and in groups determined by Jenks natural break optimization, a statistical technique that uses the distribution of data to determine naturally occurring groupings (Cox 2007; Jenks 1967). We also explored whether timing of onset of a temperature higher than 38.0°C was associated with outcomes; this temperature was chosen by comparing the univariate areas under the curve (AUCs) in relation to outcomes and selecting the temperature with the best discrimination.

Patient types

To combine all three elements of temperature examined in pyrexic patients, 12 different patient categories were created based on naturally occurring groupings, as determined by Jenks natural break optimization (Cox 2007; Jenks 1967). There were two groups of maximum temperature (low versus high), two groups of duration of pyrexia (short versus long) and three groups of timing of onset of pyrexia (early versus middle

versus late; Appendix Table 5). Patient types then were analyzed with regard to outcomes. Due to some patient types having a low number of patients, 16 patient types were created involving just two dimensions of temperature and the analyses were repeated.

Other data analysis

For each dimension of temperature analysis, pre-, intra-, and post-arrest variables recorded in PATH (Appendix Table 6) were examined to explore potential confounders. Descriptive statistics used proportions, means and standard deviations, medians and interquartile ranges, and histograms to determine the proportion or prevalence and distribution of each variable. Each potential confounder was modeled separately with the outcome prior to use in a multivariate model. Any multivariate analyses used $p<0.25$ for covariate entry into the model (Maldonado and Greenland 1993; Mickey and Greenland 1989). A parsimonious model was then created using backward stepwise procedures and likelihood ratio tests (Lemeshow and Hosmer 1982). Less than 15% of data on covariates was missing; missing data on covariates was addressed using multiple imputation conducted using 20 iterations (StataCorp 2013) and then combined using the "mi estimate" Stata command (Cañette and Marchenko 2013). Regression results were reported using odds ratios (ORs) and corresponding 95% confidence intervals (CIs). All data were analyzed using Stata v13.1 (Statacorp, College Station, TX). Additional analyses stratified by location of arrest (OHCA/IHCA) were performed, since IHCA patients are more likely to have multi-organ dysfunction and thus have elevated temperatures from other causes (Winters et al. 2013) and restricted to only patients with a maximum temperature ≥38.0°C. Finally, each component, maximum temperature,

duration of pyrexia, and timing of onset of pyrexic temperature, was tested to assess whether there was a univariate "threshold" value using receiver operating characteristic (ROC) curves and concordance statistics for discrimination. Post-estimation Hosmer-Lemeshow goodness of fit tables were used to assess validity of each chosen cut-off.

RESULTS

Out of 465 TTM-treated patients from 13 hospitals in the PATH registry treated between 2005-2015 who met inclusion criteria, 179 (38.5%) had at least one pyrexic temperature (≥38°C). Pyrexic patients had a mean age of 56.0±16.0 years, 59.8% were male, 39.5% had an initial shockable rhythm, 69.4% had a witnessed arrest, 65.9% had a suspected cardiac etiology of arrest, and 83.2% were OHCA (Table 2). In terms of demographics, they only differed significantly from non-pyrexic patients in terms of age (pyrexic: 56.0±16.0 versus non-pyrexic: 60.4±16.4; p=0.001). However, the relationship between temperature and outcomes was not modified by age.

Maximum temperature

Our primary analysis, examining the effect of maximum temperature on neurologic outcome, controlling for age, duration of arrest, whether the arrest was witnessed, location of arrest, and initial rhythm, found that higher maximum temperature was associated with worse neurologic outcome (aOR: 0.30 [95% CI: 0.10-0.84], p=0.022) and lower survival (aOR: 0.25 [95% CI: 0.10-0.59], p=0.002; Table 3A) in patients who experienced post-rewarming pyrexia (Figure 7).

When analyzing the role of pyrexia (maximum temperature: ≥38.0°C) versus non-pyrexia (maximum temperature: <38.0°C), there was no significant relationship with

neurologic outcome (Table 3B), although there was a protective effect for pyrexia with regard to survival. Further analysis revealed that this was largely driven by IHCA patients, and that, when analyzing only patients with a maximum temperature of ≥37°C, the difference became non-significant.

Duration of pyrexia

There was no significant relationship between duration of pyrexia and outcomes unless duration was calculated as time a patient experienced temperature ≥38.8°C. This is the lowest temperature at which significant associations were found with regard to either the primary or secondary outcome. When measuring duration of temperature ≥38.8°C, there was a significant association between longer duration and worse neurologic outcome and lower survival (Table 3C). This relationship was similar when duration was measured against survival as time with temperature ≥38.9°C for neurologic outcome and for all subsequent tenths of a degree until 39.5°C.

Timing of onset of pyrexia

There was no significant relationship between the timing of onset of a temperature ≥38.0°C and outcomes (aOR for neurologic outcome: 1.01 [95% CI: 0.99-1.04], p=0.233; aOR for survival: 1.02 [95% CI: 1.00-1.04], p=0.129). When pyrexia onset was measured as first time ≥38.7°C (the value with the best AUC in univariate analysis with regard to neurologic outcome [0.603 for neurologic outcome and 0.609 for survival]), there were no significant differences (aOR for neurologic outcome: 1.03 [95% CI: 0.99-1.08], p=0.168; aOR for survival: 1.01 [95% CI: 0.98-1.04], p=0.535).

Patient types

Combining these elements into "patient types," the patients with high temperatures always had lower (worse) point estimates than their low temperature counterparts, regardless of other factors. This difference was statistically significant for both neurologic outcome and survival when comparing the high temperature/early pyrexia group to the low temperature/early pyrexia group (CPC 1-2: OR: 0.33 [95% CI: 0.14-0.77], p=0.011; survival: OR: 0.25 [95%CI: 0.08-0.79], p=0.018). Compared to the low temperature/short duration group, the high temperature/long duration group was statistically worse in terms of neurologic status (OR: 0.36 [95% CI: 0.16-0.83], p=0.017).

Comparing the low temperature/long duration group to the high temperature/long duration group and to the high temperature/short duration group, the higher temperature groups had worse survival (high temperature/long duration OR: 0.35 [95% CI: 0.16-0.79], p=0.011; high temperature/short duration OR: 0.24 [95% CI: 0.07-0.90], p=0.034). There were no significant differences in either outcome for the patient types that included only duration and timing of onset. There were similar findings with regard to survival and neurologic outcome when the analysis was restricted to OHCA patients.

Using all three temperature elements to determine "patient type", there were significantly worse neurologic outcomes in the high temperature /long duration/early pyrexia group compared to the low temperature/long duration/early pyrexia group (OR: 0.25 [95% CI: 0.08-0.77], p=0.016). There also were significantly worse survival outcomes in both the high temperature/long duration/early pyrexia group (OR: 0.31 [95% CI: 0.11-0.89], p=0.029) and the high temperature/short duration/early pyrexia group (OR: 0.12 [95% CI: 0.02-0.69], p=0.017) when compared to the low temperature/long

duration/early pyrexia group. There were similar findings with regard to survival and neurologic outcome when the analysis was restricted to OHCA patients.

Other data analysis

Each component, maximum temperature, duration of pyrexia, and timing of onset of pyrexia, was tested to examine if there was a univariate "threshold" value using receiver operating characteristic (ROC) curves and concordance statistics for discrimination. There was no cut-off value that was predictive of outcomes by itself (data not shown).

DISCUSSION

In this study of serial temperatures examining TTM-treated post-arrest patients with pyrexia, there was a linear relationship between increasing maximum temperature and worsening neurologic and survival outcomes. There was no significant difference between the two other aspects of pyrexia, duration and timing, except, in the case of duration, where the risk of pyrexia increased with hours at a very elevated temperature (≥38.8°C). The importance of elevated temperatures in terms of post-arrest outcomes was reinforced when, using all three temperature elements to determine "patient type", higher (more favorable) point estimates for all low temperature types compared to their high temperature counterparts were found, as well as statistically worse outcomes when comparing high temperature groups to their low temperature counterparts holding the other temperature elements constant. This suggests a critical link between high temperature and neurologic injury in patients experiencing post-rewarming pyrexia; thus, avoidance of high temperatures might improve outcomes.

Prior clinical studies have demonstrated the complexity of assessing the relationship between post-arrest temperature and outcomes. A recent investigation found that post-rewarming pyrexia was associated with favorable survival and neurologic outcomes. However, the mean maximum temperature in this work was 37.5°C (range: 36.8-38.1°C), which supports the finding of this study that mild pyrexia may not provoke injury; in fact, markedly elevated temperatures may pose the problem with regard to outcomes (Lee et al. 2015). Other studies, defining pyrexia as ≥38.0°C, also found no relationship between being above this temperature and outcomes (Bouwes et al. 2012; Cocchi et al. 2014). A study analyzing both patients who received TTM and those who did not found that pyrexia (defined as ≥38.0°C) had no association with neurologic outcomes and was not associated with survival within the whole cohort or the patients who received TTM, but was associated with lower survival in patients who did not receive TTM, which could be explained by the difference in maximum temperature in the TTM group (37.6±1.0°C) compared to the non-TTM group (38.2±1.0°C) (Gebhardt et al. 2013). Suffoletto et al found that patients experiencing post-arrest pyrexia (≥38.0°C) had worse survival and neurologic outcomes; however, the vast majority of the patients in this study did not receive TTM and mean maximum temperature in the pyrexic group was not reported (Suffoletto et al. 2009).

Examining elevated pyrexia after TTM, defined as ≥38.5°C in the first 24 hours after TTM cessation, Winters et al found an association between a temperature ≥38.5°C and worse outcomes with regard both to survival and neurologic status, consistent with the results of this study (Winters et al. 2013). Similarly, our previous work (as mentioned

in the Methods section) found no association between patients experiencing pyrexia when defined as ≥38.0°C and outcomes, but did find that patients with "marked pyrexia" (>38.7°C) compared to those who experienced no/mild pyrexia (≤38.7°C)) had significantly worse neurologic outcomes at hospital discharge (Leary et al. 2013).

Two recent randomized trials, one in adults ("TTM trial") (Nielsen et al. 2013) and one in children (Therapeutic Hypothermia After Pediatric Cardiac Arrest trial, or THAPCA) (Moler et al. 2015), randomized patients to receive active TTM at different goal temperatures, 33°C versus 36°C in the TTM trial and 33°C versus 36.8°C in the pediatric THAPCA trial. The null results from these studies raise questions regarding mechanisms by which TTM confers benefit: whether physiologic changes resulting from mild hypothermia or prophylaxis against pyrexia is the vital component (Rittenberger and Callaway 2013; Rittenberger and Callaway 2014). Although both studies failed to find a significant difference between the two temperature goals, the second study has been criticized as potentially underpowered – that the trend toward more positive outcomes in the group at goal temperature 33.0°C (p=0.14) is not statistically significant simply because there were not enough patients in the study (Geva, Tasker, Randolph 2015; Riess, Aufderheide, Yannopoulos 2015). One possible explanation for the statistical differences in the two studies is in the different temperatures for the "normothermia" arm (36.0°C compared to 36.8°C). In the TTM trial, a goal body temperature of 36°C resulted in an upper limit of the 95% confidence interval of recorded temperatures being between 37.0-37.5°C; these patients were well protected from pyrexia (van der Jagt and Haitsma 2015). The THAPCA trial, with its goal temperature 0.8°C higher than the 36°C arm in

the TTM trial may not provide the same protection against temperatures ≥38.0°C with similar confidence bounds, although this is not necessarily the case. If higher temperatures are indeed indicative of worsened outcomes, then permitting higher temperatures may be associated with worse outcomes, which may explain the trend toward better results in THAPCA patients treated at 33°C (Moler et al. 2015).

This argument is supported by studies of the physiologic effects of elevated temperature on the brain. Laboratory investigations have suggested that a broad array of post-arrest pathophysiological processes is worsened by hyperthermia (Polderman 2008; Winters et al. 2013). Avoidance of pyrexia has been recommended in international resuscitation guidelines (Deakin et al. 2010; Peberdy et al. 2010), as pyrexia induces inflammatory cascades and increases neuronal excitotoxicity with neurotransmitter release, free radical production, increased intracellular glutamate concentration (Badjatia 2009; Zhao et al. 1997), neuroinflammation, influx of excess calcium into injured brain cells leading to hyper-metabolism, trapping of heat in injured areas (Polderman 2009), and a generalized increase in metabolic rate (Lanier 1995; Polderman 2008; Polderman 2009; Polderman 2015). As demonstrated in animal studies, high brain temperature, independent of initial severity of injury, can cause additional neurological damage (Polderman 2009; Wang et al. 2009). There is also a relationship between temperature changes and ischemia; post-ischemic injury is aggravated under hyperthermia (Busto et al. 1987; Dietrich et al. 1990; Kobayashi et al. 2008). This provides a scientific rationale for these findings on the deleterious effects of more markedly elevated temperatures.

A number of limitations are inherent in this work. This study represented an analysis of a retrospective registry. As such, this study was limited to using predefined

data points and has the risk of data entry errors or inconsistencies. Additionally, there may be information bias if the highest temperature was not recorded in the patient chart, which could result in misclassification. As a retrospective study, whether increased body temperature causes brain injury directly or merely acts as a surrogate marker for more severely damaged patients (Bro-Jeppesen et al. 2013; Winters et al. 2013) cannot be tested, although these findings are consistent with a large body of mechanistic work. Despite these limitations, use of a registry allows for a heterogeneous patient population, leading to greater external validity and generalizability.

CONCLUSIONS

In patients experiencing post-rewarming pyrexia, higher temperatures are associated with worse outcomes. Longer duration of time at pyrexic temperatures is only associated with worse outcomes at high temperatures (≥38.8°C), suggesting that avoidance of markedly elevated temperatures might improve outcomes.

CHAPTER 3

Degree, duration, and timing of temperature elevation are associated with neurologic and survival outcomes in resuscitated cardiac arrest patients with post-arrest pyrexia

INTRODUCTION

Approximately half of sudden cardiac arrest survivors suffer some degree of neurologic disability (Moulaert et al. 2009) from massive ischemic injury and subsequent reperfusion processes, known collectively as the post-cardiac arrest syndrome (PCAS) (Adrie et al. 2002; Neumar et al. 2008). Two randomized trials published in 2002 demonstrated that post-arrest therapeutic hypothermia, also known as targeted temperature management (TTM), greatly improves neurologic outcomes and survival when applied early after successful resuscitation from out of hospital cardiac arrest (OHCA) associated with an initial shockable rhythm (VF/VT)) (Bernard et al. 2002; Hypothermia after Cardiac Arrest Study Group 2002). A large number of observational studies have confirmed and extended these findings, including evidence that TTM can be applied to arrests caused by other rhythms and to IHCA (Arrich and European Resuscitation Council Hypothermia After Cardiac Arrest Registry Study Group 2007; Busch et al. 2006; Lundbye et al. 2012; Oddo et al. 2006; Perman et al. 2015; Sagalyn et al. 2009; Schefold et al. 2009; Sunde et al. 2007). However, a recent study from Europe (Nielsen et al. 2013) has challenged the current paradigm of post-arrest TTM. This investigation differed from the trials in 2002 in that both arms of the trial received active TTM, each with a different goal temperature: a “hypothermic” group with a goal of 33°C

and a “normothermic” group with an actively managed goal of 36°C. The study found no significant difference in terms of neurologic outcome or mortality, which has raised the question of whether mild hypothermia is the important component of TTM treatment or if the avoidance of elevated temperatures is (Nielsen et al. 2013; Rittenberger and Callaway 2013).

Because patients treated with TTM have their temperatures controlled, potentially masking variation and preventing extreme temperatures, we sought to explore the relationship between three different elements of post-arrest temperature and outcomes in patients not treated with TTM. Although studies examining the role of temperature in post-arrest patients prior to the widespread use of TTM exist, post-arrest care has changed dramatically since those works were conducted (Callaway et al. 2015; Hinchey et al. 2010; Kellum, Kennedy, Ewy 2006; Kellum et al. 2008; Lund-Kordahl et al. 2010; Neumar et al. 2008; Spaite et al. 2014). Additionally, the population of patients not treated with TTM has changed. The most recent studies evaluating post-arrest temperature include patients treated with TTM (Gebhardt et al. 2013; Suffoletto et al. 2009), causing difficulty in effectively ascertaining the effects of temperature in patients not treated with TTM, a group that could serve to inform comparisons regarding the protective mechanisms of TTM (Rittenberger and Callaway 2013). Investigation of patients not treated with TTM provides an opportunity to expand the scientific understanding of neurologic mechanisms underlying PCAS and post-arrest temperature.

METHODS

To evaluate how body temperature during the 72 hours following successful

resuscitation from cardiac arrest is related to outcomes, the Penn Alliance for Therapeutic Hypothermia (PATH) registry was queried. PATH is an internet-based registry established by University of Pennsylvania investigators in 2010 that includes cardiac arrest data from pre-hospital, emergency department, and in-hospital settings with a focus on post-arrest care. With participation open to any US hospital, PATH supports the tracking of all patients who experience cardiac arrest and receive cardiopulmonary resuscitation, and currently includes cases from 34 hospitals. Each patient record in PATH consists of 30 data elements required from all participating institutions. One hundred additional data elements are required for research participation and further optional data elements are also available to address specific research questions. Data are entered via a secure website, maintained on a password-protected encrypted server at the University of Pennsylvania, and collected retrospectively at each participating institution by trained PATH clinical data collection volunteers. Before entering data, data abstractors undergo structured training including mock case entry and case review. They are provided with a standardized data dictionary and subject to a formal auditing process (Leary et al. 2013). PATH currently supports 34 member hospitals and includes data from over 5000 cardiac arrests. PATH includes the capability of collecting serial temperature measurements for successfully resuscitated patients.

Serial temperatures in the 72 hours after successful resuscitation from cardiac arrest were evaluated in the current study. Only patients who did not receive TTM were included. Exclusion criteria were age <18 years; traumatic etiology of arrest; death in the first 24 hours post-arrest; and no recorded temperatures during the applicable time period. Both OHCA and IHCA were included. Pyrexia was defined as ≥38.0°C, consistent with

definitions used in other post-cardiac arrest studies on the effects of temperature (Benz-Woerner et al. 2012; Bouwes et al. 2012; Bro-Jeppesen et al. 2013; Gebhardt et al. 2013; Leary et al. 2013; Suffoletto et al. 2009; Winters et al. 2013); additionally, this temperature is also used as part of systemic inflammatory response syndrome (SIRS) criteria in sepsis, a condition that has been found to have much in common with PCAS (Adrie et al. 2002; Neumar et al. 2008). Our primary outcome was neurologic status (measured by a Cerebral Performance Category (CPC) score dichotomized into "favorable" [CPC 1-2] and "unfavorable" [CPC 3-5]) and our secondary outcome was survival, both measured at hospital discharge. The CPC score measured at discharge has been found to be reliable in terms of predicting long-term prognosis, especially survival (Hsu et al. 2014; Pachys et al. 2014; Phelps et al. 2013). There were three predefined exposures: maximum temperature, duration of pyrexia, and timing of onset of first pyrexic temperature (described below); maximum temperature was the primary analysis for which the study was powered.

Maximum temperature

Maximum temperature was defined as the highest recorded temperature in the 72 hours immediately post-arrest. Multiple classification approaches were used to account for different possibilities of how maximum temperature related to outcomes: as a continuous variable, as an ordinal variable (by one temperature degree), and as a dichotomous variable (≥38.0°C, yes/no) in separate models.

Duration of pyrexia

The duration of time a patient experienced a pyrexic temperature was calculated in three ways: a low estimate (included time between consecutive pyrexic temperatures

with an assumed 1 hour buffer for a pyrexic temperature followed by a non-pyrexic temperature (or vice versa)) (Gebhardt et al. 2013), a high estimate (included time between consecutive pyrexic temperatures with all time from the pyrexic temperature to the next non-pyrexic temperature recorded) (Gebhardt et al. 2013), and an estimate that assumed that the transition between a pyrexic to a non-pyrexic point indicated half of the time at a pyrexic temperature and half of the time at a non-pyrexic temperature. All estimates ended at 72 hours post-arrest. These calculations were repeated for every tenth of a degree, beginning with 38.0°C and ending with 42.6°C (the highest recorded temperature for any patients during the time period of interest), to measure the duration of time at or above each tenth of a degree and assess whether duration of time at increasing temperatures (e.g., 38.0°C, 38.1°C, 38.2°C, ….42.6°C) had different relationships to outcomes. Due to diversity in maximum temperature cut points across studies (Takino and Okada 1991; Zeiner et al. 2001), we analyzed each tenth of a degree to allow for a data-driven temperature threshold, as opposed to one predefined. Each measure of time then was treated first as a continuous variable (hours at temperature of interest), as an ordinal variable (divided by tertile), and as a dichotomous variable (above/below the median duration) for each temperature cut point.

Timing of pyrexia onset

Timing of onset of pyrexia was defined as the time between return of spontaneous circulation and the first recorded pyrexic temperature (≥38.0°C). Timing of onset of pyrexia was assessed in 5 ways: early (first 36 hours post-arrest) vs. late (second 36 hours post-arrest) onset, early (before the median) vs. late (after the median) onset, as a continuous variable (time from arrest to first temperature ≥38.0°C in hours), in deciles,

and in groups established using Jenks natural break optimization, a statistical technique that uses the distribution of data to determine naturally occurring groupings (Cox 2007; Jenks 1967).

Patient types

To combine all three elements of temperature examined in patients with a maximum temperature ≥38.0°C, 12 different patient types were created based on naturally occurring groupings, as determined by Jenks natural break optimization (Cox 2007; Jenks 1967). There were two groups of maximum temperature (low versus high), two groups of duration of pyrexia (short versus long) and three groups of timing of onset of pyrexia (early versus middle versus late). These patient types then were analyzed with regard to neurologic and survival outcomes. Due to some patient types having a low number of patients, 16 additional patient types were created involving just two dimensions of temperature and the analyses were repeated.

Other data analysis

For maximum temperature, duration of pyrexia, and timing of onset of pyrexia, pre-, intra-, and post-arrest variables recorded in PATH were examined to explore potential confounders. Descriptive statistics used proportions, means and standard deviations, medians and interquartile ranges, and histograms to determine the proportion or prevalence and distribution of each variable. Each potential confounder was modeled separately with the outcome prior to use in a multivariate model. Any multivariate analyses used $p<0.25$ for covariate entry into the model (Maldonado and Greenland 1993; Mickey and Greenland 1989). Parsimonious models were created using backward stepwise procedures and likelihood ratio tests (Lemeshow and Hosmer 1982). Missing

data on covariates of more than 5% but no more than 15% were addressed using multiple imputation conducted using 20 iterations (StataCorp 2013) and combined using the "mi estimate" Stata command (Cañette and Marchenko 2013). Regression results were reported using odds ratios (ORs) and corresponding 95% confidence intervals (CIs). All data were analyzed using Stata v13.1 (Statacorp, College Station, TX). Additional analyses stratified patients by location of arrest (OHCA/IHCA) and by whether the patient regained arousal shortly post-arrest or remained comatose. Finally, each component, maximum temperature, duration of pyrexia, and timing of onset of pyrexic temperature, was tested to assess whether there was a univariate "threshold" value using receiver operating characteristic (ROC) curves and concordance statistics for discrimination. Post-estimation Hosmer-Lemeshow goodness of fit tables were used to assess the validity of each chosen cut-off.

RESULTS

Out of 578 patients from 8 hospitals in the PATH registry treated from 2001-2015 who met inclusion criteria, 228 (39.5%) had at least one pyrexic temperature (≥38.0°C). Approximately 90% of patients with a pyrexic temperature had data regarding timing of pyrexia onset (206/228) and duration of pyrexia (205/228). Patients had a median age of 65 (IQR: 55, 74) years, a median 7 (IQR: 3, 15) minute duration of arrest, 31.7% had an initial shockable rhythm, 30.8% were OHCA, and 57.3% regained arousal (defined as not eligible for TTM due to purposeful following of commands) shortly post-arrest. With regard to outcomes, 62.3% of patients survived to hospital discharge; 84.7% had a CPC score of 1 or 2 at discharge. Pyrexic patients only differed significantly from non-pyrexic

patients in terms of median age (pyrexic: 64 (IQR: 52, 72) versus non-pyrexic: 66 (IQR: 56, 75); p=0.01), median duration of arrest (pyrexic: 8 (IQR: 4, 17) versus non-pyrexic: 6 (IQR: 2, 14); p=0.01), and whether the patient regained arousal shortly post-arrest (pyrexic: 49% versus non-pyrexic: 63%, p=0.001; Table 4).

Maximum temperature

When examining the effects of maximum temperature on outcome in multivariate analysis, controlling for duration of arrest, whether the arrest was witnessed, location of arrest, initial rhythm, if intra-arrest epinephrine was given, etiology of arrest, whether the patient regained arousal shortly post-arrest, time between arrest and maximum temperature, year of arrest, and treating hospital, increased maximum temperature was significantly associated with worse outcomes in all pyrexic patients, in patients with an OHCA, and in patients who remained comatose after successful resuscitation (Table 5A).

When analyzing the effect of a maximum temperature of <38.0°C versus ≥38.0°C, there was a trend toward an opposite result; a temperature ≥38.0°C appeared to be protective with regard to neurologic outcome in all patients and in patients experiencing an IHCA and with regard to both neurologic outcome and survival in comatose patients (Table 5B), compared to a temperature <38.0°C. These results were the same when analyzed by ordinal temperature degree. There was no temperature threshold that was independently predictive of outcome.

Duration of pyrexia

There was no significant relationship between duration of pyrexia and outcomes in all patients unless duration was calculated as time ≥38.7°C, the first temperature that had a significant association with outcomes. When measuring duration of temperature

≥38.7°C, there was a significant association between longer duration and worse neurologic outcome and lower survival. When restricted to only OHCAs, longer duration was significantly associated with worse neurologic outcome and lower survival starting at a temperature of 38.3°C. Once duration of pyrexia was measured at 39.0°C, all patients, patients with an OHCA, patients with an IHCA, and patients who regained arousal shortly post-arrest had a significant association between longer duration and worse outcomes. Only patients who remained comatose did not have a significant association (Table 6). There was consistency between all three measures of duration of pyrexia; the reported results are from the estimate that assumed that the transition between a pyrexic to a non-pyrexic point indicated half of the time at a pyrexic temperature and half of the time at a non-pyrexic temperature, which represents the most moderate calculation.

There were suitable pyrexia duration threshold values to serve as an independent predictor of outcome for all patients, patients with an OHCA, patients with an IHCA, and patients who regained consciousness shortly post-arrest. These thresholds ranged from 2.5-6 hours at a certain pyrexic temperature, and varied due to strata of arrest and temperature measured (Table 7).

Timing of pyrexia onset

The relationship of the timing of onset of pyrexia to outcome varied by which subgroup of patients was analyzed: in comatose patients, both middle (10.2-24.5 hours post-arrest) and late (25.5-70.4 hours post-arrest) onset were associated with worse outcomes than early (0.2-10.0 hours post-arrest) onset. In all patients and those with OHCAs, the relationship was quadratic, with early and late onset being associated with better outcomes than middle onset in all patients and associated with better neurologic

outcome in OHCAs (Table 8; characteristics of patients based on their onset of pyrexia timing in Appendix Table 7). When limited to timing of onset of a temperature ≥38.8°C, there was some evidence that this pattern of timing held, but power constraints due to the reduced number of patients in each stratum precluded associative conclusions. There was no threshold value at which timing of pyrexia onset independently predicted outcomes.

Patient types

Combining these elements into "patient types" (Appendix Table 8), both timing of onset of pyrexia and maximum temperature were found to be associated with outcomes. Higher maximum temperature and timing of pyrexia onset between 10.2-24.5 hours post-arrest were associated with worse outcomes. Patients with a low maximum temperature (38.0-39.0°C) and a timing of onset of pyrexia between 10.2-24.5 hours had significantly worse outcomes than a patient with a low maximum temperature and an early onset of pyrexia (0.0-10.5 h) (OR for CPC 1-2: 0.26 [95% CI: 0.10-0.67], p=0.01; OR for survival: 0.35 [95% CI: 0.13-0.93], p=0.04), as did a patient with a high maximum temperature (39.1°-42.6°C) and an early onset of pyrexia (OR for CPC 1-2: 0.26 [95% CI: 0.09-0.76], p=0.02; OR for survival: 0.17 [95% CI: 0.06-0.51], p<0.01; Figure 8).

The importance of timing of pyrexia onset and maximum temperature was especially pronounced in patients who remained comatose, with worse neurologic outcomes in patients with a low maximum temperature (38.0-39.0°C)/short duration of pyrexia (0.0-10.5h)/middle timing of pyrexia onset (10.2-24.5h), patients with low temperature/short duration/late timing of pyrexia onset (25.5-70.4h), patients with high maximum temperature (39.1-42.6°C)/long duration of pyrexia (10.5-54.1h)/early timing of pyrexia onset (0.2-10.0h), patients with high temperature/long duration/middle timing,

and patients with high temperature/long duration/late timing compared to patients with low temperature/short duration/early timing. In terms of survival, patients with low temperature/short duration/middle timing, high temperature/long duration/early timing, and high temperature/long duration/late timing had worse survival compared to patients with low temperature/short duration/early pyrexia (Table 9).

Other data analysis

There was no univariate "threshold" value using receiver operating characteristic (ROC) curves that would allow for independent prediction of outcome for either maximum temperature or timing of onset of pyrexia.

DISCUSSION

In this study of 578 post-arrest patients not treated with TTM, multiple aspects of post-arrest temperature were found to be important: maximum temperature, the combination of maximum temperature and duration of time at an elevated temperature, and timing of onset of pyrexia. We found a linear relationship between increasing maximum temperature and worsening neurologic and survival outcomes in pyrexic patients, although a seemingly protective effect of mild pyrexia when compared to 37.0°C, which suggests that pyrexia is harmful at temperatures >38.0°C, the traditional definition of an elevated temperature (Benz-Woerner et al. 2012; Bouwes et al. 2012; Gebhardt et al. 2013; Leary et al. 2013; Neumar et al. 2008; Suffoletto et al. 2009; Winters et al. 2013). This was supported by the finding that there were discrete durations of time at or above certain pyrexic temperatures that were predictive of outcome, and that higher temperatures had lower duration thresholds (for example, in OHCAs, a cutoff of

≤5 hours at 38.8°C and a cutoff of ≤2.5 hours at 39.5°C both had excellent predictive value; in other words, patients could experience temperatures at 38.8°C for twice as long than they could at 39.5°C before the effects of pyrexia became detrimental). Finally, we found that timing of onset of pyrexia was associated with outcomes, in a manner than might partially mirror the phases of PCAS syndrome: early (0.2-10.0 hours), middle (10.2-24.5 hours), and late (25.5-70.4 hours). In the patients who remained comatose post-arrest (those most likely to have PCAS) (Neumar et al. 2008), both the patients with middle and late timing of pyrexia onset, which have similar timing to the "intermediate" PCAS phase (Neumar et al. 2008), are associated with worse outcomes. This could reflect the impact of the systemic ischemia/reperfusion response.

Similarly, relatively small clinical studies conducted prior to the widespread use of TTM support an association between pyrexia and poor outcomes in post-arrest patients (Bro-Jeppesen et al. 2013; Langhelle et al. 2003; Takasu et al. 2001; Takino and Okada 1991; Zeiner et al. 2001). However, Takino et al found that hyperthermia (defined as >38.0°C) was associated with poor neurologic outcomes and temperatures above 39.0°C were associated with brain death (Takino and Okada 1991). In another clinical study, Zeiner et al found that for each degree over 37°C, the risk of an unfavorable neurologic recovery increased, with an odds ratio of 2.26 (Zeiner et al. 2001), which contradicts our finding that mild pyrexia is not harmful, but supports our assertion that temperature elevation beyond that is associated with worse outcomes. One explanation for our contradictory results is that mild pyrexia could be protecting against the infection commonly seen in post-arrest patients (Hypothermia after Cardiac Arrest Study Group 2002; Sunde et al. 2007) by temporarily enhancing the immune system (Kluger et al.

1996; Mace et al. 2011; Repasky, Evans, Dewhirst 2013). Another possibility is that the patient populations studied are different.

Another study analyzed the effects of post-arrest duration of pyrexia, examining 336 patients in the first 48 hours post-arrest, 65% of whom received TTM. We replicated their methodology in measuring duration of pyrexia for two of our three estimates of pyrexia duration, the low and high estimate. While both low and high duration estimates were associated with neurologic outcome in the patients treated with TTM in their study, there was no relationship between duration of pyrexia (defined as ≥38.0°C) and neurologic outcome in the patients not treated with TTM, which supports our finding when duration was analyzed at a temperature ≥38.0°C (Gebhardt et al. 2013). Another study of patients suffering from traumatic brain injury looked at the number of days a patient had a temperature ≥38.0°C and found that an increased number of days at a pyrexic temperature was associated with an increase in the likelihood of poor prognosis. The authors concluded that the amount of time at or above a pyrexic temperature may be an independent predictor for outcome (Bao et al. 2014). Although our study found similar results, that duration of time at an elevated temperature could be independently predictive of outcome, this only occurred when temperatures were at least 0.5°C above the commonly used threshold of 38.0°C.

In a 2008 American Heart Association consensus statement, an approach to comparing mortality rates using physiologic markers of post-arrest injury commonly found in PCAS was suggested; this approach classifies the early post-arrest period as 20 minutes post-ROSC to 6-12 hours post-ROSC, the intermediate period between 6-12 hours and 72 hours post-ROSC, and the recovery phase as after 72 hours post-ROSC

(Neumar et al. 2008). When looking at the association between outcomes and timing of onset of pyrexia in comatose patients (arguably those with the most severe PCAS), patients had better outcomes in the "early phase", 0-10 hours post-arrest, than in the "intermediate phase", 10.2-72 hours post-arrest. In the other groups of patients, the worsening outcomes related to the "intermediate phase" was capped at 24.5 hours, with better outcomes between 25.5-72 hours, which could speak to a potentially different course of PCAS neurologic injury in comatose versus other patients. Additionally, laboratory investigations have suggested that many PCAS pathophysiological processes are worsened by pyrexia (Polderman 2008; Winters et al. 2013), which can intensify the neurologic injury caused by the ischemic insult of SCA and contributes to poor outcomes (Adrie et al. 2002; Badjatia 2009; Bernard et al. 2002; Deakin et al. 2010; Ginsberg et al. 1992; Greer et al. 2008; Hickey et al. 2003; Hypothermia after Cardiac Arrest Study Group 2002; Langhelle et al. 2003; Neumar et al. 2015; Takasu et al. 2001; Takino and Okada 1991; Zeiner et al. 2001). This finding was contrary to that of Gebhardt et al, who found no association between timing of onset of pyrexia and outcomes, although their study only looked at the first 48 hours post-arrest and included both patients who had received TTM and those who did not (Gebhardt et al. 2013).

Clinically, if "lower" pyrexic temperatures (such as ≤38.5°C) are not particularly harmful and even possibly helpful, investigation into the ideal temperature threshold for treatment of pyrexia would be prudent. On the other hand, once a patient reaches an "elevated" pyrexic temperature, this study suggests that the length of time a patient experiences that temperature needs to be as short as possible; only a few hours at elevated temperatures are required before the duration of pyrexia becomes predictive of poor

outcomes. Moreover, the timing of temperature elevation may be a marker of continued PCAS injury.

However, as this is a retrospective registry study, there is a need for further prospective studies in this area. This would reduce the limitations of using predefined data points and the potential risk of data entry errors or inconsistencies and information bias (such as if the highest temperature was not recorded in the patient medical record, which could result in misclassification). Additionally, there may be a relationship between the timing of onset of temperature ≥38.7°C that this study was underpowered to find. As a retrospective study, whether increased body temperature causes brain injury directly or merely acts as a surrogate marker for more severely damaged patients (Bro-Jeppesen et al. 2013; Winters et al. 2013) cannot be tested, although our findings are consistent with a large body of mechanistic work. Use of only patients not treated with TTM may present a non-representative sample of all cardiac arrest patients, although this group was deliberately chosen to analyze temperature outside of TTM. Despite these limitations, use of a registry allows for a heterogeneous patient population, leading to greater external validity and generalizability.

CONCLUSION

In patients experiencing post-arrest pyrexia, higher pyrexic temperatures were associated with worse outcomes. Longer duration of pyrexia was associated with worse outcomes at higher temperatures and onset of pyrexia in the first 10 hours post-arrest was associated with better outcomes, suggesting that avoidance of high temperatures and pyrexia after 10 hours post-arrest might improve outcomes.

TABLES

Table 1: Variables Explored for Registry Risk Standardization

Age	Sex	Race
Location of arrest	Etiology of arrest	Initial pulseless rhythm
Whether patient went to the cardiac catheterization lab	Whether patient went to the electrophysiology lab	Whether patient regained consciousness shortly post-arrest
Treatment with TTM	Bystander CPR provided	If arrest was witnessed
If patient was transferred	If intra-arrest epinephrine given	Cumulative dose of intra-arrest epinephrine
Duration of arrest	Year of arrest	

Table 2. Patient Demographics Stratified by Maximum Temperature in TTM-treated Patients

	Maximum Temperature ≥38.0°C (n=179)	Maximum Temperature <38.0°C (n=286)	p-value
Age, years (mean±SD)	56.0±16.0	60.4±16.4	0.001
Race			
White	81 (45.8)	157 (56.5)	0.076
Black	84 (47.5)	108 (38.9)	
Other	12 (6.8)	13 (4.7)	
Male	107 (59.8)	164 (57.3)	ns
Witnessed	118 (69.4)	195 (72.2)	ns
Cardiac Etiology of Arrest	116 (65.9)	184 (66.2)	ns
Out-of-Hospital Arrest	149 (83.2)	234 (81.8)	ns
Initial Rhythm			
VF/VT	68 (39.5)	102 (38.5)	ns
Asystole	35 (20.4)	61 (23.0)	
PEA	69 (40.1)	102 (38.5)	
Duration of Arrest (median minutes)	20 (IQR: 10, 29)	18 (IQR: 10, 33)	ns
Survival to Discharge	93 (52.0)	118 (41.3)	0.024
CPC 1-2 at Discharge	62 (34.8)	94 (33.0)	ns

Table 3. Relationship of Temperature to Outcomes in TTM-treated Patients

	Survival	p-value	Neurologic Outcome	p-value
A: Relationship of Maximum Temperature to Outcomes				
All patients	0.25 (0.10-0.59)	0.002	0.30 (0.10-0.84)	0.022
OHCA patients	0.43 (0.21-0.88)	0.022	0.10 (0.03-0.42)	0.002
B: Relationship of Pyrexia (≥38.0°C) to Outcomes				
All patients	1.54 (1.00-2.35)	0.048	0.85 (0.52-1.40)	0.53
Patients with maximum temperature ≥37°C	1.46 (0.95-2.26)	0.088	0.85 (0.51-1.41)	0.519
OHCA patients	1.36 (0.85-2.18)	0.205	1.07 (0.63-1.81)	0.799
IHCA patients	5.58 (1.36-18.41)	0.005	1.23 (0.45-3.39)	0.689
C: Relationship of Duration to Outcomes (in hours)				
Time ≥38.0°C				
All patients	1.03 (0.99-1.07)	0.205	1.02 (0.98-1.07)	0.366
OHCA patients	1.03 (0.99-1.07)	0.207	1.04 (0.98-1.10)	0.163
Time ≥38.8°C				
All patients	0.82 (0.72-0.93)	0.002	0.86 (0.75-1.00)	0.045
OHCA patients	0.80 (0.69-0.93)	0.004	0.69 (0.54-0.89)	0.005

Table 4. Patient Demographics Stratified by Maximum Temperature in Patients Not Treated with TTM

	Maximum Temperature ≥38°C (n=228)	Maximum Temperature <38°C (n=350)	p-value
Age (median [IQR] years)	64 (52, 72)	66 (56, 75)	0.013
Race			
White	116 (53.5)	169 (51.5)	
Black	92 (42.4)	142 (43.3)	0.814
Other	9 (4.2)	17 (5.2)	
Male	141 (61.8)	191 (54.6)	0.084
Witnessed	185 (93.0)	257 (90.2)	0.283
Cardiac Etiology of Arrest	118 (54.6)	205 (61.9)	0.089
Out-of-Hospital Arrest	64 (28.1)	114 (32.6)	0.252
Initial Rhythm			
VF/VT	68 (31.3)	103 (32.0)	
Asystole	32 (14.8)	45 (14.0)	0.965
PEA	117 (53.9)	174 (54.0)	
Duration of Arrest (median [IQR] minutes)	8 (4, 17)	6 (2, 14)	0.012
Regained Arousal Shortly Post-Arrest	111 (48.7)	220 (62.9)	0.001
Survival to Discharge	141 (61.8)	219 (62.6)	0.860
CPC 1-2 at Discharge	119 (52.2)	186 (53.1)	0.823

Table 5. Relationship of Temperature to Outcomes in Patients Not Treated with TTM

	Survival	p-value	Neurologic Outcome	p-value
A: Relationship of Maximum Temperature to Outcomes				
All patients	0.57 (0.39-0.83)	0.004	0.56 (0.37-0.85)	0.006
OHCA patients	0.36 (0.14-0.88)	0.025	0.35 (0.12-1.01)	0.053
Patients Remained Comatose Post-Arrest	0.49 (0.27-0.90)	0.021	0.43 (0.22-0.85)	0.016
B: Relationship of Pyrexia (≥38.0^{o}C) to Outcomes				
All patients	1.43 (0.94-2.17)	0.093	1.51 (1.00-2.26)	0.048
Patients with maximum temperature ≥37^{o}C	1.46 (0.95-2.26)	0.088	0.85 (0.51-1.41)	0.519
IHCA patients	1.58 (0.99-2.53)	0.056	1.78 (1.11-2.83)	0.016
Patients Remained Comatose Post-Arrest	2.03 (1.16-3.57)	0.014	1.89 (1.05-3.41)	0.034

Table 6. Association of Duration of Pyrexia and Outcome in Patients Not Treated with TTM

	Survival	p-value	CPC 1-2	p-value
Time at or above 38.3°C				
All Patients	0.99 (0.96-1.02)	0.458	0.98 (0.95-1.02)	0.313
OHCA Patients	0.88 (0.79-0.98)	0.024	0.88 (0.79-0.98)	0.017
IHCA Patients	0.99 (0.96-1.03)	0.594	0.99 (0.95-1.02)	0.427
Patients Regained Arousal Shortly Post-Arrest	0.93 (0.88-0.99)	0.019	0.94 (0.89-0.99)	0.021*
Patients Remained Comatose Post-Arrest	1.02 (0.97-1.07)	0.422	1.01 (0.97-1.05)	0.670
Time at or above 38.7°C				
All Patients	0.95 (0.90-1.00)	0.034	0.94 (0.89-0.99)	0.030
OHCA Patients	0.78 (0.66-0.92)	0.003	0.74 (0.60-0.92)	0.006
IHCA Patients	0.97 (0.92-1.02)	0.211	0.95 (0.90-1.00)	0.071
Patients Regained Arousal Shortly Post-Arrest	0.88 (0.80-0.96)	0.006	0.89 (0.82-0.97)	0.007
Patients Remained Comatose Post-Arrest	0.99 (0.92-1.06)	0.744	0.97 (0.91-1.04)	0.392
Time at or above 39.0°C				
All Patients	0.90 (0.84-0.97)	0.005	0.88 (0.81-0.97)	0.006
OHCA Patients	0.74 (0.60-0.90)	0.003	0.68 (0.52-0.90)	0.006
IHCA Patients	0.93 (0.86-1.00)	0.036	0.90 (0.83-0.98)	0.018
Patients Regained Arousal Shortly Post-Arrest	0.77 (0.65-0.91)	0.002	0.80 (0.69-0.93)	0.003
Patients Remained Comatose Post-Arrest	0.95 (0.88-1.04)	0.266	0.93 (0.85-1.02)	0.136

Table 7. Thresholds of Time at Pyrexic Temperatures Predictive of Outcome in Patients Not Treated with TTM

	38.8°C	39.0°C	39.3°C	39.5°C
All patients				
Survival Time Threshold			5 hours	
Survival AUC			0.70	
CPC 1-2 Time Threshold		5 hours		
CPC AUC		0.73		
OHCA patients				
Survival Time Threshold	5 hours			2.5 hours
Survival AUC	0.78			0.93
CPC 1-2 Time Threshold	5 hours			2.5 hours
CPC AUC	0.78			0.88
IHCA patients				
Survival Time Threshold			5 hours	
Survival AUC			0.73	
CPC 1-2 Time Threshold			6 hours	
CPC AUC			0.70	
Patients who gained arousal shortly post-arrest				
Survival Time Threshold		5 hours		
Survival AUC		0.82		
CPC 1-2 Time Threshold		5 hours		
CPC AUC		0.78		

Table 8. Association of Timing of Onset of Pyrexia to Outcomes in Patients Not Treated with TTM

	Survival	p-value	CPC 1-2	p-value
All Patients				
0.17-10.0	reference		Reference	
10.2-24.5	0.23 (0.10-0.54)	0.001	0.29 (0.12-0.70)	0.006
25.5-70.4	1.11 (0.57-2.17)	0.758	1.47 (0.79-2.75)	0.225
OHCA Patients				
0.17-10.0	reference		Reference	
10.2-24.5	0.07 (0.01-0.62)	0.017	0.29 (0.07-1.24)	0.094
25.5-70.4	0.38 (0.04-3.87)	0.410	0.98 (0.21-4.58)	0.979
IHCA Patients				
0.17-10.0	reference		Reference	
10.2-24.5	0.56 (0.24-1.32)	0.187	0.41 (0.18-0.95)	0.037
25.5-70.4	0.64 (0.28-1.43)	0.276	0.78 (0.36-1.69)	0.524
Patients Regained Arousal Shortly Post-Arrest				
0.17-10.0	reference		Reference	
10.2-24.5	0.60 (0.21-1.73)	0.342	0.59 (0.22-1.59)	0.298
25.5-70.4	1.63 (0.54-4.97)	0.389	2.79 (0.96-8.08)	0.059
Patients Remained Comatose Post-Arrest				
0.17-10.0	reference		Reference	
10.2-24.5	0.25 (0.09-0.71)	0.010	0.24 (0.09-0.66)	0.006
25.5-70.4	0.28 (0.09-0.83)	0.022	0.24 (0.08-0.71)	0.009

Table 9. Association of Patient Types with Outcomes in Patients Not Treated with TTM

	Survival	p-value	CPC 1-2	p-value
All Patients				
High temperature–short duration–early onset	0.75 (0.06-9.27)	0.823	0.33 (0.04-3.03)	0.329
High temperature–short duration–middle onset	0.25 (0.04-1.74)	0.161	0.33 (0.05-2.21)	0.255
High temperature–short duration–late onset	0.25 (0.01-4.92)	0.362	0.33 (0.02-6.37)	0.466
High temperature–long duration–early onset	0.43 (0.10-1.81)	0.248	0.24 (0.06-0.95)	0.041
High temperature–long duration–middle onset	0.15 (0.04-0.63)	0.009	0.10 (0.03-0.43)	0.002
High temperature–long duration–late onset	0.30 (0.06-1.51)	0.144	0.19 (0.04-0.94)	0.041
Low temperature–short duration–early onset	REFERENCE		REFERENCE	
Low temperature–short duration–middle onset	0.40 (0.10-1.54)	0.184	0.24 (0.07-0.88)	0.031
Low temperature–short duration–late onset	0.55 (0.16-1.96)	0.359	0.55 (0.17-1.78)	0.318
Low temperature–long duration–early onset	1.00 (0.21-4.71)	0.99	1.00 (0.24-4.18)	0.999
Low temperature–long duration–middle onset	0.28 (0.07-1.20)	0.087	0.30 (0.07-1.19)	0.086
Low temperature–long duration–late onset	0.50 (0.11-2.32)	0.376	0.67 (0.15-2.92)	0.590
Patients Remained Comatose Post-Arrest				
High temperature–short duration–early onset	n/a		n/a	
High temperature–short duration–middle onset	0.06 (0.00-1.32)	0.074	0.06 (0.00-1.32)	0.074
High temperature–short duration–late onset	n/a		n/a	
High temperature–long duration–early onset	0.22 (0.02-2.42)	0.217	0.08 (0.01-0.84)	0.036
High temperature–long duration–middle onset	0.07 (0.01-0.75)	0.027	0.03 (0.00-0.31)	0.004
High temperature–long duration–late onset	0.07 (0.01-0.82)	0.035	0.02 (0.00-0.30)	0.006
Low temperature–short duration–early onset	REFERENCE		REFERENCE	
Low temperature–short duration–middle onset	0.10 (0.01-0.98)	0.049	0.05 (0.00-0.53)	0.013
Low temperature–short duration–late onset	0.11 (0.01-1.09)	0.060	0.05 (0.00-0.51)	0.012

Low temperature–long duration–early onset	0.44 (0.02-9.03)	0.598	0.44 (0.02-9.03)	0.598
Low temperature–long duration–middle onset	0.09 (0.01-1.03)	0.053	0.09 (0.01-1.03)	0.053
Low temperature–long duration–late onset	0.09 (0.01-1.03)	0.053	0.09 (0.01-1.03)	0.053

ILLUSTRATIONS

Figure 1. Comparison of ROC Curves between Registry and Administrative Data in All Patients

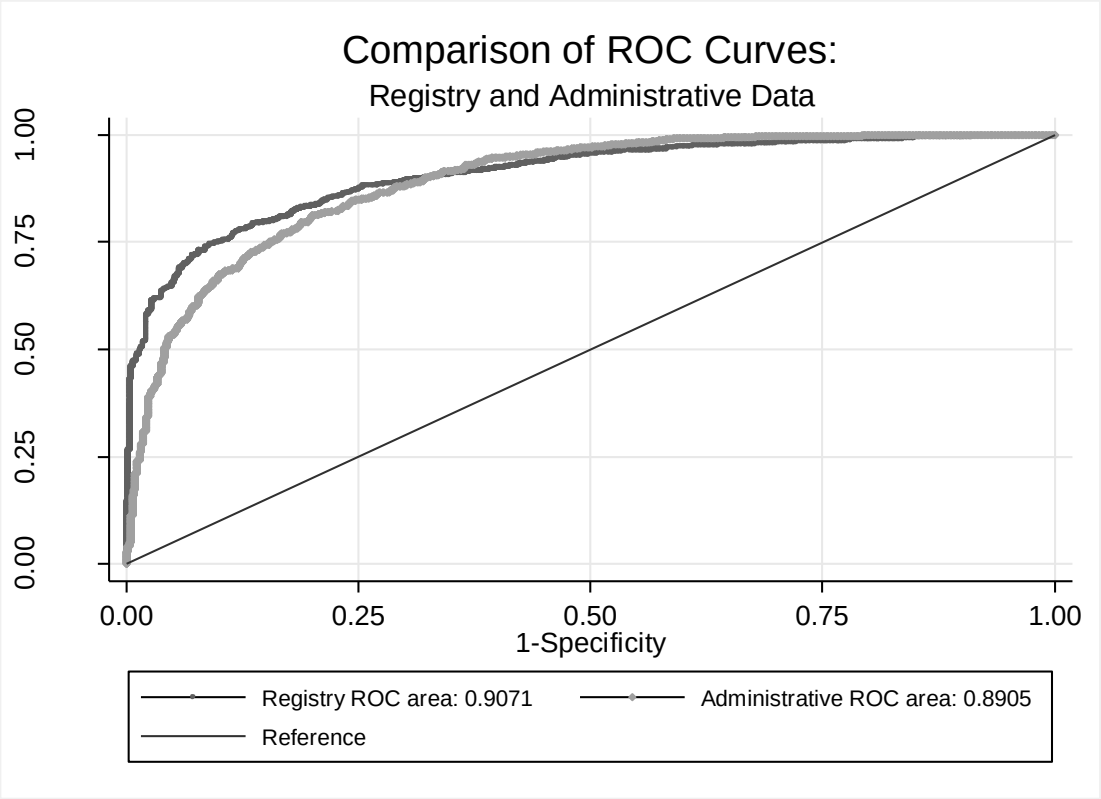


Figure 2. Bland Altman Plot of Agreement between Registry and Administrative Risk Standardization Models in All Patients

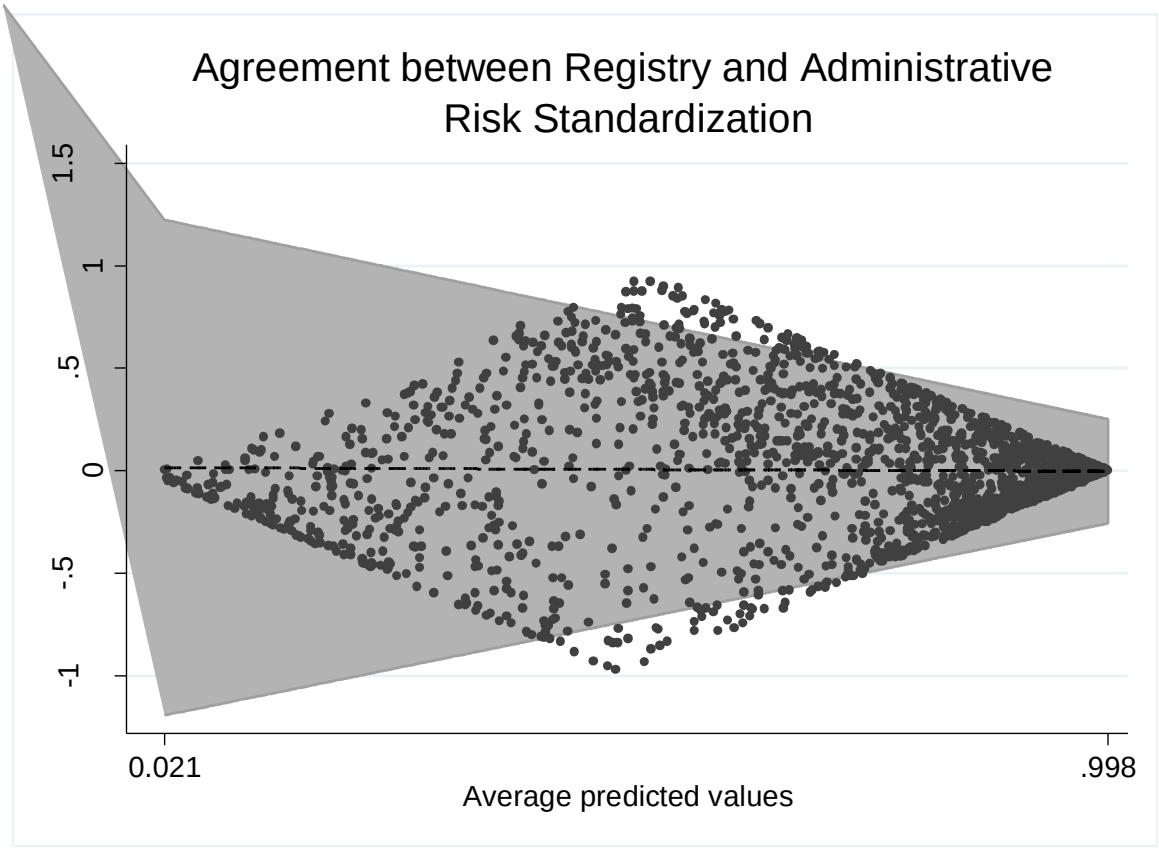


Figure 3. Calibration Plot for Registry Data in All Patients

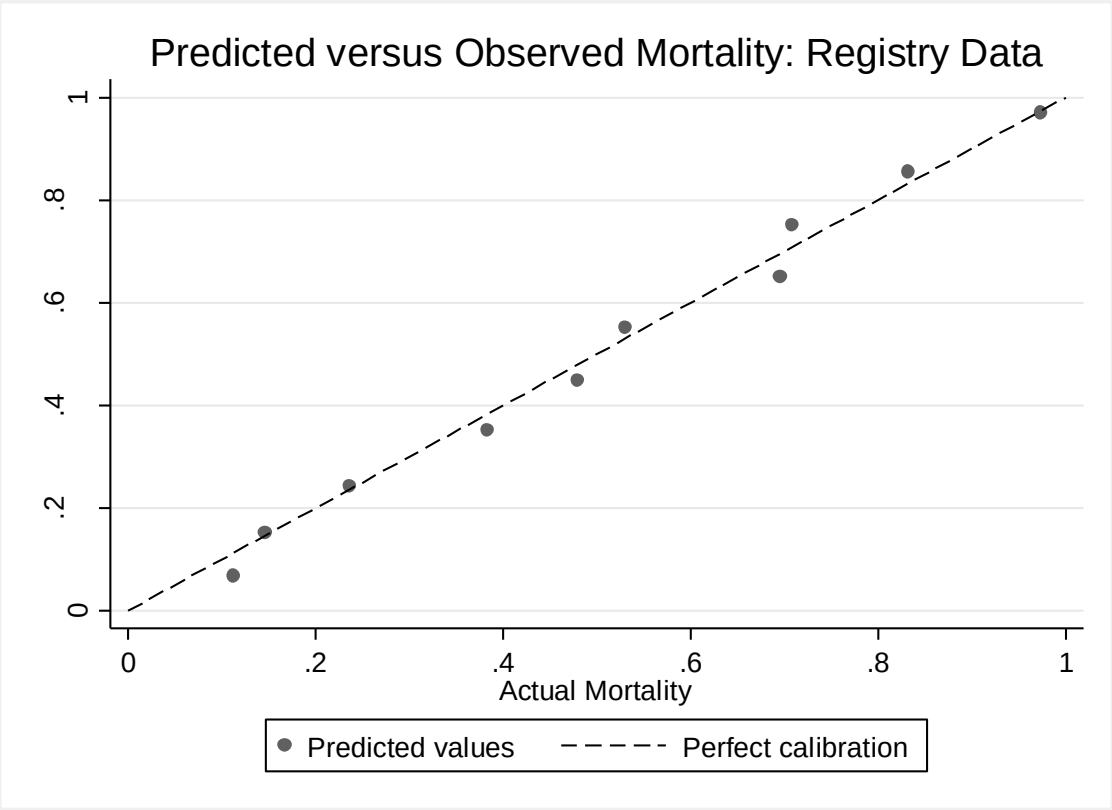


Figure 4. Calibration Plot for Administrative Data in All Patients

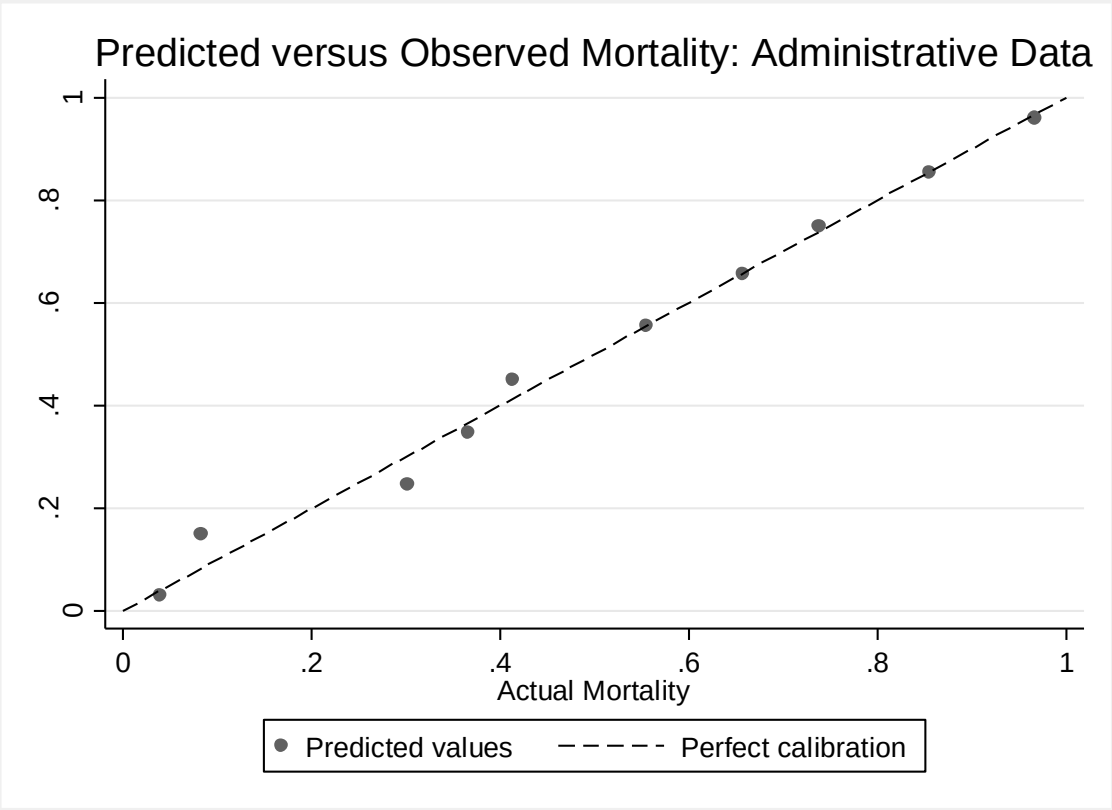


Figure 5. Comparison of ROC Curves between Registry and Administrative Data in Out-of-Hospital Cardiac Arrest

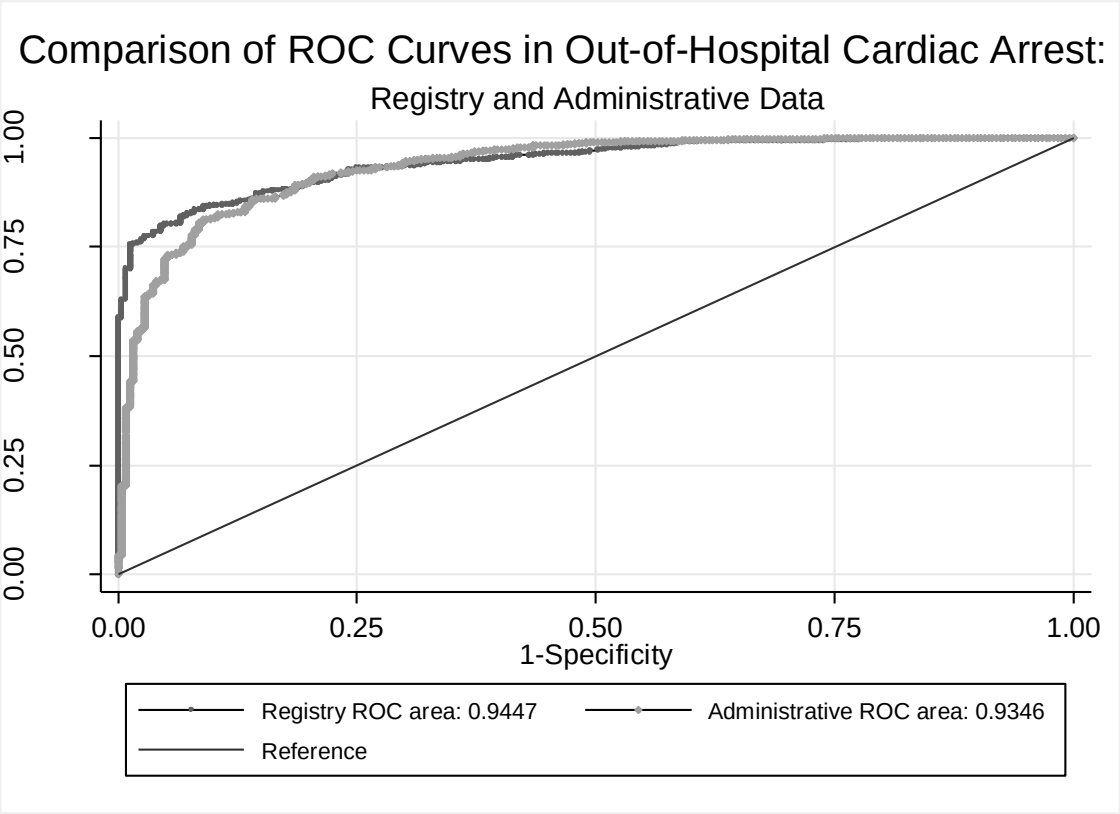


Figure 6. Comparison of ROC Curves between Registry and Administrative Data in In-Hospital Cardiac Arrest

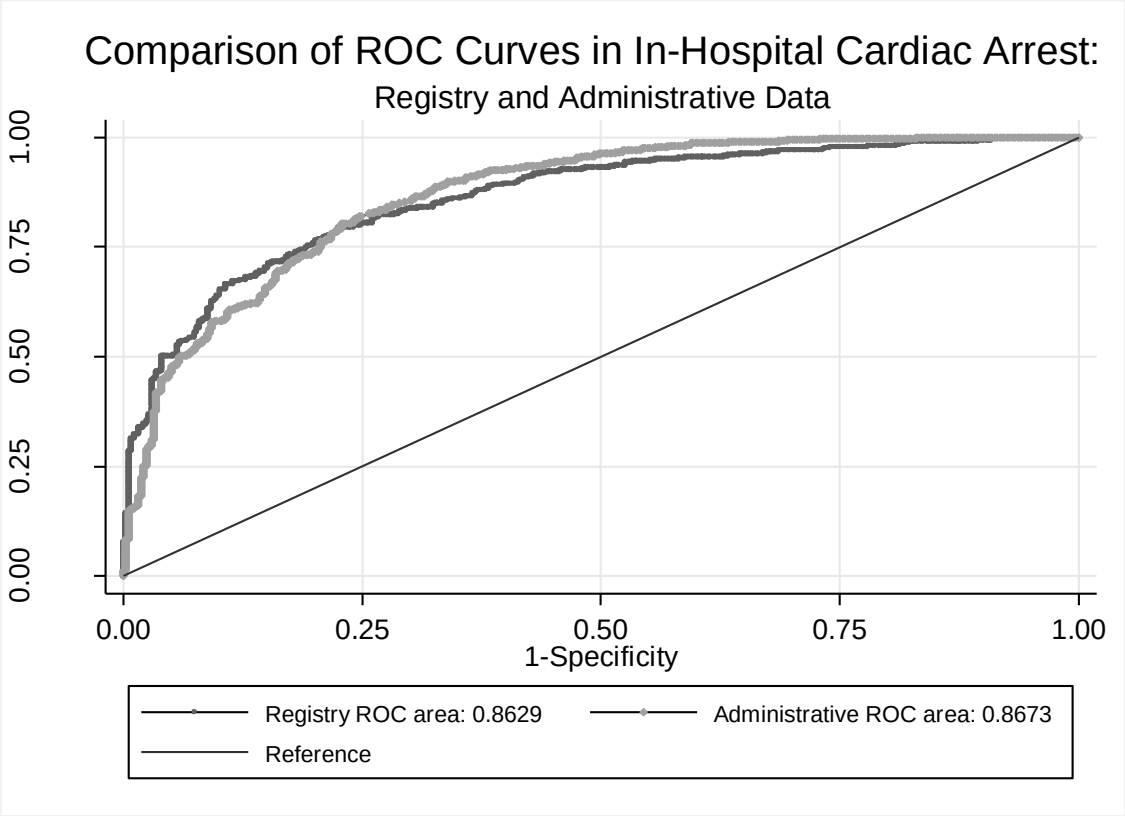


Figure 7. Association between Maximum Temperature and Neurologic Outcome in TTM-treated Patients. The data are presented as the marginal probability (with 95% confidence interval) of a favorable outcome (defined as a Cerebral Performance Category [CPC] score of 1-2 at hospital discharge) given maximum temperature, controlling for initial rhythm, whether the arrest was witnessed, duration of arrest, age, duration of TTM maintenance, and year of arrest.

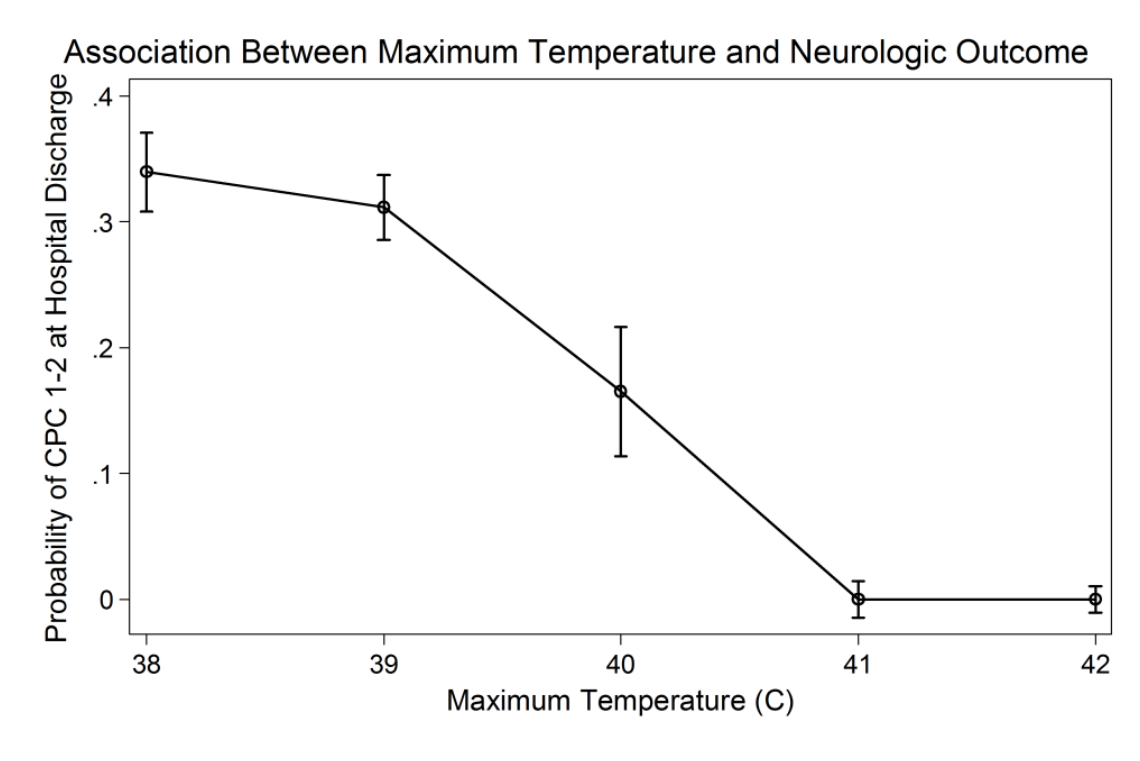
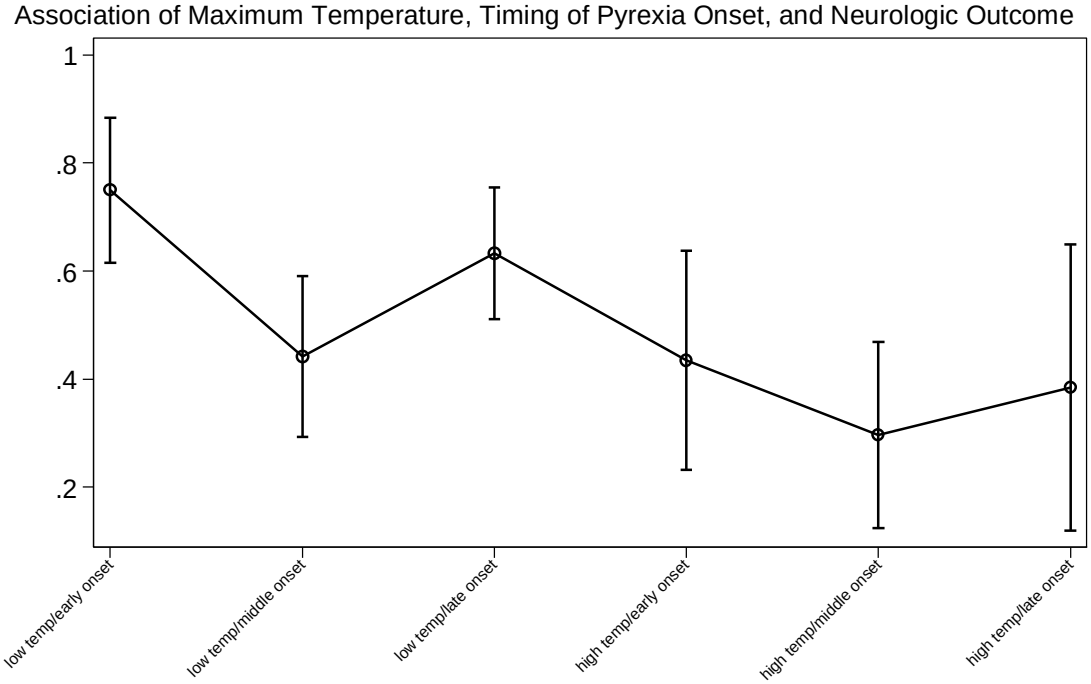


Figure 8. Association between Maximum Temperature, Timing of Pyrexia Onset, and Neurologic Outcome in Patients Not Treated with TTM. The data are presented as the marginal probability (with 95% confidence interval) of a favorable outcome (defined as a Cerebral Performance Category [CPC] score of 1-2 at hospital discharge) given maximum temperature and timing of pyrexia onset. Low temp = 38.0°C -39.0°C; high temp=39.1°C-42.6°C; early onset=0.2-10.0 hours post-arrest; middle onset=10.2-24.5 hours post-arrest; late onset=24.5-70.4 hours post-arrest



APPENDIX

Appendix Table 1: Patient Demographics in Registry Data

	Matched N=2453	Not Matched N=169	p-value
Age (median)	63 (51, 74)	63 (51, 74)	0.668
Male	1409 (57.8)	97 (57.4)	0.915
Race			
White	967 (44.1)	52 (31.1)	
Black	1088 (49.6)	99 (59.3)	0.003
Other	140 (6.4)	16 (9.6)	
Initial Rhythm			
Asystole	604 (26.2)	40 (26.5)	
PEA	1129 (49.0)	59 (39.1)	0.017
VF/VT	571 (24.8)	52 (34.4)	
Cardiac Etiology of Arrest	899 (60.6)	124 (75.6)	<0.001
OHCA	1305 (53.7)	125 (74.4)	<0.001
Witnessed Arrest	1066 (74.8)	136 (82.9)	0.022
Bystander CPR (OHCA only)	144 (26.3)	28 (26.9)	0.899
Epinephrine Given	1031 (83.5)	118 (73.3)	0.001
Epinephrine Dose (median)	2 (0, 3)	1 (0, 3)	0.049
Duration of Arrest (median)*	11 (5, 26)	21 (10, 34)	<0.001
ROSC achieved	1532 (62.5)	169 (100.0)	<0.001
TTM Performed*	473 (19.8)	133 (11.5)	<0.001
Patient Regained Consciousness after ROSC*	356 (17.4)	35 (31.3)	<0.001
Survival to Hospital Discharge	633 (25.8)	73 (43.2)	<0.001
CPC at Hospital Discharge	486 (20.0)	65 (38.5)	<0.001

*only calculated on patients with ROSC

Appendix Table 2: Administrative Data Elements Used in Risk Standardization Model for All Patients

Atrial Fibrillation (427.31)	Age	Opioid dependence (304)
Anoxic Brain Damage (348.1)	Any use of atropine (order)	Blood culture (order)
Cardiac Panel (order)	Annuloplasty (35.33)	CK (order)
Blood alcohol level taken (order)	Pure hypercholesterolemia (272)	150 mg of Amiodarone (order)
Emergency endotracheal intubation (31500)	Human immunodeficiency virus [HIV] disease (42)	Dissection of thoracic aorta (441.01)
Right heart angiocardiogram (88.52)	Malignant neoplasm of ovary and other uterine adnexa (183)	Respiratory failure (518.81, 518.83, 518.84, 799.1)
Any use of cistatracurium (order)	Fiber-optic bronchoscopy (33.22)	Toxic encephalopathy (349.82)
Rheumatic heart failure (398.91)	Obstructive sleep apnea (327.23)	Pneumococcal pneumonia (481)
Compression of brain (348.4)	Cerebral edema (348.5)	Urinary tract infection (599)
Secondary malignant neoplasm of respiratory and digestive systems (197)	Methicillin-resistant Staphylococus aureus septicemia (38.11)	Acute venous embolism and thrombosis of other specified veins (453.8)

Right heart cardiac catheterization (37.21)	Left heart cardiac catheterization (37.22)	Right/left heart cardiac catheterization (37.23)
Tricuspid valve disease (397)	Food/vomit pneumonitis (507)	Bone marrow biopsy (41.31)
Cardiogenic shock (785.51)	Hemopericardium (423)	Long QT syndrome (426.82)
Takotsubo syndrome (429.83)	Aortic atherosclerosis (440)	Pulmonary collapse (518)
Perforation of intestine (569.83)	History of tobacco use (V15.82)	Any use of nitroglycerin (order)
Venous blood gas (order)	Acute necrosis of liver (570)	Acute kidney failure (584.9)
Chronic kidney disease stage V (585.5)	Other intubation of respiratory tract (96.05)	Malfunctioning cardiac pacemaker (996.01)
Cellulitis of neck (682.1)	Drug dermatitis (693)	Coma (780.01)
Persistent vegetative state (780.03)	Measure blood oxygen level (94760)	Injection or infusion of immunoglobulin (99.14)
Bacteremia (790.7)	AICD check (89.49)	Anaphylactic shock (995)
Insert endotracheal tube (96.04)	Sepsis (995.91)	Atrial cardioversion (99.61)
Insertion of drug-eluting coronary artery stent(s) (36.07)	Packed red blood cell use (order)	Chronic kidney disease (585.9)
Malfunctioning prosthetic heart valve (996.02)	Ventilator associated pneumonia (997.31)	Accidental poisoning – psychstimulant (E85.42)
Cardiology/Cardiovascular Consultation (order)	Cardiopulmonary resuscitation (92950, 93.93, 99.60)	Do not resuscitate order (V49.86, order)
1 mg of Epinephrine (order)	E. coli infection (41.4)	Fresh frozen plasma (order)
Hypoxemia (799.02)	Race	Year of arrest
Morbid obesity (278.01)	Chest X-ray (order)	Arterial blood gas (order)
Urine culture (order)	Chest X-ray (order)	500 mg of Flagyl (order)
Lymphoid leukemia (204)	CK-MB & Troponin (order)	CK-MB Isoenzyme (order)
Intestinal infection due to clostridium difficile (8.45)	Insertion Of Intercostal Catheter For Drainage (34.04)	Dopamine 800 mg infusion (order)
Hemiplegia (342.9)	Atrioventricular block (426.1)	Liver transplant (50.59)
Angioplasty or atherectomy of other non-coronary vessel(s) (39.5)	Acute or chronic combined systolic and diastolic heart failure (428.41, 428.43)	Open and other replacement of aortic valve with tissue graft (35.21)
Open and other replacement of aortic valve (35.22)	Critical illness myopathy (359.81)	Insertion of other (naso)gastric tube (96.07)
(Aorto)coronary bypass of two coronary arteries (36.12)	(Aorto)coronary bypass of three coronary arteries (36.13)	Other gram negative bacteria (41.85)
Systemic inflammatory response syndrome due to noninfectious process without acute organ dysfunction (995.93)	Emergency department visit for the evaluation and management of a patient, high complexity medical decision making (99285)	Initial insertion of transvenous leads [electrodes] into ventricle or atrium and ventricle (37.71, 37.72)
Removal of lead(s) [electrode] without replacement (37.77)	Respiratory system disease (519.8)	Implantable heart assist system (37.66)
Extracorporeal circulation auxiliary to open heart surgery (39.61)	Acute myocardial infarction of inferoposterior wall, initial episode of care (410.31)	Mobitz (type) II atrioventricular block (426.12)
Coronary atherosclerosis of native coronary artery (414.01)	Chronic ischemic heart disease (414.8)	Intermediate coronary syndrome (411.1)

Other diagnostic procedures on heart and pericardium (37.29)	Enteral infusion of concentrated nutritional substances (96.6)	Complications of transplanted bone marrow (996.85)
Percutaneous [endoscopic] gastrostomy [PEG] (43.11)	Occlusion and stenosis of carotid artery (433.1)	Cerebral embolism with cerebral infarction (434.11)
Acute venous embolism and thrombosis of other specified veins (453.84)	Chronic venous embolism and thrombosis of internal jugular veins (453.76)	Chronic venous embolism and thrombosis of other thoracic veins (453.77)
Local infection due to central venous catheter (999.33)	Other specified disorders of circulatory system (459.89)	Pulmonary artery wedge monitoring (89.64)
Personal history of transient ischemic attack (TIA), and cerebral infarction without residual deficits (V12.54)	Personal history of (corrected) congenital malformations of heart and circulatory system (V13.65)	Continuous invasive mechanical ventilation for 96 consecutive hours or more (96.72)
Pacemaker (414.06)	Sepsis (order)	
Ultrasound guidance for vascular access requiring ultrasound evaluation of potential access sites, documentation of selected vessel patency, concurrent real-time ultrasound visualization of vascular needle entry, with permanent recording and reporting (76937)		
Any poisoning (963.0, 963.1, 964.2, 965.00, 965.02, 965.09, 965.8, 967.0, 967.8, 969.03, 969.3, 969.7, 969.72, 970.81, 971.2, 971.3, 972.6, E85.04, E85.1, E85.29, E85.42, E85.55, E85.56, E85.82, E85.89, E868.9, E95.00, E95.01, E95.04, E980.2)		
Implantation of cardiac resynchronization defibrillator or automatic cardioverter/ defibrillator, total system (0.51, 37.94)		

Appendix Table 3: Administrative Data Elements Used in Risk Standardization Model for Out-of-Hospital Cardiac Arrest Patients

Atrial Fibrillation (427.31)	Age	150 mg of Amiodarone (order)
Spinal tap (3.31)	Any use of aspirin (order)	Hyperpotassemia (276.7)
Delirium due to conditions classified elsewhere (293)	Ventilator associated pneumonia (997.31)	Cardiopulmonary resuscitation (92950)
Anoxic Brain Damage (348.1)	Pure hypercholesterolemia (272)	Insert endotracheal tube (96.04)
Cardiogenic shock (785.51)	Cerebral edema (348.5)	Food/vomit pneumonitis (507)
Bacteremia (790.7)	Acidosis (276.2)	Anaphylactic shock (995)
Fluid overload (276.69)	Sepsis (995.91)	Fresh frozen plasma (order)
Intestinal infection due to clostridium difficile (8.45)	Insertion of drug-eluting coronary artery stent(s) (36.07)	Do not resuscitate order (V49.86, order)
Obesity (278)	Race	Year of arrest
Hemiplegia (342.9)	Any use of epinephrine (order)	Hemodialysis (39.95)
Other pulmonary embolism and infarction (415.19)	Chronic ischemic heart disease (414.8)	Other gram negative bacteria (41.85)
Percutaneous [endoscopic] gastrostomy [PEG] (43.11)	Insertion of non-drug-eluting coronary artery stent(s) (36.06)	Implant of pulsation balloon (37.61)
Acute myocardial infarction of other inferior wall, initial episode of care (410.41)	Insertion of temporary transvenous pacemaker system (37.78)	Video and radio-telemetered electroencephalographic monitoring (89.19)
Coronary atherosclerosis of	Acute myocardial infarction of	Injection or infusion of other

native coronary artery (414.01)	other anterior wall, initial episode of care (410.11)	therapeutic or prophylactic substance (99.2)
Venous catheterization, not elsewhere classified (38.93)	Interruption of the vena cava (38.7)	Insertion of two vascular stents (0.46)
Other dependence on machines, Appendix oxygen (V46.2)	Other complications due to renal dialysis device, implant, and graph (996.73)	Other and unspecified Escherichia coli [E. coli] (41.49)
Septicemia (38.9)	Mitral valve disorder (424)	Ventricular fibrillation (427.41)
Sinoatrial node dysfunction (427.81)	Chronic systolic heart failure (428.22)	Acute on chronic systolic heart failure (428.23)
Unspecified acute edema of lung (518.4)	Angiocardiography of left heart structures (88.53)	Combined right and left heart angiocardiography (88.54)
Old myocardial infarct (412)	Packed cell transfusion (99.04)	Foreign body in trachea (934)
Insertion of temporary indwelling catheter, simple (51702)	Continuous invasive mechanical ventilation for less than 96 consecutive hours (96.71)	Continuous invasive mechanical ventilation for 96 consecutive hours or more (96.72)
Poisoning by cocaine (970.81)	Arterial pressure monitor (89.61)	Any use of nitroglycerin (order)
Ultrasound guidance for vascular access requiring ultrasound evaluation of potential access sites, documentation of selected vessel patency, concurrent real-time ultrasound visualization of vascular needle entry, with permanent recording and reporting (76937)		
Echocardiography, transthoracic, real-time with image documentation (2D), includes M-mode recording, when performed, follow-up or limited study (93308)		
Emergency department visit for the evaluation and management of a patient, high complexity medical decision making (99285)		

Appendix Table 4: Administrative Data Elements Used in Risk Standardization Model for In-Hospital Cardiac Arrest Patients

Age	Acidosis (276.2)	Opioid dependence (304)
Right heart angiocardiogram (88.52)	Human immunodeficiency virus [HIV] disease (42)	Acute and chronic respiratory failure (518.84)
Takotsubo syndrome (429.83)	Annuloplasty (35.33)	Urinary tract infection (599)
Compression of brain (348.4)	Shock (785.5)	Long QT syndrome (426.82)
Secondary malignant neoplasm of respiratory and digestive systems (197)	Angioplasty or atherectomy of other non-coronary vessel(s) (39.5)	Initial insertion of transvenous leads [electrodes] into ventricle (37.71)
Right heart cardiac catheterization (37.21)	Left heart cardiac catheterization (37.22)	Chronic kidney disease stage V (585.5)
Fiber-optic bronchoscopy (33.22)	Food/vomit pneumonitis (507)	Obstructive sleep apnea (327.23)
Spinal tap (3.31)	Acute necrosis of liver (570)	Sepsis (995.91)
Persistent vegetative state (780.03)	CK-MB and troponin order in the ER (order)	Do not resuscitate status (V49.86)
AICD check (89.49)	Drug dermatitis (693)	Coma (780.01)
Malfunctioning prosthetic heart valve (996.02)	Ventilator associated pneumonia (997.31)	Subarachnoid hemorrhage (852.05, 430)

Perforation of intestine (569.83)	Percutaneous [endoscopic] gastrostomy [PEG] (43.11)	Septicemia due to escherichia coli [E. coli] (038.42)
Friedländer's bacillus infection in conditions classified elsewhere and of unspecified site (041.3)	Implantation or replacement of automatic cardioverter/ defibrillator, total system (37.94)	Other pulmonary insufficiency, not elsewhere classified (518.82)
Hypoxemia (799.02)	Arterial blood gas (order)	Year of arrest
Critical illness myopathy (359.81)	Dependence on respirator, status (V46.11)	Other respiratory complications (997.39)
Intestinal infection due to clostridium difficile (8.45)	Intermediate coronary syndrome (411.1)	History of sudden cardiac arrest (V12.53)
Hemiplegia (342.9)	Severe sepsis (995.92)	Liver transplant (50.59)
(Aorto)coronary bypass of two coronary arteries (36.12)	(Aorto)coronary bypass of three coronary arteries (36.13)	Other diagnostic procedures on heart and pericardium (37.29)
Extracorporeal circulation auxiliary to open heart surgery (39.61)	Chronic venous embolism and thrombosis of internal jugular veins (453.76)	Chronic venous embolism and thrombosis of other thoracic veins (453.77)
Acute venous embolism and thrombosis of other specified veins (453.84)	Enteral infusion of concentrated nutritional substances (96.6)	Pseudomonas infection in conditions classified elsewhere and of unspecified site (041.7)
Chronic hepatitis C with hepatic coma (070.44)	Local infection due to central venous catheter (999.33)	Critical illness polyneuropathy (357.82)
Infusion of a vasopressor (0.17)	Open aortic valvuloplasty (35.11)	Hemiplegia/hemiparesis (438.2)
Noninvasive programmed electrical stimulation [NIPS] (37.20)	Initial insertion of transvenous leads [electrodes] into atrium and ventricle (37.72)	Percutaneous transluminal coronary angioplasty [PTCA] (00.66)
Candidiasis of lung (112.4)	Obesity (278)	Diagnostic ultrasound of heart (88.72)
Implant of pulsation balloon (37.61)	Initial insertion of dual-chamber device (37.83)	Interruption of the vena cava (38.7)
Occlusion and stenosis of carotid artery with cerebral infarction (433.11)	Central venous catheter placement with guidance (38.97)	Other specified alveolar and parietoalveolar pneumonopathies (516.8)
Angiocardiography of venae cavae (88.51)	Other pulmonary embolism and infarction (415.19)	Other primary cardiomyopathies (425.4)
Respiratory arrest (799.1)	Systolic heart failure (428.2)	Intracerebral hemorrhage (431)
Other second degree atrioventricular block (426.13)	Pneumonia due to Pseudomonas (482.1)	Influenza with pneumonia (487)
Osteoporosis (733)	Syncope and collapse (780.2)	Retention of urine (788.2)
Continuous invasive mechanical ventilation for less than 96 consecutive hours (96.71)	Continuous invasive mechanical ventilation for 96 consecutive hours or more (96.72)	Chronic stomach ulcer with hemorrhage (531.4)
Complete kidney transplant (996.81)	Complete liver transplant (996.82)	Complete lung transplant (996.84)
Insertion of temporary non-implantable extracorporeal circulatory assist device (37.62)		
Suicide and self-inflicted poisoning by other specified drugs and medicinal substances (E95.04)		

Appendix Table 5. Patient Types for Patients Treated with TTM

	n	Maximum temperature (^{o}C)	Duration of Pyrexia (hours)	Timing (hours)
Low temperature – short duration – early timing	37	38.00-38.72	0.40-9.15	0.0-16.5
Low temperature – short duration – middle timing	13	38.00-38.72	0.40-9.15	18.0-40.2
Low temperature – short duration – late timing	14	38.00-38.72	0.40-9.15	43.4-70.9
Low temperature – long duration – early timing	25	38.00-38.72	9.75-60.75	0.0-16.5
Low temperature – long duration – middle timing	21	38.00-38.72	9.75-60.75	18.0-40.2
Low temperature – long duration – late timing	5	38.00-38.72	9.75-60.75	43.4-70.9
High temperature – short duration – early timing	10	38.78-42.20	0.40-9.15	0.0-16.5
High temperature – short duration – middle timing	2	38.78-42.20	0.40-9.15	18.0-40.2
High temperature – short duration – late timing	1	38.78-42.20	0.40-9.15	43.4-70.9
High temperature – long duration – early timing	38	38.78-42.20	9.75-60.75	0.0-16.5
High temperature – long duration – middle timing	10	38.78-42.20	9.75-60.75	18.0-40.2
High temperature – long duration – late timing	3	38.78-42.20	9.75-60.75	43.4-70.9

Appendix Table 6. Potential Covariates for Patients Treated with TTM

Sex	Age	Year of arrest	Race
Intra-arrest epinephrine given	Cumulative dose of intra-arrest epinephrine	Duration of TTM maintenance	Duration of TTM rewarming
Treating hospital	Witnessed arrest	Bystander CPR	Duration of arrest
Location of arrest	Initial pulseless rhythm	Length of hospital stay	Time to TTM target temperature

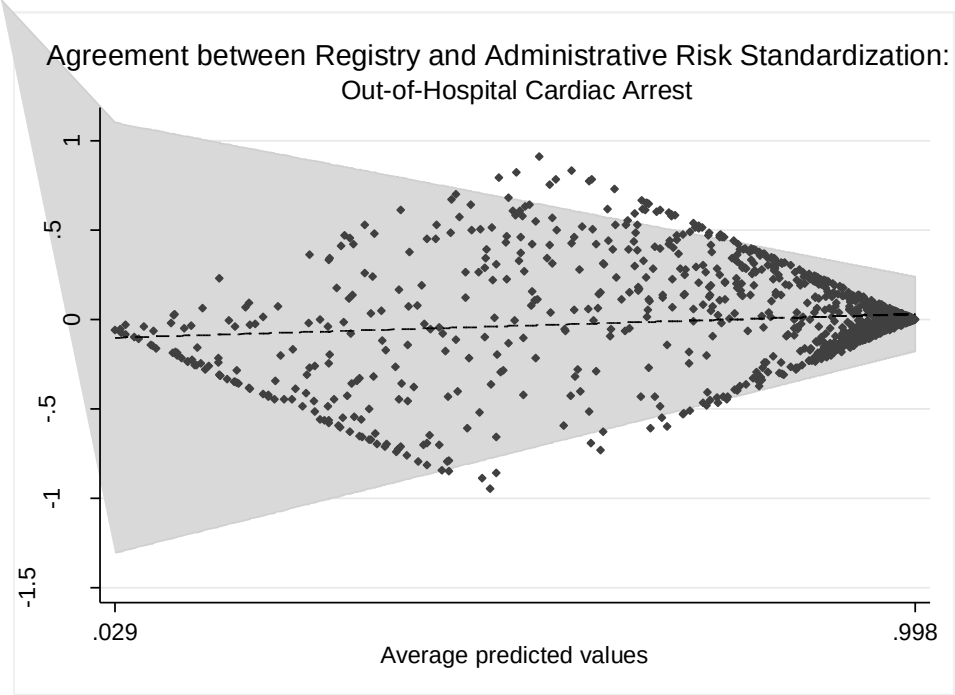
Appendix Table 7. Characteristics of Patients by Timing of Onset of Pyrexia in Patients Not Treated with TTM

	"Early Onset" (0.2-10.0 hours post-arrest; n=63)	"Middle Onset" (10.2-24.5 hours post-arrest; n=70)	"Late Onset" (25.5-70.4 hours post-arrest; n=73)	p-value
Age (median [IQR] years)	61 [48, 71]	65 [56, 74]	66 [55, 75]	0.127
Race				
White	34 (56.7)	32 (47.1)	40 (57.1)	
Black	22 (36.7)	32 (47.1)	30 (42.9)	0.140
Other	4 (6.7)	4 (5.9)	0 (0.0)	
Male	40 (63.5)	42 (60.0)	48 (65.8)	0.773
Witnessed	47 (94.0)	59 (95.2)	62 (92.5)	0.924
Cardiac Etiology of Arrest	32 (52.5)	37 (56.9)	35 (50.7)	0.762
Out-of-Hospital Arrest	11 (17.5)	27 (38.6)	19 (26.0)	0.023
Initial Rhythm				
VF/VT	22 (35.5)	15 (22.7)	25 (36.2)	
Asystole	10 (16.1)	7 (10.6)	11 (15.9)	0.187
PEA	30 (48.4)	44 (66.7)	33 (47.8)	
Duration of Arrest (median [IQR] mins)	7 [4, 16]	10 [4, 20]	8.5 [4, 16]	0.387
Regained Arousal Shortly Post-Arrest	35 (55.6)	30 (42.9)	40 (54.8)	0.246
Survival to Discharge	47 (74.6)	36 (51.4)	48 (65.8)	0.019
CPC 1-2 at Discharge	40 (63.5)	27 (38.6)	43 (58.9)	0.008

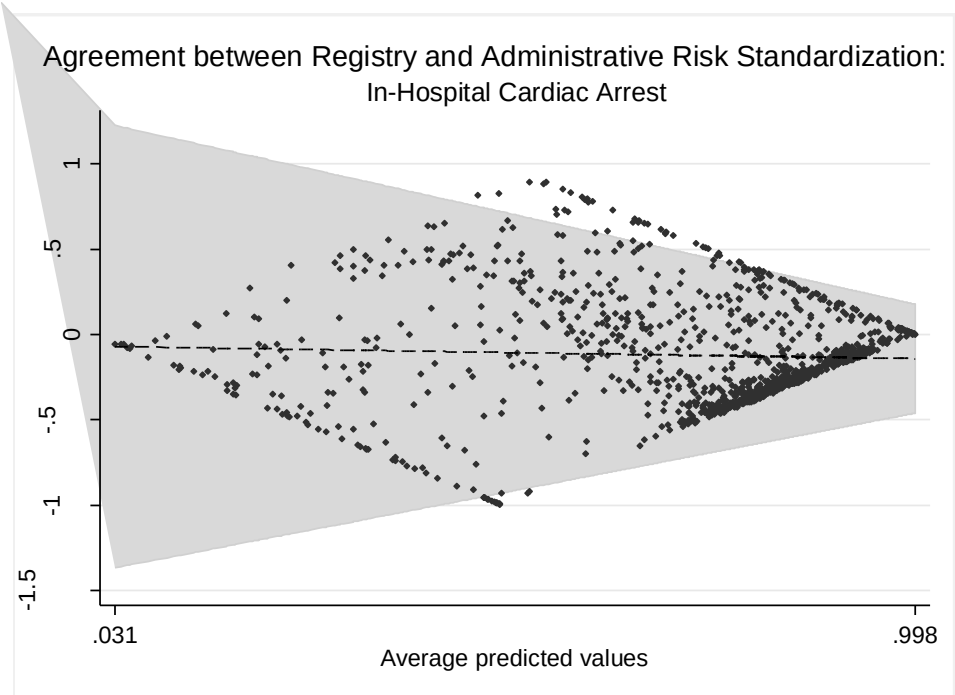
Appendix Table 8. Patient Types for Patients Not Treated with TTM

	n	Maximum temperature (°C)	Duration of Pyrexia (h)	Timing of Onset (h)
Low temperature – short duration – early onset	20	38.0-39.0	0.0-10.5	0.17-10.0
Low temperature – short duration – middle onset	26	38.0-39.0	0.0-10.5	10.2-24.5
Low temperature – short duration – late onset	45	38.0-39.0	0.0-10.5	25.5-70.4
Low temperature – long duration – early onset	20	38.0-39.0	10.5-54.1	0.17-10.0
Low temperature – long duration – middle onset	17	38.0-39.0	10.5-54.1	10.2-24.5
Low temperature – long duration – late onset	15	38.0-39.0	10.5-54.1	25.5-70.4
High temperature – short duration – early onset	4	39.1-42.6	0.0-10.5	0.17-10.0
High temperature – short duration – middle onset	6	39.1-42.6	0.0-10.5	10.2-24.5
High temperature – short duration – late onset	2	39.1-42.6	0.0-10.5	25.5-70.4
High temperature – long duration – early onset	19	39.1-42.6	10.5-54.1	0.17-10.0
High temperature – long duration – middle onset	21	39.1-42.6	10.5-54.1	10.2-24.5
High temperature – long duration – late onset	11	39.1-42.6	10.5-54.1	25.5-70.4

Appendix Figure 1. Bland Altman Plot of Agreement between Registry and Administrative Risk Standardization Models in Out-of-Hospital Cardiac Arrest



Appendix Figure 2. Bland Altman Plot of Agreement between Registry and Administrative Risk Standardization Models in In-Hospital Cardiac Arrest



BIBLIOGRAPHY

Adielsson A, Hollenberg J, Karlsson T, Lindqvist J, Lundin S, Silfverstolpe J, Svensson L, Herlitz J. 2011. Increase in survival and bystander CPR in out-of-hospital shockable arrhythmia: Bystander CPR and female gender are predictors of improved outcome. experiences from sweden in an 18-year perspective. Heart 97(17):1391-6.

Adrie C, Adib-Conquy M, Laurent I, Monchi M, Vinsonneau C, Fitting C, Fraisse F, Dinh-Xuan AT, Carli P, Spaulding C, et al. 2002. Successful cardiopulmonary resuscitation after cardiac arrest as a "sepsis-like" syndrome. Circulation 106(5):562-8.

Albrecht RF,2nd, Wass CT, Lanier WL. 1998. Occurrence of potentially detrimental temperature alterations in hospitalized patients at risk for brain injury. Mayo Clin Proc 73(7):629-35.

Arrich J and European Resuscitation Council Hypothermia After Cardiac Arrest Registry Study Group. 2007. Clinical application of mild therapeutic hypothermia after cardiac arrest. Crit Care Med 35(4):1041-7.

Badjatia N. 2009. Hyperthermia and fever control in brain injury. Crit Care Med 37(7 Suppl):S250-7.

Bao L, Chen D, Ding L, Ling W, Xu F. 2014. Fever burden is an independent predictor for prognosis of traumatic brain injury. PLoS One 9(3):e90956.

Becker LB, Aufderheide TP, Graham R. 2015. Strategies to improve survival from cardiac arrest: A report from the institute of medicine. JAMA .

Benz-Woerner J, Delodder F, Benz R, Cueni-Villoz N, Feihl F, Rossetti AO, Liaudet L, Oddo M. 2012. Body temperature regulation and outcome after cardiac arrest and therapeutic hypothermia. Resuscitation 83(3):338-42.

Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. 2002. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 346(8):557-63.

Bouwes A, Robillard LB, Binnekade JM, de Pont AC, Wieske L, Hartog AW, Schultz MJ, Horn J. 2012. The influence of rewarming after therapeutic hypothermia on outcome after cardiac arrest. Resuscitation 83(8):996-1000.

Bro-Jeppesen J, Hassager C, Wanscher M, Soholm H, Thomsen JH, Lippert FK, Moller JE, Kober L, Kjaergaard J. 2013. Post-hypothermia fever is associated with

increased mortality after out-of-hospital cardiac arrest. Resuscitation 84(12):1734-40.

Busch M, Soreide E, Lossius HM, Lexow K, Dickstein K. 2006. Rapid implementation of therapeutic hypothermia in comatose out-of-hospital cardiac arrest survivors. Acta Anaesthesiol Scand 50(10):1277-83.

Busto R, Dietrich WD, Globus MY, Valdes I, Scheinberg P, Ginsberg MD. 1987. Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury. J Cereb Blood Flow Metab 7(6):729-38.

Cabanas JG, Brown LH, Gonzales L, Hinchey PR. 2015. Derivation and initial application of a standard population for out-of-hospital cardiac arrest (SPOHCA). Resuscitation 90:30-4.

Callaway CW, Donnino MW, Fink EL, Geocadin RG, Golan E, Kern KB, Leary M, Meurer WJ, Peberdy MA, Thompson TM, et al. 2015. Part 8: Post-cardiac arrest care: 2015 american heart association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 132(18 Suppl 2):S465-82.

Cañette I and Marchenko Y. Combining results other than coefficients in e(b) with multiply imputed data. StataCorp [Internet]. cited June 30, 2015. College Station, TX:StataCorp. Available from http://www.stata.com/ support/faqs/statistics/combine-results-with-multiply-imputed-data/.

Carr BG, Kahn JM, Merchant RM, Kramer AA, Neumar RW. 2009a. Inter-hospital variability in post-cardiac arrest mortality. Resuscitation 80(1):30-4.

Carr BG, Goyal M, Band RA, Gaieski DF, Abella BS, Merchant RM, Branas CC, Becker LB, Neumar RW. 2009b. A national analysis of the relationship between hospital factors and post-cardiac arrest mortality. Intensive Care Med 35(3):505-11.

Chan PS, Berg RA, Spertus JA, Schwamm LH, Bhatt DL, Fonarow GC, Heidenreich PA, Nallamothu BK, Tang F, Merchant RM, et al. 2013. Risk-standardizing survival for in-hospital cardiac arrest to facilitate hospital comparisons. J Am Coll Cardiol 62(7):601-9.

Chen LM, Nallamothu BK, Spertus JA, Li Y, Chan PS, American Heart Association's Get With the Guidelines-Resuscitation (formerly the National Registry of Cardiopulmonary Resuscitation) Investigators. 2013. Association between a hospital's rate of cardiac arrest incidence and cardiac arrest survival. JAMA Intern Med 173(13):1186-95.

Chen TT, Ma MH, Chen FJ, Hu FC, Lu YC, Chiang WC, Ko PC. 2015. The relationship between survival after out-of-hospital cardiac arrest and process measures for emergency medical service ambulance team performance. Resuscitation .

Cocchi MN, Boone MD, Giberson B, Giberson T, Farrell E, Salciccioli JD, Talmor D, Williams D, Donnino MW. 2014. Fever after rewarming: Incidence of pyrexia in postcardiac arrest patients who have undergone mild therapeutic hypothermia. J Intensive Care Med 29(6):365-9.

Coppler PJ, Rittenberger JC, Wallace DJ, Callaway CW, Elmer J, Pittsburgh Post Cardiac Arrest Service. 2016. Billing diagnoses do not accurately identify out-of-hospital cardiac arrest patients: An analysis of a regional healthcare system. Resuscitation 98:9-14.

Cox NJ. GROUP1D: Stata module for grouping or clustering in one dimension. EconPapers [Internet]. cited October 26, 2015. Boston College: Department of Economics. Available from http://fmwww.bc.edu/RePEc/bocode/g.

Cronberg T, Lilja G, Horn J, Kjaergaard J, Wise MP, Pellis T, Hovdenes J, Gasche Y, Aneman A, Stammet P, et al. 2015. Neurologic function and health-related quality of life in patients following targeted temperature management at 33 degrees C vs 36 degrees C after out-of-hospital cardiac arrest: A randomized clinical trial. JAMA Neurol 72(6):634-41.

Cummins RO, Chamberlain DA, Abramson NS, Allen M, Baskett PJ, Becker L, Bossaert L, Delooz HH, Dick WF, Eisenberg MS. 1991. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: The utstein style. A statement for health professionals from a task force of the american heart association, the european resuscitation council, the heart and stroke foundation of canada, and the australian resuscitation council. Circulation 84(2):960-75.

Deakin CD, Morrison LJ, Morley PT, Callaway CW, Kerber RE, Kronick SL, Lavonas EJ, Link MS, Neumar RW, Otto CW, et al. 2010. Part 8: Advanced life support: 2010 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Resuscitation 81 Suppl 1:e93-e174.

Dietrich WD, Busto R, Valdes I, Loor Y. 1990. Effects of normothermic versus mild hyperthermic forebrain ischemia in rats. Stroke 21(9):1318-25.

Donnino MW, Miller JC, Bivens M, Cocchi MN, Salciccioli JD, Farris S, Gautam S, Cutlip D, Howell M. 2012. A pilot study examining the severity and outcome of the post-cardiac arrest syndrome: A comparative analysis of two geographically distinct hospitals. Circulation 126(12):1478-83.

Ferreira-Gonzalez I, Marsal JR, Mitjavila F, Parada A, Ribera A, Cascant P, Soriano N, Sanchez PL, Aros F, Heras M, et al. 2009. Patient registries of acute coronary syndrome: Assessing or biasing the clinical real world data? Circ Cardiovasc Qual Outcomes 2(6):540-7.

Fothergill RT, Watson LR, Chamberlain D, Virdi GK, Moore FP, Whitbread M. 2013. Increases in survival from out-of-hospital cardiac arrest: A five year study. Resuscitation 84(8):1089-92.

Fredriksson M, Herlitz J, Nichol G. 2003. Variation in outcome in studies of out-of-hospital cardiac arrest: A review of studies conforming to the utstein guidelines. Am J Emerg Med 21(4):276-81.

Fugate JE, Brinjikji W, Mandrekar JN, Cloft HJ, White RD, Wijdicks EF, Rabinstein AA. 2012. Post-cardiac arrest mortality is declining: A study of the US national inpatient sample 2001 to 2009. Circulation 126(5):546-50.

Galati JC, Royston P, Carlin JB. 2013. mim. Package for analysis and manipulation of multiply imputed datasets [computer program]. Version 2.1.8.

Gebhardt K, Guyette FX, Doshi AA, Callaway CW, Rittenberger JC, Post Cardiac Arrest Service. 2013. Prevalence and effect of fever on outcome following resuscitation from cardiac arrest. Resuscitation 84(8):1062-7.

Geva A, Tasker RC, Randolph AG. 2015. Therapeutic hypothermia in children. N Engl J Med 373(10):979.

Giavarina D. 2015. Understanding bland altman analysis. Biochem Med (Zagreb) 25(2):141-51.

Ginsberg MD, Sternau LL, Globus MY, Dietrich WD, Busto R. 1992. Therapeutic modulation of brain temperature: Relevance to ischemic brain injury. Cerebrovasc Brain Metab Rev 4(3):189-225.

Grasner JT, Herlitz J, Koster RW, Rosell-Ortiz F, Stamatakis L, Bossaert L. 2011. Quality management in resuscitation--towards a european cardiac arrest registry (EuReCa). Resuscitation 82(8):989-94.

Greer DM, Funk SE, Reaven NL, Ouzounelli M, Uman GC. 2008. Impact of fever on outcome in patients with stroke and neurologic injury: A comprehensive meta-analysis. Stroke 39(11):3029-35.

Harrison DA, Patel K, Nixon E, Soar J, Smith GB, Gwinnutt C, Nolan JP, Rowan KM, National Cardiac Arrest Audit. 2014. Development and validation of risk models to

predict outcomes following in-hospital cardiac arrest attended by a hospital-based resuscitation team. Resuscitation 85(8):993-1000.

Heffner AC, Pearson DA, Nussbaum ML, Jones AE. 2012. Regionalization of post-cardiac arrest care: Implementation of a cardiac resuscitation center. Am Heart J 164(4):493,501.e2.

Hickey RW, Kochanek PM, Ferimer H, Alexander HL, Garman RH, Graham SH. 2003. Induced hyperthermia exacerbates neurologic neuronal histologic damage after asphyxial cardiac arrest in rats. Crit Care Med 31(2):531-5.

Hinchey PR, Myers JB, Lewis R, De Maio VJ, Reyer E, Licatese D, Zalkin J, Snyder G, Capital County Research Consortium. 2010. Improved out-of-hospital cardiac arrest survival after the sequential implementation of 2005 AHA guidelines for compressions, ventilations, and induced hypothermia: The wake county experience. Ann Emerg Med 56(4):348-57.

Hollenberg J, Svensson L, Rosenqvist M. 2013. Out-of-hospital cardiac arrest: 10 years of progress in research and treatment. J Intern Med 273(6):572-83.

Hsu CH, Li J, Cinousis MJ, Sheak KR, Gaieski DF, Abella BS, Leary M. 2014. Cerebral performance category at hospital discharge predicts long-term survival of cardiac arrest survivors receiving targeted temperature management*. Crit Care Med 42(12):2575-81.

Hypothermia after Cardiac Arrest Study Group. 2002. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 346(8):549-56.

Iwami T, Kitamura T, Kawamura T, Mitamura H, Nagao K, Takayama M, Seino Y, Tanaka H, Nonogi H, Yonemoto N, et al. 2012. Chest compression-only cardiopulmonary resuscitation for out-of-hospital cardiac arrest with public-access defibrillation: A nationwide cohort study. Circulation 126(24):2844-51.

Iwami T, Nichol G, Hiraide A, Hayashi Y, Nishiuchi T, Kajino K, Morita H, Yukioka H, Ikeuchi H, Sugimoto H, et al. 2009. Continuous improvements in "chain of survival" increased survival after out-of-hospital cardiac arrests: A large-scale population-based study. Circulation 119(5):728-34.

Jacobs I, Nadkarni V, Bahr J, Berg RA, Billi JE, Bossaert L, Cassan P, Coovadia A, D'Este K, Finn J, et al. 2004. Cardiac arrest and cardiopulmonary resuscitation outcome reports: Update and simplification of the utstein templates for resuscitation registries: A statement for healthcare professionals from a task force of the international liaison committee on resuscitation (american heart association, european resuscitation council, australian resuscitation council, new zealand

resuscitation council, heart and stroke foundation of canada, InterAmerican heart foundation, resuscitation councils of southern africa). Circulation 110(21):3385-97.

Japanese Circulation Society Resuscitation Science Study Group. 2013. Chest-compression-only bystander cardiopulmonary resuscitation in the 30:2 compression-to-ventilation ratio era. nationwide observational study. Circ J 77(11):2742-50.

Jenks GF. 1967. The data model concept in statistical mapping . International Yearbook of Cartography 7:186-190.

Kellum MJ, Kennedy KW, Ewy GA. 2006. Cardiocerebral resuscitation improves survival of patients with out-of-hospital cardiac arrest. Am J Med 119(4):335-40.

Kellum MJ, Kennedy KW, Barney R, Keilhauer FA, Bellino M, Zuercher M, Ewy GA. 2008. Cardiocerebral resuscitation improves neurologically intact survival of patients with out-of-hospital cardiac arrest. Ann Emerg Med 52(3):244-52.

Khuri SF, Daley J, Henderson W, Hur K, Demakis J, Aust JB, Chong V, Fabri PJ, Gibbs JO, Grover F, et al. 1998. The department of veterans affairs' NSQIP: The first national, validated, outcome-based, risk-adjusted, and peer-controlled program for the measurement and enhancement of the quality of surgical care. national VA surgical quality improvement program. Ann Surg 228(4):491-507.

Kitamura T, Iwami T, Kawamura T, Nagao K, Tanaka H, Hiraide A, Implementation Working Group for the All-Japan Utstein Registry of the Fire and Disaster Management Agency. 2010. Nationwide public-access defibrillation in japan. N Engl J Med 362(11):994-1004.

Kitamura T, Iwami T, Kawamura T, Nitta M, Nagao K, Nonogi H, Yonemoto N, Kimura T, Japanese Circulation Society Resuscitation Science Study Group. 2012. Nationwide improvements in survival from out-of-hospital cardiac arrest in japan. Circulation 126(24):2834-43.

Kluger MJ, Kozak W, Conn CA, Leon LR, Soszynski D. 1996. The adaptive value of fever. Infect Dis Clin North Am 10(1):1-20.

Kobayashi MS, Asai S, Ishikawa K, Nishida Y, Nagata T, Takahashi Y. 2008. Global profiling of influence of intra-ischemic brain temperature on gene expression in rat brain. Brain Res Rev 58(1):171-91.

Lagu T, Lindenauer PK, Rothberg MB, Nathanson BH, Pekow PS, Steingrub JS, Higgins TL. 2011. Development and validation of a model that uses enhanced administrative data to predict mortality in patients with sepsis. Crit Care Med 39(11):2425-30.

Langhelle A, Tyvold SS, Lexow K, Hapnes SA, Sunde K, Steen PA. 2003. In-hospital factors associated with improved outcome after out-of-hospital cardiac arrest. A comparison between four regions in norway. Resuscitation 56(3):247-63.

Lanier WL. 1995. Cerebral metabolic rate and hypothermia: Their relationship with ischemic neurologic injury. J Neurosurg Anesthesiol 7(3):216-21.

Leary M, Grossestreuer AV, Iannacone S, Gonzalez M, Shofer FS, Povey C, Wendell G, Archer SE, Gaieski DF, Abella BS. 2013. Pyrexia and neurologic outcomes after therapeutic hypothermia for cardiac arrest. Resuscitation 84(8):1056-61.

Lee BK, Song KH, Jung YH, Lee DH, Youn CS, Lee SM, Cho YS, Jeung KW. 2015. The influence of post-rewarming temperature management on post-rewarming fever development after cardiac arrest. Resuscitation 97:20-6.

Lemeshow S and Hosmer DW,Jr. 1982. A review of goodness of fit statistics for use in the development of logistic regression models. Am J Epidemiol 115(1):92-106.

Lundbye JB, Rai M, Ramu B, Hosseini-Khalili A, Li D, Slim HB, Bhavnani SP, Nair SU, Kluger J. 2012. Therapeutic hypothermia is associated with improved neurologic outcome and survival in cardiac arrest survivors of non-shockable rhythms. Resuscitation 83(2):202-7.

Lund-Kordahl I, Olasveengen TM, Lorem T, Samdal M, Wik L, Sunde K. 2010. Improving outcome after out-of-hospital cardiac arrest by strengthening weak links of the local chain of survival; quality of advanced life support and post-resuscitation care. Resuscitation 81(4):422-6.

Mace TA, Zhong L, Kilpatrick C, Zynda E, Lee CT, Capitano M, Minderman H, Repasky EA. 2011. Differentiation of CD8+ T cells into effector cells is enhanced by physiological range hyperthermia. J Leukoc Biol 90(5):951-62.

Madden LK and DeVon HA. 2015. A systematic review of the effects of body temperature on outcome after adult traumatic brain injury. J Neurosci Nurs .

Maldonado G and Greenland S. 1993. Simulation study of confounder-selection strategies. Am J Epidemiol 138(11):923-36.

Merchant RM, Berg RA, Yang L, Becker LB, Groeneveld PW, Chan PS, American Heart Association's Get With the Guidelines-Resuscitation Investigators. 2014. Hospital variation in survival after in-hospital cardiac arrest. J Am Heart Assoc 3(1):e000400.

Merchant RM, Abella BS, Peberdy MA, Soar J, Ong ME, Schmidt GA, Becker LB, Vanden Hoek TL. 2006. Therapeutic hypothermia after cardiac arrest: Unintentional

overcooling is common using ice packs and conventional cooling blankets. Crit Care Med 34(12 Suppl):S490-4.

Mickey RM and Greenland S. 1989. The impact of confounder selection criteria on effect estimation. Am J Epidemiol 129(1):125-37.

Moler FW, Silverstein FS, Holubkov R, Slomine BS, Christensen JR, Nadkarni VM, Meert KL, Clark AE, Browning B, Pemberton VL, et al. 2015. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. N Engl J Med 372(20):1898-908.

Morrison LJ, Nichol G, Rea TD, Christenson J, Callaway CW, Stephens S, Pirrallo RG, Atkins DL, Davis DP, Idris AH, et al. 2008. Rationale, development and implementation of the resuscitation outcomes consortium epistry-cardiac arrest. Resuscitation 78(2):161-9.

Moulaert VR, Verbunt JA, van Heugten CM, Wade DT. 2009. Cognitive impairments in survivors of out-of-hospital cardiac arrest: A systematic review. Resuscitation 80(3):297-305.

Neumar RW, Eigel B, Callaway CW, Estes NA,3rd, Jollis JG, Kleinman ME, Morrison L, Peberdy MA, Rabinstein A, Rea TD, et al. 2015. The american heart association response to the 2015 institute of medicine report on strategies to improve cardiac arrest survival. Circulation .

Neumar RW, Nolan JP, Adrie C, Aibiki M, Berg RA, Bottiger BW, Callaway C, Clark RS, Geocadin RG, Jauch EC, et al. 2008. Post-cardiac arrest syndrome: Epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the international liaison committee on resuscitation (american heart association, australian and new zealand council on resuscitation, european resuscitation council, heart and stroke foundation of canada, InterAmerican heart foundation, resuscitation council of asia, and the resuscitation council of southern africa); the american heart association emergency cardiovascular care committee; the council on cardiovascular surgery and anesthesia; the council on cardiopulmonary, perioperative, and critical care; the council on clinical cardiology; and the stroke council. Circulation 118(23):2452-83.

Newgard CD, Fildes JJ, Wu L, Hemmila MR, Burd RS, Neal M, Mann NC, Shafi S, Clark DE, Goble S, et al. 2013. Methodology and analytic rationale for the american college of surgeons trauma quality improvement program. J Am Coll Surg 216(1):147-57.

Nichol G and Soar J. 2010. Regional cardiac resuscitation systems of care. Curr Opin Crit Care 16(3):223-30.

Nichol G, Thomas E, Callaway CW, Hedges J, Powell JL, Aufderheide TP, Rea T, Lowe R, Brown T, Dreyer J, et al. 2008. Regional variation in out-of-hospital cardiac arrest incidence and outcome. JAMA 300(12):1423-31.

Nichol G, Guffey D, Stiell IG, Leroux B, Cheskes S, Idris A, Kudenchuk PJ, Macphee RS, Wittwer L, Rittenberger JC, et al. 2015. Post-discharge outcomes after resuscitation from out-of-hospital cardiac arrest: A ROC PRIMED substudy. Resuscitation 93:74-81.

Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, Horn J, Hovdenes J, Kjaergaard J, Kuiper M, et al. 2013. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. N Engl J Med 369(23):2197-206.

Nishiyama C, Brown SP, May S, Iwami T, Koster RW, Beesems SG, Kuisma M, Salo A, Jacobs I, Finn J, et al. 2014. Apples to apples or apples to oranges? international variation in reporting of process and outcome of care for out-of-hospital cardiac arrest. Resuscitation 85(11):1599-609.

Niven DJ and Laupland KB. 2013. Pharmacotherapy of fever control among hospitalized adult patients. Expert Opin Pharmacother 14(6):735-45.

Oddo M, Schaller MD, Feihl F, Ribordy V, Liaudet L. 2006. From evidence to clinical practice: Effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest. Crit Care Med 34(7):1865-73.

Pachys G, Kaufman N, Bdolah-Abram T, Kark JD, Einav S. 2014. Predictors of long-term survival after out-of-hospital cardiac arrest: The impact of activities of daily living and cerebral performance category scores. Resuscitation 85(8):1052-8.

Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M, Gabrielli A, Silvers SM, Zaritsky AL, Merchant R, et al. 2010. Part 9: Post-cardiac arrest care: 2010 american heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 122(18 Suppl 3):S768-86.

Perkins GD, Jacobs IG, Nadkarni VM, Berg RA, Bhanji F, Biarent D, Bossaert LL, Brett SJ, Chamberlain D, de Caen AR, et al. 2014. Cardiac arrest and cardiopulmonary resuscitation outcome reports: Update of the utstein resuscitation registry templates for out-of-hospital cardiac arrest: A statement for healthcare professionals from a task force of the international liaison committee on resuscitation (american heart association, european resuscitation council, australian and new zealand council on resuscitation, heart and stroke foundation of canada, InterAmerican heart foundation, resuscitation council of southern africa, resuscitation council of asia); and the

american heart association emergency cardiovascular care committee and the council on cardiopulmonary, critical care, perioperative and resuscitation. Circulation 132(13):1286-300.

Perman SM, Grossestreuer AV, Wiebe DJ, Carr BG, Abella BS, Gaieski DF. 2015. The utility of therapeutic hypothermia for post-cardiac arrest syndrome patients with an initial nonshockable rhythm. Circulation 132(22):2146-51.

Phelps R, Dumas F, Maynard C, Silver J, Rea T. 2013. Cerebral performance category and long-term prognosis following out-of-hospital cardiac arrest. Crit Care Med 41(5):1252-7.

Pichon N, Amiel JB, Francois B, Dugard A, Etchecopar C, Vignon P. 2007. Efficacy of and tolerance to mild induced hypothermia after out-of-hospital cardiac arrest using an endovascular cooling system. Crit Care 11(3):R71.

Polderman KH. 2015. An injured brain needs cooling down: Yes. Intensive Care Med 41(6):1126-8.

Polderman KH. 2009. Mechanisms of action, physiological effects, and complications of hypothermia. Crit Care Med 37(7 Suppl):S186-202.

Polderman KH. 2008. Induced hypothermia and fever control for prevention and treatment of neurological injuries. Lancet 371(9628):1955-69.

Raina KD, Callaway C, Rittenberger JC, Holm MB. 2008. Neurological and functional status following cardiac arrest: Method and tool utility. Resuscitation 79(2):249-56.

Render ML, Kim HM, Welsh DE, Timmons S, Johnston J, Hui S, Connors AF,Jr, Wagner D, Daley J, Hofer TP, et al. 2003. Automated intensive care unit risk adjustment: Results from a national veterans affairs study. Crit Care Med 31(6):1638-46.

Repasky EA, Evans SS, Dewhirst MW. 2013. Temperature matters! and why it should matter to tumor immunologists. Cancer Immunol Res 1(4):210-6.

Riess ML, Aufderheide TP, Yannopoulos D. 2015. Therapeutic hypothermia in children. N Engl J Med 373(10):979-80.

Rittenberger JC and Callaway CW. 2014. Targeted temperature management after cardiac arrest. N Engl J Med 370(14):1360-1.

Rittenberger JC and Callaway CW. 2013. Temperature management and modern post-cardiac arrest care. N Engl J Med 369(23):2262-3.

Ro YS, Shin SD, Song KJ, Lee EJ, Kim JY, Ahn KO, Chung SP, Kim YT, Hong SO, Choi JA, et al. 2013. A trend in epidemiology and outcomes of out-of-hospital cardiac arrest by urbanization level: A nationwide observational study from 2006 to 2010 in south korea. Resuscitation 84(5):547-57.

Sadaka F. 2013. Therapeutic hypothermia for brain injury from near hanging: Review of the literature. Ther Hypothermia Temp Manag 3(1):13-6.

Sagalyn E, Band RA, Gaieski DF, Abella BS. 2009. Therapeutic hypothermia after cardiac arrest in clinical practice: Review and compilation of recent experiences. Crit Care Med 37(7 Suppl):S223-6.

Saper CB and Breder CD. 1994. The neurologic basis of fever. N Engl J Med 330(26):1880-6.

Sasson C, Rogers MA, Dahl J, Kellermann AL. 2010. Predictors of survival from out-of-hospital cardiac arrest: A systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 3(1):63-81.

Sasson C, Forman J, Krass D, Macy M, Kellermann AL, McNally BF. 2009. A qualitative study to identify barriers to local implementation of prehospital termination of resuscitation protocols. Circ Cardiovasc Qual Outcomes 2(4):361-8.

Sasson C, Forman J, Krass D, Macy M, Hegg AJ, McNally BF, Kellermann AL. 2010. A qualitative study to understand barriers to implementation of national guidelines for prehospital termination of unsuccessful resuscitation efforts. Prehosp Emerg Care 14(2):250-8.

Schefold JC, Storm C, Joerres A, Hasper D. 2009. Mild therapeutic hypothermia after cardiac arrest and the risk of bleeding in patients with acute myocardial infarction. Int J Cardiol 132(3):387-91.

Smith K, Andrew E, Lijovic M, Nehme Z, Bernard S. 2015. Quality of life and functional outcomes 12 months after out-of-hospital cardiac arrest. Circulation 131(2):174-81.

Spaite DW, Bobrow BJ, Stolz U, Berg RA, Sanders AB, Kern KB, Chikani V, Humble W, Mullins T, Stapczynski JS, et al. 2014. Statewide regionalization of postarrest care for out-of-hospital cardiac arrest: Association with survival and neurologic outcome. Ann Emerg Med 64(5):496,506.e1.

StataCorp. 2013. Stata multiple imputation reference manual: Release 13.

Stub D, Schmicker RH, Anderson ML, Callaway CW, Daya MR, Sayre MR, Elmer J, Grunau BE, Aufderheide TP, Lin S, et al. 2015. Association between hospital post-

resuscitative performance and clinical outcomes after out-of-hospital cardiac arrest. Resuscitation 92:45-52.

Suffoletto B, Peberdy MA, van der Hoek T, Callaway C. 2009. Body temperature changes are associated with outcomes following in-hospital cardiac arrest and return of spontaneous circulation. Resuscitation 80(12):1365-70.

Sunde K, Pytte M, Jacobsen D, Mangschau A, Jensen LP, Smedsrud C, Draegni T, Steen PA. 2007. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. Resuscitation 73(1):29-39.

Tagami T, Hirata K, Takeshige T, Matsui J, Takinami M, Satake M, Satake S, Yui T, Itabashi K, Sakata T, et al. 2012. Implementation of the fifth link of the chain of survival concept for out-of-hospital cardiac arrest. Circulation 126(5):589-97.

Takasu A, Saitoh D, Kaneko N, Sakamoto T, Okada Y. 2001. Hyperthermia: Is it an ominous sign after cardiac arrest? Resuscitation 49(3):273-7.

Takino M and Okada Y. 1991. Hyperthermia following cardiopulmonary resuscitation. Intensive Care Med 17(7):419-20.

van der Jagt M and Haitsma I. 2015. An injured brain needs cooling down: No. Intensive Care Med 41(6):1129-31.

Wang CX, Stroink A, Casto JM, Kattner K. 2009. Hyperthermia exacerbates ischaemic brain injury. Int J Stroke 4(4):274-84.

Weisfeldt ML, Sitlani CM, Ornato JP, Rea T, Aufderheide TP, Davis D, Dreyer J, Hess EP, Jui J, Maloney J, et al. 2010. Survival after application of automatic external defibrillators before arrival of the emergency medical system: Evaluation in the resuscitation outcomes consortium population of 21 million. J Am Coll Cardiol 55(16):1713-20.

Winters SA, Wolf KH, Kettinger SA, Seif EK, Jones JS, Bacon-Baguley T. 2013. Assessment of risk factors for post-rewarming "rebound hyperthermia" in cardiac arrest patients undergoing therapeutic hypothermia. Resuscitation 84(9):1245-9.

Wissenberg M, Lippert FK, Folke F, Weeke P, Hansen CM, Christensen EF, Jans H, Hansen PA, Lang-Jensen T, Olesen JB, et al. 2013. Association of national initiatives to improve cardiac arrest management with rates of bystander intervention and patient survival after out-of-hospital cardiac arrest. JAMA 310(13):1377-84.

Wrotek SE, Kozak WE, Hess DC, Fagan SC. 2011. Treatment of fever after stroke: Conflicting evidence. Pharmacotherapy 31(11):1085-91.

Zeiner A, Holzer M, Sterz F, Schorkhuber W, Eisenburger P, Havel C, Kliegel A, Laggner AN. 2001. Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. Arch Intern Med 161(16):2007-12.

Zhao H, Asai S, Kanematsu K, Kunimatsu T, Kohno T, Ishikawa K. 1997. Real-time monitoring of the effects of normothermia and hypothermia on extracellular glutamate re-uptake in the rat following global brain ischemia. Neuroreport 8(9-10):2389-93.