APPLYING STATISTICAL METHODS IN A REGISTRY DATASET OF CARDIOPULMONARY RESUSCITATION TO PREDICT PROBABILITY OF SURVIVAL BY CHEST COMPRESSION TIME IN CHILDREN

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ABSTRACT

The focus of this thesis was to apply advanced statistical methods to the American Heart Association Get With The Guidelines-Resuscitation (AHA GWTG-R) registry, a registry data set derived from a prospective multi-sites observational study, the American Heart Association's National Registry of Cardiopulmonary Resuscitation (NRCPR). The data comprise comprehensive information related to the cardiopulmonary resuscitation (CPR) process, patients' outcome, and characteristics of both the patients and the hospitals. The purpose of the registry data is to provide information that can be used to improve the outcomes of sudden cardiac arrest (SCA) patients and updates protocol of CPR.

This thesis has two purposes. The first one is to investigate the relationship between the patients' disease and survival for SCA patients receiving different durations of chest compression. The second one is to establish a model for predicting the probability of survival according to the duration of CPR. In the clinical setting, a categorized variable may provide more meaningful inferences. To explore this option, a Generalized additive model (GAM) was used to identify cutoff points for the categorization of chest compression duration. This categorized variable was then used for the development of prediction models for survival and the Net reclassification index (NRI) was used to select the appropriate predictors for this model.

Logistic regression, generalized estimating equations (GEE), and a generalized linear mixed model (GLMM) were performed to obtain the estimates of parameters. Thereafter, the probability of survival was estimated based on the results of the regression model.

Comprehensive registry data have been established for many healthcare problems, which include many observations and variables. A systematic process to analyze registry data is necessary. This thesis used multiple statistical techniques to create meaningful variables, select appropriate predictors, fit regression models, and predict the probabilities of outcome. The public health significance of this thesis is the identification of subgroups of SCA patients who may benefit from prolonged CPR duration and to assess significance of cluster effects in the registry data.

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1.0 INTRODUCTION

Sudden cardiac arrest (SCA) is defined as sudden, unexpected loss of heart function, breath and consciousness. If appropriate treatment is not provided immediately, these patients cannot survive. The common causes of SCA include arrhythmia, valvular heart disease, coronary heart disease, and so on. The Centers for Disease Control and Prevention (CDC) estimated that 2,000 SCA deaths occur in the population of individuals that were younger than 25 years old (Kung, Hoyert, Xu and Murphy 2008). The general incidence of SCA is hard to estimate. The reported incidence of cardiovascular-related, out-of-hospital cardiac arrest (OHCA) in children and adolescents in the US ranges between 0.61 and 1.44 per 100,000 pediatric person-years (Meyer, et al. 2012). The age-adjusted risk of SCA was higher in athletic young adults (Corrado, Basso, Rizzoli, Schiavon and Thiene 2003). Furthermore, SCA accounted for 0.7% to 3% of pediatric hospital admission and up to 5.5% of pediatric intensive care unit (ICU) admissions (Reis, Nadkarni, Perondi, Grisi and Berg 2002). Thus the costs of healthcare and rehabilitation following SCA lead to significant family, social and medical burden.

Survival rates have increased in the decades after an improved standard resuscitation protocol was implemented (Girotra, et al. 2013, Sutton, et al. 2014). Among the patients with SCA, children with cardiac disease had better survival, but those who with trauma had the worst outcome (Meert, et al. 2009). The potential factors that are associated with survival of pediatric SCA patients have been investigated. A Japanese nationwide population-based study indicated that pediatric patients with OHCA can benefit from bystander cardiopulmonary resuscitation (CPR) and public access-automated external defibrillator (Akahane, et al. 2013). A prospective study based on the National Registry of Cardiopulmonary Resuscitation showed that patients with bradycardia, which is arrhythmia with slow heart rate, were more likely to survive after CPR (Donoghue, et al. 2009). A prospective, multinational, observational study investigated factors that impact survival on hospital discharge for 502 in-hospital pediatric SCA patients. The study concluded that low developmental index, underlying diseases, such as cancer, longer compression duration, and more inotropic drug use were associated with mortality of these patients (Lopez-Herce, et al. 2013).

Though longer chest compression duration is considered an indicator of a poor survival outcome for SCA patients, some pediatric patients may benefit from prolonged chest compression and their characteristics were not thoroughly studied. More medical staffs and drugs are required for prolonged CPR. In order to balance the medical cost and survival benefits of prolonged CPR for SCA patients, it is important to identify specific characteristics of SCA patients whose chance of survival is increased with prolonged chest compressions. This study aimed to identify the disease categories of the SCA patients who can benefit from prolonged CPR duration and predict the probability of survival based on CPR duration for each disease category. I will explore the relationship of the illness categories, chest compression duration, and their survival outcomes by using the AHA GWTG-R data (see below). The following process illustrates the statistical methods used for analyzing a registry data set to establish a model to predict survival of pediatric SCA patients.

1.1 RESUSCITATION DATA

The American Heart Association Get With The Guidelines-Resuscitation (AHA GWTG-R) is derived from the American Heart Association's National Registry of Cardiopulmonary Resuscitation (NRCPR). NRCPR is a prospective, multi-site, observational study starting in 1999 and was incorporated into GWTG in 2010. This is an ongoing study. The primary aim of the study is quality improvement of the CPR protocol, so that more lives can be saved through appropriate CPR procedure. The program collects resuscitation data from participating hospitals and then provides these hospitals with feedback on their resuscitation practice and outcomes of patients. Furthermore, new evidence-based guidelines can be developed from the data (www.heart.org/resuscitation) (Peberdy, et al. 2003).

1.2 OBJECTIVES

1.2.1 Survival outcome

The study aimed to investigate the relationship between illness categories of pediatric SCA patients and their outcomes on hospital discharge in each chest compression duration group. Furthermore, this study also determined the characteristics of patients and CPR factors that can predict the probability of survival.

2.0 METHODOLOGY

2.1 DESIGN

The AHA GWTG-R is a prospective, multicenter registry of in-hospital cardiac arrest (IHCA) and resuscitation events using Utstein-style data reporting (Cummins, et al. 1997, Jacobs, et al. 2004). This study included subjects registered in 328 US and Canadian hospitals from January 1st, 2000 through December 31st, 2009.

2.2 SUBJECTS (INCLUSION/EXCLUSION CRITERIA)

All subjects <18 years of age with pulseless IHCA events were included in this study. The subjects must accept at least 1 minute of chest compression. Patients experiencing the events in hospitals and in the other locations (outpatient clinics within the hospital, visitors, and inpatients of rehabilitation, skilled nursing, and mental health facilities attached to study hospitals) were included. The subjects with events that happened outside of the hospital or in the neonatal intensive care unit (NICU), delivery room, or nursery were excluded. The subjects with the variable illness categories of newborn, obstetric, or other illnesses were excluded, too. If the subjects received more than 180 minutes of chest compression, the chest compression duration was winsorized at a pre-determined maximum of 180 minutes to reduce the effects of the possible extreme outliers.

2.3 MEASURES

Index events indicated the first cardiopulmonary arrest event during the patient's hospitalization. The illness categories were defined by the characteristics of the patient at the time of cardiopulmonary arrest. General medical condition indicated a non-cardiovascular medical illness. Medical cardiac patients had a primary diagnosis of a cardiovascular medical illness. General surgical patients were enrolled at preoperative status with a general surgical illness or at a postoperative status after non-cardiovascular surgery. Surgical cardiac condition indicated a postoperative status after cardiovascular surgery. Trauma patients were subjects experiencing single or multiple injuries. Patients with "do not attempt resuscitation" before their first IHCA were excluded.

The primary outcome was survival on hospital discharge. Compared to continuous variables, categorized variables may be more practical in the clinical setting. Therefore, the chest compression duration was categorized based on the results of generalized additive model (GAM).

2.4 DATA ANALYSIS

2.4.1 Generalized Additive Model (GAM)

A generalized additive model (GAM) was used to determine transformation of the chest compression duration variable. This method extends the usual likelihood-based regression models and develops its estimation. GAM assumes that the mean of the dependent variable depends on an additive predictor through a nonlinear link function. For a linear model with covariates, $X_1, X_2, \cdots, X_p$, the linear function, $\sum_1^p \beta_i X_i$, of the likelihood-based regression model is replaced by an smooth function, $\sum_1^p s_i(X_i)$, that defines the additive component.

For a generalized linear model (GLM), $g\{\mu\} = \beta_0 + \sum_{i=1}^p \beta_i(X_i)$, where μ is the conditional expectation of Y given $x_1, \cdots, x_p$. Therefore, GAM is $g\{\mu\} = \eta = s_0 + \sum_{i=1}^p s_i(X_i)$.

The *local scoring algorithm* and the *weighted backfitting algorithm* are used to estimate the $s_i(\cdot)$'s. The algorithms find new estimates of the functions by smoothing the partial residuals till the partial functions converge. The local scoring algorithm is used when the dependent variables are categorical, and the backfitting algorithm is used for the model with continuous dependent variables. Any nonparametric smoothing method, such as lowess and B-spline, can be used to estimate the $s_i(\cdot)$'s. This procedure can reduce a multiple regression to a series of two-dimensional partial regression problems. The results can be plotted on a two dimensional graph to show the partial effects of each X_i on Y (Hastie and Tibshirani 1986).

The GAM provides a nonparametric method to see the relationship between the predictors and the outcome. In a clinical setting, categorizing some continuous variables may be more applicable, especially for predicting clinical outcomes. Therefore, information obtained from GAM can be used to determine appropriate cutoff points based on the data. In GAM, the relationship between X's, the horizontal axis, and $s(X)$, the vertical axis, can be plotted. The line for $s(X)= 0$ indicates the average value of the covariate. The average-risk cutoff points are those x's $\in X$, such that $s(x)=0$. Furthermore, the points where the slopes change are the extra cut-off points. The selection of the extra cut-off points are based on the graphical visualization of the slopes and the clinical significance (Barrio, Arostegui, Quintana and Group 2013).

In this analysis, only one predictor, a continuous variable of chest compression duration, was used in the GAM. And the survival status on discharge was the dependent variable. Categorization of the continuous chest compression duration variable was determined by the GAM method and expert opinions.

2.4.2 Net Reclassification Index (NRI)

The AHA GWTG-R includes variables recording clinical and administrative data in each resuscitation event. The purpose of this study is to predict the probability of survival according to the characteristics of subjects. In order to determine the appropriate covariates for the models, the net reclassification index (NRI) was used. This method quantifies whether a new independent variable can provide a clinically relevant improvement in the prediction of the dependent variable. The model with established predictors is indicated as the "old" model. The model with one additional new predictor is denoted as the "new" model. The NRI is estimated by the following equations:

Event NRI: $NRI_e = P\ (up|event) - P\ (down|event)$, where

$$\begin{cases} \text{"up": the new risk model places a person into a higher risk category than the old model} \\ \text{"down": the new model places a person into a lower risk category} \\ \text{"event"}: cases - persons\ who\ survive \\ \text{"noevent"}: controls - persons\ who\ die \end{cases}$$

Non-event NRI: $NRI_{ne} = P\ (up|noevent) - P\ (down|noevent)$

An NRI is the sum of event NRI and non-event NRI, yielding

$NRI = P\ (up|event) - P\ (down|event) + P\ (down|nonevent) - P\ (up|nonevent)$.

If the new predictor increases the predicted risk for an event and decreases the predicted risk for a non-event, *P (up|event)* and *P (down|event)* provide the positive components of the NRI. However, the risk of the event moving down and the risk of the non-event moving up indicate that the new predictor compromises the prediction ability of the model (Pencina, D'Agostino, D'Agostino and Vasan 2008).

The potential predictors were selected based on the results of descriptive statistics and opinions of experts, the emergent physicians. The most important predictors, determined by physicians, formed the basic model. A new predictor was added into the basic model, and NRI was performed for the new predictor. If the new predictor significantly increased the prediction power of the survival outcome, the new predictor was incorporated into the old model and formed the new basic model. If the new predictor could not improve prediction of the survival outcome, the predictor was dropped. The chosen predictors were then used for further analyses.

2.4.3 Logistic Regression Model

The outcome is a binary variable and logistic regression is the approach of choice in this setting. One goal of the study was to model the conditional probability *P(Y= 1 | X= x)* as a function of *x*. One assumption of a logistic regression model is the independence of every subject or observation. The unknown parameters in the function were estimated by maximum likelihood.

The general form of logistic regression model is

$$logit(P[Y_i = 1|X_i]) = ln\left(\frac{p(\boldsymbol{X_i})}{1-p(\boldsymbol{X_i})}\right) = \boldsymbol{X_i\beta}, \text{ where } \begin{cases} \boldsymbol{\beta}(parameter): \beta_0, \beta_1, \beta_2, \cdots, \beta_p \\ \boldsymbol{X}(variable): 1,\ x_1, x_2, \cdots, x_p \\ \boldsymbol{i}(subject): 1, 2, \cdots, n \end{cases}.$$

Solving for $p(\boldsymbol{X}_i)$, the probability of the event occurring, the result is

$$p(X_i) = \frac{e^{X_i\beta}}{1+e^{X_i\beta}} = \frac{1}{1+e^{-(X_i\beta)}}.$$

In this analysis, the major outcome was survival of the subjects. The first purpose was to test whether patients in some illness categories had higher odds of survival in a specific compression duration category. The hypothesis was that the odds of survival are not the same for patients with different illness categories and in different chest compression duration categories. In other words, compression duration categories were the effect modifier of the relationship between illness categories and survival. The interaction of illness and compression duration categories was included in the regression model.

The second purpose was to predict the probability of survival for patients with different illness categories based on the chest compression duration. This predictive model was established based on the results of the NRI. After the values of the parameters were estimated, the probability of survival for chest compression duration from 0 minute through 180 minutes was calculated. The average values of the other covariates were used in calculating the probability of survival. The prediction indicated the probability of survival for an average patient receiving chest compression from 0 through 180 minutes.

2.4.4 Generalized Estimating Equation Model (GEE)

Though the procedure of CPR has been established and standardized, the survival of SCA subjects may depend on the quality of critical care within the hospitals. Therefore, the survival of subjects within the same hospital may be correlated. To obtain the population average estimates by considering the correlated data within each hospital, a generalized estimating equation (GEE) model was used (Zeger and Liang 1986). The outcome and covariates were the same as those in the logistic model.

The GEE model: $logit\left(P\left[Y_{ij} = 1\middle|X_{ij}\right]\right) = \boldsymbol{X_{ij}\beta}, \begin{cases} \boldsymbol{i}: 1 - N\ clusters \\ \boldsymbol{j}: 1 - J\ subjects \end{cases}$,

Marginal mean (population-average mean): $\mu_{ij} = E\left(Y_{ij}\middle|X_{ij}\right) = P(Y_{ij} = 1|X_{ij})$

Variance-covariance matrix for correlated data (N clusters and J observation per cluster):

$$V = \begin{pmatrix} V_1 & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & V_N \end{pmatrix}$$

$$= \begin{pmatrix} Cov(Y_{1j}, Y_{1k}) & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & Cov(Y_{Nj}, Y_{Nk}) \end{pmatrix}, \quad j, k=1, \ldots, J$$

$$= \begin{pmatrix} \emptyset A_1^{1/2} R_1 A_1^{1/2} & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & \emptyset A_N^{1/2} R_N A_N^{1/2} \end{pmatrix}$$

$V=V(Y)$: a $N \times N$ variance-covariance matrix of the dependent variable

A_i: a $J \times J$ diagonal matrix with $V(\mu_{ij})$ as the jth diagonal element

R_i: a $J \times J$ working correlation matrix

$\emptyset$: a overdispersion parameter

Working variance-covariance matrix for Y_i is equal to $V_i = \emptyset A_i^{1/2} R_i A_i^{1/2}$

Common working correlation structure:

Independence, where $R_{jk}=0$

$$R_i = \begin{bmatrix} 1 & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & 1 \end{bmatrix}$$

Exchangeable, where $R_{jk}=\rho$

$$R_i = \begin{bmatrix} 1 & \cdots & \rho \\ \vdots & \ddots & \vdots \\ \rho & \cdots & 1 \end{bmatrix}$$

Autoregressive, AR(1), where $R_{jk}=\rho^{|j-k|}$

$$R_i = \begin{bmatrix} 1 & \cdots & \rho^{J-1} \\ \vdots & \ddots & \vdots \\ \rho^{J-1} & \cdots & 1 \end{bmatrix}$$

Unstructured, where $R_{jk}=\rho_{jk}$

$$R_i = \begin{bmatrix} 1 & \cdots & \rho_{1,J} \\ \vdots & \ddots & \vdots \\ \rho_{J,1} & \cdots & 1 \end{bmatrix}$$

The major assumption of the GEE model is that the data satisfy the missing completely at random (MCAR) assumption. The registry data were established by the trained coordinators who record all required variables during resuscitation and the following clinical results. The data collection procedure was consistent within each hospital. Therefore, the missing values were not likely to be associated with covariates and outcomes. For the purposes of this analysis, we assume that the MCAR assumption was not violated.

The purpose of the analysis was to compare the GEE model to the logistic regression model, so the covariates in the models were the same. Quasilikelihood under the independence model criterion (QIC) was used to determine the appropriate working correlation structure (Pan 2001).

2.4.5 Generalized Linear Mixed Model (GLMM)

The third model is the generalized linear mixed model (GLMM). Contrary to GEE that estimates a population-average mean, GLMM estimates a conditional mean (Williams 1982).

The general form of the model is

$$\overbrace{\boldsymbol{y}}^{N\times 1} = \overbrace{\underbrace{\boldsymbol{X}}_{N\times p}\ \underbrace{\boldsymbol{\beta}}_{p\times 1}}^{N\times 1} + \overbrace{\underbrace{\boldsymbol{Z}}_{N\times q}\ \underbrace{\boldsymbol{\gamma}}_{q\times 1}}^{N\times 1} + \overbrace{\boldsymbol{\varepsilon}}^{N\times 1}\ .$$

$$\boldsymbol{logit}(\boldsymbol{P}[\boldsymbol{Y}=\mathbf{1}|\boldsymbol{X}]) = \boldsymbol{ln}\left(\frac{\boldsymbol{p}(\boldsymbol{X})}{\mathbf{1}-\boldsymbol{p}(\boldsymbol{X})}\right) = \boldsymbol{X\beta}+\boldsymbol{Z\gamma},$$

$\boldsymbol{N}=\sum_{j=1}^{q}\boldsymbol{n_j}$, where *j*: *1-q* clusters

$\boldsymbol{\gamma}\sim\boldsymbol{N}(\mathbf{0},\boldsymbol{G})$, where $\boldsymbol{G}=\boldsymbol{\sigma^2_{int}}$ for a random intercept.

GLMM uses a logistic link function for a binary outcome.

This registry data set was established through participating hospitals, so this study can be considered as a clustered study design. A random intercept effect was applied to this model. The covariates in GLMM were the same as those in the logistic regression model.

3.0 RESULTS

3.1 DEMOGRAPHIC CHARACTERISTICS

A total of 2,564 subjects were eligible in this study. Figure 1 showed the distribution of chest compression duration. More than 50% of the subjects received less than 25 minutes of chest compression. Table 1 showed the demographic characteristics of the subjects. More than 40% of patients were in the general medical group. Only 194 subjects were in a general surgical group. Overall, 40% of the subjects received chest compression for less than 16 minutes. For subjects with general surgical condition or with trauma, almost half of them had less than 16 minutes of chest compression. Compared to the other patients, a higher proportion of subjects with cardiac diseases accepted longer chest compression duration. Nearly half of the patients with a surgical cardiac condition were younger than 1 month; however, more than 50% of trauma patients were 8 years of age and older. Gender was not significantly different across all illness groups. Most of the SCA patients were inpatients of healthcare facilities. Most SCA events happened in the intensive care unit (ICU). In all illness categories, patients mainly presented hypotension or hypoperfusion. Most patients required invasive airway establishment and mechanical ventilator support, especially for those patients with a surgical or traumatic condition. Twenty-three percent of patients with a surgical cardiac condition needed a pacemaker. Pre-existing respiratory insufficiency and hypotension/hypoperfusion were common across all illness groups. Otherwise, incidence of other pre-existing health conditions was low. More than 40% of traumatic patients were sent to the emergency department (ED) during the weekend. For patients with a general medical or a general surgical condition, their first pulseless rhythm was mainly presented as asystole; however, the trauma and surgical cardiac patients mainly experienced pulseless electrical activity (PEA). More than 80% of all patients used epinephrine, but other vasopressors were not administered for most patients. More patients with a surgical cardiac condition required invasive procedures, such as an invasive airway insertion, pacemaker, and continuous sedation.

More than 70% of SCA patients died after CPR. Table 2 showed the outcomes of patients with individual illness categories. Patients with surgical condition had higher survival rates, but only 10% of trauma patients survived. Table 3 showed the survival rate of SCA patients in each chest compression duration category. Forty-six percent of the patients receiving less than 16 minutes of chest compression duration survived. The survival rates were similar for patients receiving 16-35 minutes and longer than 35 minutes of chest compression duration.

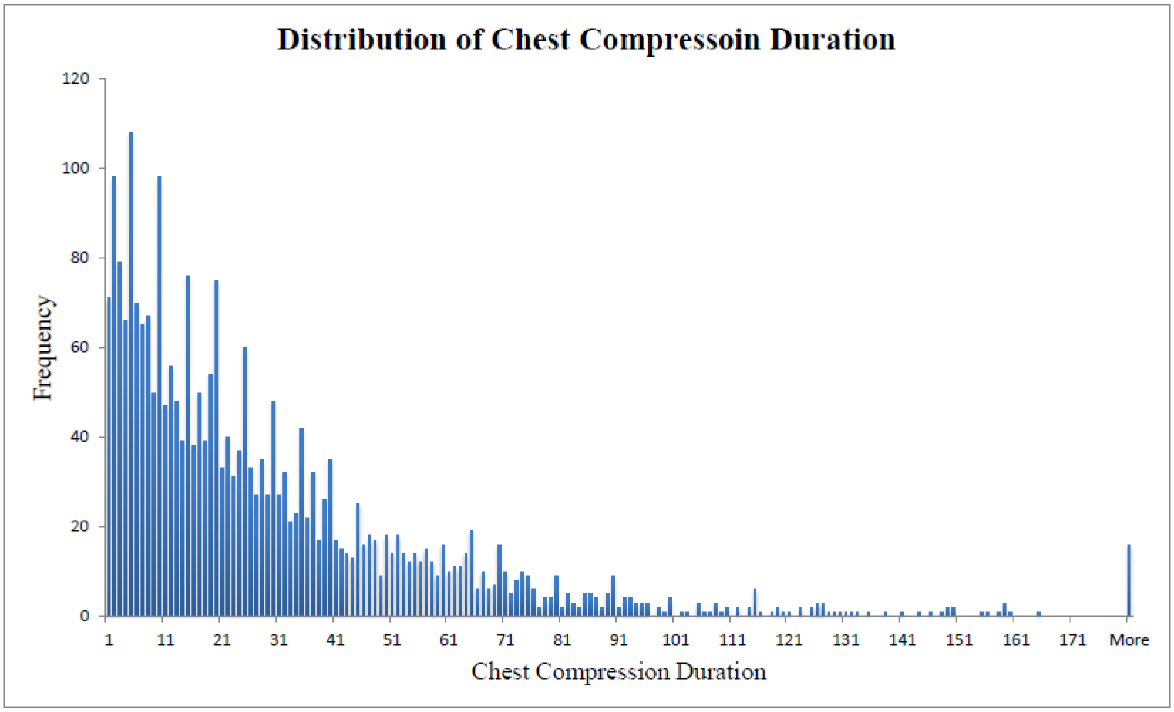

Figure 1. Distribution of Chest Compression Duration

Table 1. Demographic Characteristics

		Illness Category					
	All (N=2,564)	Medical, cardiac (N=444)	General, medical (N=1,111)	Surgical, cardiac (N=541)	General, surgical (N=194)	Trauma (N=274)	
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	P-value
Chest compression group							<0.001
0-15	1038 (40.48)	157 (35.36)	434 (39.06)	211 (39)	94 (48.45)	142 (51.82)	
16-35	772 (30.11)	149 (33.56)	360 (32.4)	129 (23.84)	48 (24.74)	86 (31.39)	
>35	754 (29.41)	138 (31.08)	317 (28.53)	201 (37.15)	52 (26.8)	46 (16.79)	
Age group							<0.001
<1 month	498 (19.42)	80 (18.02)	116 (10.44)	269 (49.72)	28 (14.43)	5 (1.82)	
1 month - <1 year	682 (26.6)	149 (33.56)	298 (26.82)	152 (28.1)	56 (28.87)	27 (9.85)	
1 yr - <8yr	659 (25.7)	124 (27.93)	331 (29.79)	73 (13.49)	50 (25.77)	81 (29.56)	
8 yr - <18 yr	725 (28.28)	91 (20.5)	366 (32.94)	47 (8.69)	60 (30.93)	161 (58.76)	
Gender							0.189
Male	1457 (56.83)	237 (53.38)	624 (56.17)	312 (57.67)	113 (58.25)	171 (62.41)	
Female	1107 (43.17)	207 (46.62)	487 (43.83)	229 (42.33)	81 (41.75)	103 (37.59)	
Race							<0.001
White	1391 (54.79)	237 (53.86)	567 (51.59)	324 (60.56)	116 (60.10)	147 (50.04)	
Black	560 (22.06)	93 (21.14)	281 (25.57)	83 (15.51)	38 (19.69)	65 (23.90)	
Asian/Pacific	61 (2.40)	12 (2.73)	26 (2.37)	10 (1.87)	6 (3.11)	7 (2.57)	
Native American	27 (1.06)	7 (1.59)	9 (0.82)	4 (0.75)	1 (0.52)	6 (2.21)	
Other	240 (9.45)	58 (13.18)	102 (9.28)	47 (8.79)	15 (7.77)	18 (6.62)	
Unknown	260 (10.24)	33 (7.50)	114 (10.37)	67 (12.52)	17 (8.81)	29 (10.66)	

Table 1 Continued

Hispanic							0.01
No	1897 (81.35)	311 (78.73)	823 (82.71)	401 (79.56)	142 (78.45)	220 (85.60)	
Yes	435 (18.65)	84 (21.27)	172 (17.29)	103 (20.44)	39 (21.55)	37 (14.40)	
Event Location							<0.001
ICU	1717 (66.97)	276 (62.16)	675 (60.76)	476 (87.99)	118 (60.82)	172 (62.77)	
Emergency	367 (14.31)	172 (62.77)	216 (19.44)	2 (0.37)	2 (1.03)	68 (24.82)	
General Inpatient	265 (10.34)	42 (9.46)	166 (14.94)	25 (4.62)	26 (13.4)	6 (2.19)	
Procedure room	144 (5.62)	32 (7.21)	24 (2.16)	21 (3.88)	45 (23.2)	22 (8.03)	
Others	71 (2.77)	15 (3.38)	30 (2.7)	17 (3.14)	3 (1.55)	6 (2.19)	
Time of Day (Night=11pm-6am/Day=6:01am-10:59pm)							0.257
Day	1711 (66.73)	297 (66.89)	736 (66.25)	367 (67.84)	140 (72.16)	171 (62.41)	
night	853 (33.27)	147 (33.11)	375 (33.75)	174 (32.16)	54 (27.84)	103 (37.59)	
Weekend (Fri 11pm-Mon 7am)							<0.001
No	1676 (65.37)	285 (64.19)	715 (64.36)	388 (71.72)	138 (71.13)	150 (54.74)	
Yes	888 (34.63)	159 (35.81)	396 (35.64)	153 (28.28)	56 (28.87)	124 (45.26)	
SubjectType							<0.001
Hospital Inpatient	2145 (83.66)	345 (77.7)	877 (78.94)	533 (98.52)	190 (97.94)	200 (72.99)	
Emergency Dep	372 (14.51)	80 (18.02)	217 (19.53)	2 (0.37)	2 (1.03)	71 (25.91)	
Outpatient	32 (1.25)	16 (3.6)	10 (0.9)	4 (0.74)	2 (1.03)	0 (0.00)	
Visitor or Employee	2 (0.08)	1 (0.23)	1 (0.09)	0 (0.00)	0 (0.00)	0 (0.00)	
Rehab Inpatient	2 (0.08)	0 (0.00)	2 (0.18)	0 (0.00)	0 (0.00)	0 (0.00)	
Skilled Nursing Inpatient	10 (0.39)	2 (0.45)	3 (0.27)	2 (0.37)	0 (0.00)	3 (1.09)	
Mental Health Inpatient	1 (0.04)	0 (0.00)	1 (0.09)	0 (0.00)	0 (0.00)	0 (0.00)	
Witnessed							<0.001
No	208 (8.11)	56 (12.61)	109 (9.81)	13 (2.4)	14 (7.22)	16 (5.84)	
Yes	2356 (91.89)	388 (87.39)	1002 (90.19)	528 (97.6)	180 (92.78)	258 (94.16)	

Table 1 Continued

Witness OR monitor							<0.001
No	107 (4.17)	32 (7.21)	62 (5.58)	3 (0.55)	5 (2.58)	5 (1.82)	
Yes	2457 (95.83)	412 (92.79)	1049 (94.42)	538 (99.45)	189 (97.42)	269 (98.18)	
Cause: Drug Overdose							0.006
No	2550 (99.45)	443 (99.77)	1098 (98.83)	541 (100)	194 (100)	274 (100)	
Yes	14 (0.55)	1 (0.23)	13 (1.17)	0 (0.00)	0 (0.00)	0 (0.00)	
Cause: Hypotension/Hypoperfusion							<0.001
No	1177 (45.9)	222 (50)	567 (51.04)	194 (35.86)	96 (49.48)	98 (35.77)	
Yes	1387 (54.1)	222 (50)	544 (48.96)	347 (64.14)	98 (50.52)	176 (64.23)	
Cause: Acute Pulmonary Edema							0.259
No	2500 (97.5)	434 (97.75)	1076 (96.85)	533 (98.52)	191 (98.45)	266 (97.08)	
Yes	64 (2.5)	10 (2.25)	35 (3.15)	8 (1.48)	3 (1.55)	8 (2.92)	
Cause: Metabolic Electrolyte Abnormality							0.001
No	2192 (85.49)	396 (89.19)	921 (82.9)	482 (89.09)	165 (85.05)	228 (83.21)	
Yes	372 (14.51)	48 (10.81)	190 (17.1)	59 (10.91)	29 (14.95)	46 (16.79)	
Cause: Invasive Airway Displacement							0.004
No	2525 (98.48)	440 (99.1)	1093 (98.38)	536 (99.08)	185 (95.36)	271 (98.91)	
Yes	39 (1.52)	4 (0.9)	18 (1.62)	5 (0.92)	9 (4.64)	3 (1.09)	
Cause: Inadequate Natural Airway							<0.001
No	2479 (96.68)	435 (97.97)	1066 (95.95)	531 (98.15)	178 (91.75)	269 (98.18)	
Yes	85 (3.32)	9 (2.03)	45 (4.05)	10 (1.85)	16 (8.25)	5 (1.82)	
Cause: Inadequate Invasive Airway							0.043
No	2496 (97.35)	437 (98.42)	1079 (97.12)	530 (97.97)	183 (94.33)	267 (97.45)	
Yes	68 (2.65)	7 (1.58)	32 (2.88)	11 (2.03)	11 (5.67)	7 (2.55)	
Cause: Conscious Sedation							0.078
No	2545 (99.26)	439 (98.87)	1107 (99.64)	538 (99.45)	190 (97.94)	271 (98.91)	
Yes	19 (0.74)	5 (1.13)	4 (0.36)	3 (0.55)	4 (2.06)	3 (1.09)	
Cause: Hypothermia							0.007

Table 1 Continued

No	2514 (98.05)	436 (98.2)	1090 (98.11)	535 (98.89)	192 (98.97)	261 (95.26)	
Yes	50 (1.95)	8 (1.8)	21 (1.89)	6 (1.11)	2 (1.03)	13 (4.74)	
Pre-existing condition: Cardiac Malformation Acyanotic							<0.001
No	2477 (96.61)	431 (97.07)	1098 (98.83)	486 (89.83)	188 (96.91)	274 (100)	
Yes	87 (3.39)	13 (2.93)	13 (1.17)	55 (10.17)	6 (3.09)	0 (0.00)	
Pre-existing condition: Cardiac Malformation Cyanotic							<0.001
No	2364 (92.2)	392 (88.29)	1102 (99.19)	403 (74.49)	193 (99.48)	274 (100)	
Yes	200 (7.8)	52 (11.71)	9 (0.81)	138 (25.51)	1 (0.52)	0 (0.00)	
Pre-existing condition: Hypotension/Hypoperfusion							<0.001
No	1547 (60.34)	303 (68.24)	734 (66.07)	250 (46.21)	117 (60.31)	143 (52.19)	
Yes	1017 (39.66)	141 (31.76)	377 (33.93)	291 (53.79)	77 (39.69)	131 (47.81)	
Pre-existing condition: Respiratory Insufficiency							<0.001
No	1044 (40.72)	197 (44.37)	413 (37.17)	210 (38.82)	78 (40.21)	146 (53.28)	
Yes	1520 (59.28)	247 (55.63)	698 (62.83)	331 (61.18)	116 (59.79)	128 (46.72)	
Pre-existing condition: Renal Insufficiency							<0.001
No	2307 (89.98)	409 (92.12)	962 (86.59)	501 (92.61)	174 (89.69)	261 (95.26)	
Yes	257 (10.02)	35 (7.88)	149 (13.41)	40 (7.39)	20 (10.31)	13 (4.74)	
Pre-existing condition: Hepatic Insufficiency							<0.001
No	2440 (95.16)	431 (97.07)	1042 (93.79)	527 (97.41)	174 (89.69)	266 (97.08)	
Yes	124 (4.84)	13 (2.93)	69 (6.21)	14 (2.59)	20 (10.31)	8 (2.92)	
Pre-existing condition: Metabolic ElectrolyteAbn							0.02
No	2065 (80.54)	372 (83.78)	862 (77.59)	449 (82.99)	157 (80.93)	225 (82.12)	
Yes	499 (19.46)	72 (16.22)	249 (22.41)	92 (17.01)	37 (19.07)	49 (17.88)	
Pre-existing condition: Diabetes Mellitus							<0.001
No	2522 (98.36)	433 (97.52)	1083 (97.48)	539 (99.63)	193 (99.48)	274 (100)	
Yes	42 (1.64)	11 (2.48)	28 (2.52)	2 (0.37)	1 (0.52)	0 (0.00)	
Pre-existing condition: Baseline Depression In CNS Function							<0.001
No	2134 (83.23)	403 (90.77)	837 (75.34)	520 (96.12)	155 (79.9)	219 (79.93)	

Table 1 Continued

Yes	430 (16.77)	41 (9.23)	274 (24.66)	21 (3.88)	39 (20.1)	55 (20.07)	
Pre-existing condition: Pneumonia							<0.001
No	2329 (90.83)	410 (92.34)	940 (84.61)	526 (97.23)	187 (96.39)	266 (97.08)	
Yes	235 (9.17)	34 (7.66)	171 (15.39)	15 (2.77)	7 (3.61)	8 (2.92)	
Pre-existing condition: Septicemia							<0.001
No	2183 (85.14)	391 (88.06)	869 (78.22)	493 (91.13)	163 (84.02)	267 (97.45)	
Yes	381 (14.86)	53 (11.94)	242 (21.78)	48 (8.87)	31 (15.98)	7 (2.55)	
Pre-existing condition: Major Trauma							<0.001
No	2276 (88.77)	442 (99.55)	1094 (98.47)	541 (100)	182 (93.81)	17 (6.2)	
Yes	288 (11.23)	2 (0.45)	17 (1.53)		12 (6.19)	257 (93.8)	
Pre-existing condition: Metastatic/Hematologic Malignancy							<0.001
No	2422 (94.46)	436 (98.2)	988 (88.93)	539 (99.63)	185 (95.36)	274 (100)	
Yes	142 (5.54)	8 (1.8)	123 (11.07)	2 (0.37)	9 (4.64)	0 (0.00)	
Pulse Rhythm							0.7617
AIVR (Accelerated Idioventricular Rhythm)	515 (81.36)	88 (80.00)	217 (80.97)	135 (81.82)	38 (90.48)	37 (77.08)	
Bradycardia	6 (0.95)	1 (0.91)	1 (0.37)	4 (2.42)	0 (0.00)	0 (0.00)	
Pacemaker	48 (7.58)	8 (7.27)	19 (7.09)	13 (7.88)	3 (7.14)	5 (10.42)	
SVT	5 (0.79)		3 (1.12)	1 (0.61)	0 (0.00)	1 (2.08)	
Sinus	14 (2.21)	2 (1.82)	6 (2.24)	3 (1.82)	0 (0.00)	3 (6.25)	
VT with a Pulse	5 (0.79)	1 (0.91)	3 (1.12)	1 (0.61)	0 (0.00)	0 (0.00)	
Unknown	40 (6.32)	10 (9.09)	19 (7.09)	8 (4.85)	1 (2.38)	2 (4.17)	
Pulse Sequence							0.001
Pulseless	1933 (75.39)	334 (75.23)	845 (76.06)	376 (69.5)	152 (78.35)	226 (82.48)	
Pulse THEN Pulseless	631 (24.61)	110 (24.77)	266 (23.94)	165 (30.5)	42 (21.65)	48 (17.52)	
Prior CPA							<0.001

Table 1 Continued

Pre-Hospital (precipitating this admission)	247 (9.63)	45 (10.14)	108 (9.72)	11 (2.03)	10 (5.15)	73 (26.64)	
Other (previous admission, same or other hospital)	103 (4.02)	34 (7.66)	41 (3.69)	17 (3.14)	8 (4.12)	3 (1.09)	
Both	15 (0.59)	4 (0.9)	7 (0.63)	2 (0.37)	0 (0.00)	2 (0.73)	
None/None Documented	2199 (85.76)	361 (81.31)	955 (85.96)	511 (94.45)	176 (90.72)	196 (71.53)	
Prior Emergency Department Discharge within 24 hours							<0.001
No	606 (75.47)	102 (76.69)	223 (67.58)	198 (97.54)	47 (83.93)	36 (44.44)	
Yes	197 (24.53)	31 (23.31)	107 (32.42)	5 (2.46)	9 (16.07)	45 (55.56)	
First Pulseless Rhythm							<0.001
Asystole	981 (38.26)	164 (36.94)	508 (45.72)	133 (24.58)	83 (42.78)	93 (33.94)	
PEA	910 (35.49)	138 (31.08)	341 (30.69)	250 (46.21)	69 (35.57)	112 (40.88)	
Pulseless VF	207 (8.07)	58 (13.06)	55 (4.95)	61 (11.28)	11 (5.67)	22 (8.03)	
Pulseless VT	130 (5.07)	28 (6.31)	44 (3.96)	34 (6.28)	3 (1.55)	21 (7.66)	
Unknown	336 (13.1)	56 (12.61)	163 (14.67)	63 (11.65)	28 (14.43)	26 (9.49)	
Instrument: Invasive Airway							<0.001
No	991 (38.65)	231 (52.03)	494 (44.46)	138 (25.51)	76 (39.18)	52 (18.98)	
Yes	1573 (61.35)	213 (47.97)	617 (55.54)	403 (74.49)	118 (60.82)	222 (81.02)	
Instrument: Apnea Monitor							<0.001
No	2289 (89.27)	407 (91.67)	1024 (92.17)	430 (79.48)	176 (90.72)	252 (91.97)	
Yes	275 (10.73)	37 (8.33)	87 (7.83)	111 (20.52)	18 (9.28)	22 (8.03)	
Instrument: Pacemaker							<0.001
No	2399 (93.56)	415 (93.47)	1103 (99.28)	415 (76.71)	192 (98.97)	274 (100)	
Yes	165 (6.44)	29 (6.53)	8 (0.72)	126 (23.29)	2 (1.03)	0 (0.00)	
Instrument: Pulse Oximeter							<0.001
No	371 (14.47)	85 (19.14)	216 (19.44)	24 (4.44)	15 (7.73)	31 (11.31)	

Table 1 Continued

Yes	2193 (85.53)	359 (80.86)	895 (80.56)	517 (95.56)	179 (92.27)	243 (88.69)	
Instrument: Vascular Access IO							0.109
No	2529 (98.63)	438 (98.65)	1093 (98.38)	539 (99.63)	192 (98.97)	267 (97.45)	
Yes	35 (1.37)	6 (1.35)	18 (1.62)	2 (0.37)	2 (1.03)	7 (2.55)	
Instrument: Vascular Access Peripheral Vein							0.1136
No	2003 (78.12)	354 (79.73)	885 (79.66)	402 (74.31)	147 (75.77)	215 (78.47)	
Yes	561 (21.88)	90 (20.27)	226 (20.34)	139 (25.69)	47 (24.23)	59 (21.53)	
Instrument: Vascular Access UAC							<0.001
No	2538 (98.99)	439 (98.87)	1109 (99.82)	523 (96.67)	193 (99.48)	274 (100)	
Yes	26 (1.01)	5 (1.13)	2 (0.18)	18 (3.33)	1 (0.52)	0 (0.00)	
Instrument: Assisted Or Mechanical Ventilator							<0.001
No	964 (37.60)	214 (48.20)	485 (43.65)	136 (25.14)	72 (37.11)	57 (20.80)	
Yes	1600 (62.40)	230 (51.80)	626 (56.35)	405 (74.86)	122 (62.89)	217 (79.2)	
Instrument: Supplemental Oxygen							0.001
No	2034 (79.33)	324 (72.97)	898 (80.83)	432 (79.85)	148 (76.29)	232 (84.67)	
Yes	530 (20.67)	120 (27.03)	213 (19.17)	109 (20.15)	46 (23.71)	42 (15.33)	
Instrument: Continuous Sedative Narcotic							<0.001
No	2330 (90.87)	421 (94.82)	1036 (93.25)	432 (79.85)	179 (92.27)	262 (95.62)	
Yes	234 (9.13)	23 (5.18)	75 (6.75)	109 (20.15)	15 (7.73)	12 (4.38)	
Instrument: Conscious Sedation							0.4902
No	2466 (96.18)	427 (96.17)	1071 (96.4)	518 (95.75)	183 (94.33)	267 (97.45)	
Yes	98 (3.82)	17 (3.83)	40 (3.6)	23 (4.25)	11 (5.67)	7 (2.55)	
Instrument: IVIO Continuous Vasoactive Agents							<0.001
No	1552 (60.53)	299 (67.34)	767 (69.04)	192 (35.49)	142 (73.2)	152 (55.47)	
Yes	1012 (39.47)	145 (32.66)	344 (30.96)	349 (64.51)	52 (26.8)	122 (44.53)	
Management: Cardiopulmonary Bypass							<0.001
No	2393 (93.33)	412 (92.79)	1084 (97.57)	436 (80.59)	187 (96.39)	274 (100)	
Yes	171 (6.67)	32 (7.21)	27 (2.43)	105 (19.41)	7 (3.61)	0 (0.00)	

Table 1 Continued

Management: Thoracentesis							0.016
No	2536 (98.91)	443 (99.77)	1094 (98.47)	536 (99.08)	189 (97.42)	274 (100)	
Yes	28 (1.09)	1 (0.23)	17 (1.53)	5 (0.92)	5 (2.58)	0 (0.00)	
Management: Pericardiocentesis							0.292
No	2511 (97.93)	432 (97.3)	1090 (98.11)	534 (98.71)	187 (96.39)	268 (97.81)	
Yes	53 (2.07)	12 (2.7)	21 (1.89)	7 (1.29)	7 (3.61)	6 (2.19)	
Management: Central Venous Line Inserted							0.014
No	2410 (93.99)	405 (91.22)	1045 (94.06)	522 (96.49)	180 (92.78)	258 (94.16)	
Yes	154 (6.01)	39 (8.78)	66 (5.94)	19 (3.51)	14 (7.22)	16 (5.84)	
Management: Needle Thoracostomy							0.031
No	2493 (97.23)	435 (97.97)	1074 (96.67)	535 (98.89)	186 (95.88)	263 (95.99)	
Yes	71 (2.77)	9 (2.03)	37 (3.33)	6 (1.11)	8 (4.12)	11 (4.01)	
Management: Transcutaneous Pacemaker							<0.001
No	2435 (94.97)	412 (92.79)	1075 (96.76)	495 (91.5)	185 (95.36)	268 (97.81)	
Yes	129 (5.03)	32 (7.21)	36 (3.24)	46 (8.5)	9 (4.64)	6 (2.19)	
Management: Blood Transfusion							<0.001
No	2264 (88.3)	408 (91.89)	1025 (92.26)	444 (82.07)	166 (85.57)	221 (80.66)	
Yes	300 (11.7)	36 (8.11)	86 (7.74)	97 (17.93)	28 (14.43)	53 (19.34)	
Management: Chest Tube Inserted							<0.001
No	2462 (96.02)	440 (99.1)	1058 (95.23)	526 (97.23)	184 (94.85)	254 (92.7)	
Yes	102 (3.98)	4 (0.9)	53 (4.77)	15 (2.77)	10 (5.15)	20 (7.3)	
Drug: Other Alkalinizing Agent							0.019
No	2530 (98.67)	438 (98.65)	1089 (98.02)	540 (99.82)	190 (97.94)	273 (99.64)	
Yes	34 (1.33)	6 (1.35)	22 (1.98)	1 (0.18)	4 (2.06)	1 (0.36)	
Drug: Amiodarone							<0.001
No	2393 (93.33)	394 (88.74)	1051 (94.6)	502 (92.79)	185 (95.36)	261 (95.26)	
Yes	171 (6.67)	50 (11.26)	60 (5.4)	39 (7.21)	9 (4.64)	13 (4.74)	
Drug: Any Antiarrhythmic							<0.001

Table 1 Continued

No	2144 (83.62)	343 (77.25)	961 (86.5)	435 (80.41)	170 (87.63)	235 (85.77)	
Yes	420 (16.38)	101 (22.75)	150 (13.5)	106 (19.59)	24 (12.37)	39 (14.23)	
Drug: Atropine							<0.001
No	1493 (58.23)	257 (57.88)	610 (54.91)	384 (70.98)	109 (56.19)	133 (48.54)	
Yes	1071 (41.77)	187 (42.12)	501 (45.09)	157 (29.02)	85 (43.81)	141 (51.46)	
Drug: Sodium Bicarbonate							<0.001
No	969 (37.79)	155 (34.91)	442 (39.78)	160 (29.57)	85 (43.81)	127 (46.35)	
Yes	1595 (62.21)	289 (65.09)	669 (60.22)	381 (70.43)	109 (56.19)	147 (53.65)	
Drug: Calcium Chloride/Calcium Gluconate							<0.001
No	1350 (52.65)	234 (52.7)	629 (56.62)	188 (34.75)	110 (56.7)	189 (68.98)	
Yes	1214 (47.35)	210 (47.3)	482 (43.38)	353 (65.25)	84 (43.3)	85 (31.02)	
Drug: Dextrose Bolus							<0.001
No	2409 (93.95)	409 (92.12)	1029 (92.62)	524 (96.86)	180 (92.78)	267 (97.45)	
Yes	155 (6.05)	35 (7.88)	82 (7.38)	17 (3.14)	14 (7.22)	7 (2.55)	
Drug: Dobutamine							0.0029
No	2432 (94.85)	408 (91.89)	1052 (94.69)	515 (95.19)	191 (98.45)	266 (97.08)	
Yes	132 (5.15)	36 (8.11)	59 (5.31)	26 (4.81)	3 (1.55)	8 (2.92)	
Drug: Dopamine							<0.001
No	1923 (75)	342 (77.03)	841 (75.7)	364 (67.28)	161 (82.99)	215 (78.47)	
Yes	641 (25)	102 (22.97)	270 (24.3)	177 (32.72)	33 (17.01)	59 (21.53)	
Drug: Epinephrine Bolus							0.205
No	296 (11.54)	57 (12.84)	124 (11.16)	57 (10.54)	31 (15.98)	27 (9.85)	
Yes	2268 (88.46)	387 (87.16)	987 (88.84)	484 (89.46)	163 (84.02)	247 (90.15)	
Drug: FluidBolus							0.62
No	1511 (58.93)	273 (61.49)	651 (58.6)	321 (59.33)	114 (58.76)	152 (55.47)	
Yes	1053 (41.07)	171 (38.51)	460 (41.4)	220 (40.67)	80 (41.24)	122 (44.53)	
Drug: Magnesium Sulfate							0.049
No	2414 (94.15)	413 (93.02)	1049 (94.42)	500 (92.42)	189 (97.42)	263 (95.99)	

Table 1 Continued

Yes	150 (5.85)	31 (6.98)	62 (5.58)	41 (7.58)	5 (2.58)	11 (4.01)	
Drug: Norepinephrine							<0.001
No	2394 (93.37)	432 (97.3)	1029 (92.62)	522 (96.49)	178 (91.75)	233 (85.04)	
Yes	170 (6.63)	12 (2.7)	82 (7.38)	19 (3.51)	16 (8.25)	41 (14.96)	
Drug: Neuromuscular Block Muscle Relax							<0.001
No	2417 (94.27)	414 (93.24)	1066 (95.95)	486 (89.83)	183 (94.33)	268 (97.81)	
Yes	147 (5.73)	30 (6.76)	45 (4.05)	55 (10.17)	11 (5.67)	6 (2.19)	
Drug: Sedative Induction Agent							<0.001
No	2335 (91.07)	395 (88.96)	1044 (93.97)	456 (84.29)	174 (89.69)	266 (97.08)	
Yes	229 (8.93)	49 (11.04)	67 (6.03)	85 (15.71)	20 (10.31)	8 (2.92)	
Teach							<0.001
Primary	1629 (66.19)	279 (65.03)	633 (59.66)	405 (77.14)	132 (70.21)	180 (69.77)	
Secondary	605 (24.58)	104 (24.24)	303 (28.56)	104 (19.81)	41 (21.81)	53 (20.54)	
Tertiary	227 (9.22)	46 (10.72)	125 (11.78)	16 (3.05)	15 (7.98)	25 (9.69)	

Table 2. Outcome for each illness category

	Discharge Survival		ALL
	Dead	**Alive**	
	N (%)	**N (%)**	**N**
Illness Category			
Medical, cardiac	306 (68.92)	138 (31.08)	444
Medical, noncardiac	832 (74.89)	279 (25.11)	1111
Surgical, cardiac	329 (60.81)	212 (39.19)	541
Surgical, noncardiac	119 (61.34)	75 (38.66)	194
Trauma	246 (89.78)	28 (10.22)	274

Table 3. Outcome for each chest compression category

	Discharge Survival		ALL
	Dead	**Alive**	
	N (%)	**N (%)**	**N**
Compression category			
0-15	561 (54.05)	477 (45.95)	1038
16-35	636 (82.38)	136 (17.62)	772
>35	635 (84.22)	119 (15.78)	754

3.2 GAM ANALYSIS

A GAM analysis was performed with survival status as the dependent variable and continuous chest compression duration (minutes) as the independent variable. The model used the spline smoother. Figure 2 showed the graph of chest compression duration and the smooth function. The curve of the smooth function approached zero at about 15 minutes and 65 minutes of chest compression duration. The slope of the curve changed at about 35 minutes and 140 minutes of compression duration. Large variation of the smooth function estimate after 50 minutes of chest compression indicated that the outcome varied as the compression duration increased and that the number of subjects may be very small. Therefore, the cutoff points after 50 minutes of chest compression were ignored. The categories of the compression duration were determined as 0-15, 16-35, and more than 35 minutes.

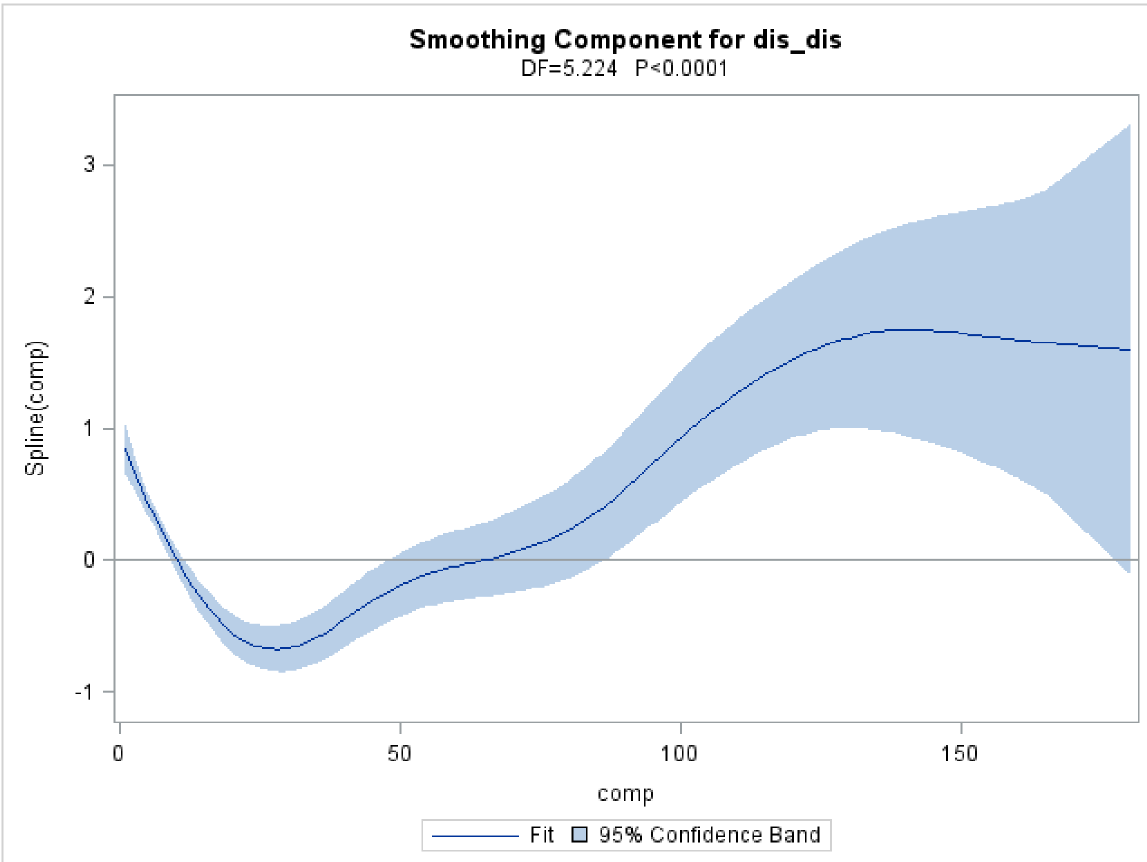

Figure 2. Generalized Additive Model based on chest compression duration of all subjects

3.3 NRI ANALYSIS

The net reclassification index (NRI) was used to determine the independent covariates for the model to predict the survival outcome. The base model was determined by expert opinions. The chosen variables were illness categories, chest compression duration, pulse rhythm on visit, age groups, event location, weekend on visit, daytime on visit, bypass procedure, calcium gluconate injection, previous septicemia episode, previous renal insufficient condition, and use of continuous vasoactive agents. All the above variables must be in the predictive model.

Table 4 showed the NRI test results. The candidate variables were selected based on the expert opinions and the results of descriptive statistics in table 1. The variables being statistically different across the illness categories were tested by NRI. Only variables with p-value <0.05 and with positive NRI, indicating that they provided positive prediction toward survival, were included in the final model. The variable of prior major trauma was excluded from the final model because it was closely related to one of the illness categories, “Trauma”. Excluding this variable also avoided the problem of collinearity. In addition to the base model, five more variables were added into the final model. These five variables were use of sodium bicarbonate, prior cardiopulmonary arrest, use of apnea monitor, use of pulse monitor, and pre-existing condition of hypotension/hypoperfusion.

Table 4. NRI and test results for all possible covariates

New variable	Label	NRI	p-value
adm_cpcp	Pediatric cerebral performance category on admission	0.0268	0.1720
rx_bicar	**Drug: Sodium Bicarbonate**	**0.0549**	**0.0404**
prec_t	Pre-existing condition: Metastatic/Hematologic Malignancy	0.0231	0.0890
rx_Epineph	Drug: Epinephrine	-0.0220	0.3441
cpa_pri	**Prior cardiopulmonary arrest (CPA)**	**0.0659**	**0.0016**
ipa_apne	**Instrument: Apnea monitor**	**0.0592**	**0.0024**
rx_atro	Drug: Atropine	0.0422	0.0533
rx_dex	Drug: Dextrose	0.0200	0.0941
cau_o	Cause: Conscious sedation	0.0071	0.3188
Hisp	Hispanic	-0.0016	0.8053
ipa_puls	**Instrument: Pulse oxymeter**	**0.0493**	**0.0090**
cau_l	Cause: Inadequate natural airway	-0.0054	0.6559
nrx_tran	Management: blood transfusion	-0.0085	0.5241
prec_i	Pre-existing condition: Hepatic insufficiency	0.0088	0.3773
prec_s	Pre-existing condition: Major trauma	0.1174	0.0000
ipa_pace	Instrument: Pacemaker	0.0283	0.0735
cau_b	Pre-existing condition: Hypotension/hypoperfusion	0.0274	0.1223
ipa_vent	Instrument: Assisted or mechanical ventilator	0.0291	0.0926
cau_d	Cause: Acute pulmonary edema	0.0131	0.1135
cau_j	Cause: Invasive airway displacement	0.0022	0.7621
cau_5	Cause: Drug overdose	0.0052	0.2373
pul_seq	Pulse sequence	-0.0027	0.7619
rx_norep	Drug: Norepinephrine	0.0036	0.6688
ipa_air	Instrument: Invasive airway	0.0115	0.4264
Race	Race	-0.0011	0.9075
prec_f	**Pre-existing condition: Hypotension/Hypoperfusion**	**0.0501**	**0.0013**
prec_j	Pre-existing condition: Metabolic electrolyte abnormality	-0.0137	0.2153
prec_m	Pre-existing condition: Baseline depression of CNS function	-0.0257	0.0527
prec_2+prec_3	Pre-existing condition: Cardiac malformation	-0.0120	0.2256
ipa_vape	Instrument: Vascular access peripheral vein	-0.0005	0.8594
ipa_vaio	Instrument: Vascular access IO	-0.0000	0.9973
ipa_vaua	Instrument: Vascular access UAC	0.0027	0.6973

Table 4 Continued

ipb_sed2	Instrument: Continuous sedative narcotics	0.0011	0.8623
ipb_anti	Instrument: Continuous antiarrhythmics	-0.0019	0.8929
ipb_oxy	Instrument: Supplemental oxygen	0.0027	0.6631
ipb_seda	Instrument: Conscious sedation	-0.0087	0.4215
ed_pri	Prior ED discharge within 24 hours	-0.0094	0.6588
subj_ty	Subject types	-0.0115	0.2017
cau_h	Cause: Metabolic electrolyte abnormality	-0.0167	0.2345
cau_m	Cause: Inadequate invasive airway	0.0038	0.5924
cau_r	Cause: Hypothermia	-0.0016	0.7839
inv_a	Invasive airway insertion	-0.0217	0.0261
inv_b	Invasive airway reinsertion	0.0063	0.6218
inv_c	Invasive airway already in place	0.0003	0.9879
Witness	Witness present	0.0200	0.1829
Witnessormonitor	Witness or monitor	0.0184	0.1406
rx_fliud	Drug: Fluid bolus	-0.0263	0.0648
rx_dopa	Drug: Dopamine	-0.0178	0.1290
rx_sedat	Drug: Sedation	0.0011	0.9227
rx_magne	Drug: Magnesium sulfate	0.0027	0.7225
rx_amiod	Drug: Amiodarone	0.0003	0.9732
rx_relax	Drug: Muscle relaxant	0.0047	0.6259
rx_dobut	Drug: Dobutamine	-0.0033	0.6002
rx_alko	Drug: Alkalinizing agent	-0.0030	0.5415
nrx_line	Management: Central venous line insertion	0.0088	0.0672
nrx_need	Management: Needle thoracostomy	-0.0093	0.1414
nrx_pace	Management: Pacemaker transcutaneous	-0.0060	0.2890
nrx_cent	Management: Pericardiocentesis	-0.0047	0.2911
nrx_cen2	Management: Thoracentesis	-0.0000	0.9986

3.4 REGRESSION COEFFICIENTS FROM THE THREE MODELS

This study aimed to evaluate the association of illness categories with survival across different compression duration groups. The hypothesis was that the relationship of illness and survival was modified by compression duration. Interaction of compression duration groups and illness categories was included in the regression model. Though the type 3 analysis of effects for the interaction term was not statistically significant, several individual levels of the interaction term were statistically significant. Therefore, the interaction term was kept in the model.

Logistic regression, generalized estimating equation (GEE), and generalized linear mixed model (GLMM) were used for the analysis of all eligible subjects. Four different correlation structures, including independent, exchangeable, autoregressive, and unstructured, working correlation structures were used in the GEE model. Quasilikelihood under the independence model criterion (QIC) was used to select the most appropriate working correlation structure. Table 5 showed the QIC values of the models with the four working correlation structures. Though the model with the first order of autoregressive working correlation structure had the smallest QIC, the QIC values for all correlation structures were similar. The exchangeable correlation structure is more appropriate for the characteristics of the data. Therefore, the coefficients in table 6 and odds ratios in table 7 were obtained from the GEE model with exchangeable working correlation structure.

Table 5. QIC for different working correlation structure

Working correlation structure	Criterion	Value
Independent	QIC	2437.1185
Exchangeable	QIC	2437.7513
Autoregressive (1)	QIC	2436.9282
Unstructured	QIC	2439.5321

Table 6 summarized the estimates of parameters from the logistic regression, GEE model, and GLMM model. In general, the estimates of parameters were similar among the three models. Though the standard deviation of most estimates was slightly higher in the GEE and GLMM, the conclusion derived from the three models are similar. In the regression model, the type 3 analysis of effects showed significant effects for most covariates, except for time and weekend of events. However, the expert opinion preferred keeping them in the final model. The two major interests of the study, compression duration groups and illness categories, were significantly related to survival of the subjects. When inspecting the individual covariates, the odds of survival were not significantly different between the age group of 1 -8 years and the age group of younger than 1 month for the logistic model and GLMM. However, GEE showed significant different survival odds between the two groups. On the contrary, the odds of survival for the subjects experiencing SCA in the procedure room was significantly different from the odds of survival for the subjects experiencing SCA in the ICU for the logistic model and GLMM, but not for the GEE model.

Table 6. Coefficients of covariates in logistic regression, GEE, and Mixed model (random intercept)

		Logistic regression			GEE (AR1)			Mixed model		
Covariates		**Estimate**	**StdErr**	**p-value**	**Estimate**	**Stderr**	**p-value**	**Estimate**	**StdErr**	**p-value**
Intercept		-2.3116	0.4108	<.0001	-2.3446	0.3681	<.0001	-2.3418	0.4134	<.0001
Compression duration categories										
0-15		1.7218	0.2297	<.0001	1.7445	0.2681	<.0001	1.7188	0.2306	<.0001
16-35		0.6396	0.2458	0.0093	0.6497	0.2561	0.0112	0.6323	0.2464	0.0109
Illness categories										
Medical, cardiac		0.788	0.2987	0.0083	0.8213	0.3018	0.0065	0.7829	0.2996	0.0095
Surgical, cardiac		1.0413	0.2889	0.0003	1.0569	0.3265	0.0012	1.0612	0.2901	0.0003
General, surgical		0.0901	0.4959	0.8558	0.0516	0.3985	0.897	0.09467	0.4977	0.8493
Trauma		-0.7196	0.7626	0.3454	-0.6818	0.774	0.3784	-0.7077	0.7636	0.3549
Interaction of illness and compression duration										
0-15	Medical, cardiac	-0.3697	0.3628	0.3082	-0.4188	0.3696	0.2571	-0.3648	0.3638	0.3179
0-15	Surgical, cardiac	-0.0265	0.3341	0.9367	-0.0883	0.3362	0.7929	-0.0245	0.3347	0.9418
0-15	General, surgical	0.2122	0.5555	0.7024	0.2042	0.4479	0.6484	0.2074	0.5576	0.7105
0-15	Trauma	-0.5565	0.8067	0.4903	-0.6195	0.8314	0.4562	-0.5676	0.8076	0.4835
16-35	Medical, cardiac	-0.9794	0.4034	0.0152	-1.0398	0.3604	0.0039	-0.9617	0.4047	0.0190
16-35	Surgical, cardiac	-0.3507	0.3727	0.3468	-0.3565	0.4087	0.3831	-0.3413	0.3731	0.3619
16-35	General, surgical	0.4451	0.6218	0.4741	0.4897	0.5082	0.3352	0.4498	0.6238	0.4722

Table 6 Continued

16-35 Trauma	-0.9734	0.935	0.2978	-0.9668	1.026	0.3461	-0.9685	0.9361	0.3028
Pulse rhythm									
Asystole	-0.6823	0.1618	<.0001	-0.688	0.1653	<.0001	-0.6798	0.163	<.0001
PEA	-0.3575	0.1625	0.0278	-0.3591	0.1703	0.035	-0.3428	0.1653	0.0389
Pulseless VF	-0.3336	0.2239	0.1362	-0.3463	0.235	0.1407	-0.3421	0.2248	0.1291
Pulseless VT	-0.0971	0.2607	0.7095	-0.1131	0.2665	0.6714	-0.08988	0.2617	0.7315
Age group									
1 month - <1 year	0.5764	0.1554	0.0002	0.5812	0.1297	<.0001	0.5804	0.1559	0.0002
1 yr - <8yr	0.3214	0.1676	0.0552	0.3084	0.1351	0.0225	0.3212	0.1682	0.0572
8 yr - <18 yr	0.1856	0.1729	0.2832	0.1765	0.1822	0.3328	0.1921	0.1736	0.2694
Weekend									
Yes	0.0103	0.1118	0.9266	0.0233	0.1034	0.822	0.01298	0.1122	0.9081
Time of Day									
Day	0.0266	0.1125	0.8131	0.0358	0.1382	0.7955	0.02845	0.1128	0.8013
Management: Bypass									
Yes	0.9637	0.2189	<.0001	0.928	0.204	<.0001	0.9192	0.2206	0.0003
Drug: Calcium gluconate									
Yes	-0.3935	0.1235	0.0014	-0.412	0.1104	0.0002	-0.404	0.1247	0.0016
Pre-existing condition: Septicemia									
Yes	-0.5863	0.1697	0.0006	-0.5733	0.1669	0.0006	-0.591	0.1704	0.0008
Pre-existing condition: Renal insufficiency									
Yes	-0.7905	0.2095	0.0002	-0.7667	0.2427	0.0016	-0.7909	0.2102	0.0003
Instrument: Continuous vasoactive agent									
Yes	-0.766	0.1303	<.0001	-0.7883	0.1592	<.0001	-0.7809	0.1311	<.0001
Event location									
Emergency	-0.1632	0.1804	0.3657	-0.1717	0.1836	0.3496	-0.1657	0.1822	0.3642

Table 6 Continued

General Inpatient	0.1318	0.1852	0.4767	0.1002	0.1883	0.5945	0.1359	0.186	0.4655
Procedure room	0.6002	0.2321	0.0097	0.5981	0.3195	0.0612	0.5962	0.2334	0.0113
Others	0.1375	0.308	0.6552	0.0881	0.2818	0.7545	0.1335	0.3105	0.6676
Drug: Sodium bicarbonate									
Yes	-0.6393	0.1192	<.0001	-0.6355	0.1468	<.0001	-0.6331	0.1199	<.0001
Prior CPA									
Both	0.2513	0.8401	0.7648	0.2689	0.7189	0.7084	0.2357	0.8425	0.7802
None/None Documented	1.0227	0.2385	<.0001	1.0483	0.2608	<.0001	1.0364	0.2395	<.0001
Other (previous admission, same or other hospital)	1.2146	0.3395	0.0003	1.2395	0.3517	0.0004	1.2049	0.3408	0.0006
Instrument: Apnea monitor									
Yes	0.6097	0.1674	0.0003	0.6118	0.1781	0.0006	0.6106	0.1781	0.0016
Instrument: Pulse oxymeter									
Yes	0.2523	0.1704	0.1386	0.2679	0.1747	0.1251	0.2397	0.1719	0.166
Pre-existing condition: Hypotension/Hypoperfusion									
Yes	-0.3013	0.1186	0.0111	-0.2968	0.0968	0.0022	-0.2834	0.12	0.0201

3.5 ODDS RATIOS

Table 7 showed the odds ratios of the other illness categories vs. the general medical condition in each compression duration group. In the group of chest compression less than 16 minutes, patients with medical cardiac condition and with surgical cardiac condition had higher odds of survival compared to subjects with general medical condition. On the contrary, subjects with trauma were less likely to survive. In the group of chest compression duration between 16 and 35 minutes, only subjects with a surgical cardiac condition had a better odds to survive compared to the subjects with a general medical condition. And the subjects with trauma still had the worse outcome. In the group of chest compression longer than 35 minutes, the subjects with a medical cardiac or with a surgical cardiac condition had a better outcome. Similar results can be obtained from GEE and GLMM models. In the group of chest compression less than 16 minutes, the odds of survival for the subjects with medical cardiac condition and for the subjects with general medical condition were not statistically different in the GLMM model; however, the odds ratios and their 95% confidence intervals were greater than 1 in the logistic model and GEE model. Comparing the estimates and the 95% confidence intervals of the results in the three models, they were still very similar and the lower limit of the confidence interval derived from GLMM was slightly smaller than 1. Therefore, we still concluded that the results from the three models were not significantly different.

Table 7. Odds ratios of illness categories for survival within each compression duration category for logistic regression, GEE, and mixed model

	Logistic regression			GEE			Mixed Model		
Label	**OR**	**LowerCL**	**UpperCL**	**OR**	**LowerCL**	**UpperCL**	**OR**	**LowerCL**	**UpperCL**
Medical cardiac vs general medical <15 min	1.5194	1.0057	2.2955	1.4955	1.0204	2.1917	1.519	0.9998	2.3078
surgical cardiac vs general medical <15 min	2.7588	1.8326	4.153	2.6344	1.8718	3.7077	2.8198	1.8569	4.2821
surgical noncardiac vs general medical <15 min	1.353	0.8022	2.2819	1.2915	0.7797	2.1392	1.3527	0.7963	2.2979
Trauma vs general medical <15 min	0.2791	0.1634	0.4769	0.2722	0.1505	0.4923	0.2794	0.1622	0.481
Medical cardiac vs general medical 15-35 min	0.8258	0.4802	1.4201	0.8037	0.4741	1.3626	0.8362	0.4824	1.4496
surgical cardiac vs general medical 15-35 min	1.995	1.1652	3.4156	2.0147	1.2798	3.1716	2.0541	1.1906	3.5439
surgical noncardiac vs general medical 15-35 min	1.7078	0.8014	3.6394	1.7182	0.8221	3.591	1.7237	0.8012	3.7081
Trauma vs general medical 15-35 min	0.184	0.06288	0.5381	0.1923	0.04938	0.7492	0.1871	0.06311	0.5546
Medical cardiac vs general medical >35 min	2.199	1.2244	3.9491	2.2734	1.2584	4.1072	2.1877	1.2094	3.9576
surgical cardiac vs general medical >35 min	2.8329	1.6081	4.9904	2.8775	1.5173	5.4569	2.8897	1.6278	5.1299
surgical noncardiac vs general medical >35 min	1.0943	0.414	2.8924	1.0529	0.4822	2.2993	1.0993	0.4106	2.9428
Trauma vs general medical >35 min	0.4869	0.1092	2.1708	0.5057	0.1109	2.3055	0.4928	0.1088	2.2327

3.6 PREDICTION MODEL

The estimates of parameters were similar in logistic regression, GEE, and GLMM. To simplify the process of prediction, the predicted probability of survival was estimated based on the results of logistic regression. All variables selected by NRI were included in the model. Interaction of continuous chest compression duration and illness categories was included in the model. The average value of each covariate was used in the model for the prediction of the probability of survival.

Figure 3 showed the predicted probability of survival for each illness category from 0 minutes through 180 minutes of chest compression. Patients with a surgical cardiac condition had the best probability of survival. Within 10 minutes of chest compression, the survival probability for this group of patients was up to 50%. The probabilities of survival were similar in the beginning for subjects with a medical cardiac and a general medical condition. However, the probability dropped faster for the subjects with a general medical condition as the duration of chest compression increased. Though patients with a general surgical condition had a higher probability of survival in the beginning compared to those who with a general medical condition, the probabilities were tied after 70 minutes of chest compression. Both groups of patients had a survival probability of less than 10%.

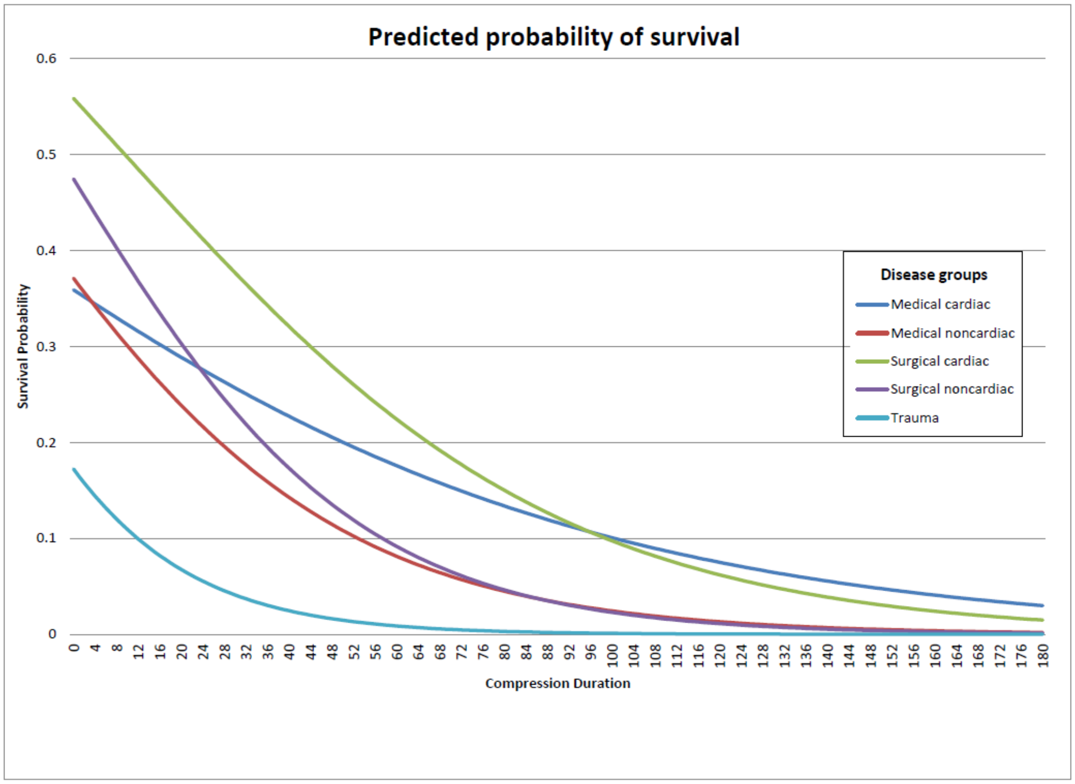

Figure 3. Predicated probability of survival for each illness category

4.0 DISCUSSION

4.1 CONCLUSION

4.1.1 Generalized Additive Model (GAM) analysis

Though continuous variables may provide more information, they may not be practical in the clinical setting. A GAM can appropriately categorize continuous predictors based on the relationship of the predictors and the outcome through a nonparametric smoothing function. This method determined several cutoff points of chest compression duration for this data set. However, not all cutoff points should be used. The variance increased dramatically for longer chest compression duration because fewer cases received such a long duration of chest compression. The slope of the curve did not change dramatically after 35 minutes of chest compression duration. Therefore, the cutoff points after 35 minutes were not used in this study.

4.1.2 Net Reclassification Index (NRI) analysis

Many characteristics of the patients were significantly different across the disease groups (Table 1). Though they can be included in the predictive model, the problems of over-fitting and computational demand may compromise the feasibility of the models. Also, the final model with too many predictors is not practical in the clinical setting. Using the NRI to determine the most appropriate variables for prediction has become popular recently. This method can specifically select the variables predicting the desired outcome, but not predicting the opposite outcome. Therefore, the model determined by NRI can be more precise.

4.1.3 Logistic regression, Generalized Estimating Equation (GEE), and Generalized Linear Mixed Model (GLMM) analyses

This study showed that estimates of parameters obtained from a logistic regression model, a GEE model, and a GLMM were similar and the conclusion derived from the three modeling methods was the same. The hospital based registry data were considered as a clustered observational study design. The subjects within the same cluster were correlated because the clinical practice and patients' characteristics may be similar within a specific cluster, but different from the other clusters. Both GEE and GLMM can deal with correlated data. However, the benefits of the two complicated methods were not confirmed in this study.

Several factors may undermine the performance of GEE and GLMM. First, the sizes of clusters were diverse. Some clusters had hundreds of patients, but small sized clusters were more common in the data set. Therefore, subjects may be independent. Second, survival of SCA may mainly depend on appropriate CPR procedure and characteristics of subjects, but not on characteristics related to the hospitals. Therefore, the hospital effect is limited. Random effects may not be necessary to analyze data related to SCA patients.

The methods for correlated data may not be necessary for problems that are mainly related to characteristics of patients but not depend on features of clusters.

4.2 PUBLIC HEALTH ASPECT

The registry data that include comprehensive variables have been established for many healthcare problems. In order to explore the data appropriately and to derive clinically applicable inferences, a systematic process is necessary. This study demonstrated the process used to analyze hospital based registry data of SCA episodes.

The process involves the categorization of observations for clinical application, the establishment of an appropriate model to predict outcome, and the computation of estimates through methods that take correlated data into consideration. The similar results from the three methods in this study may be caused by the specific entity of the health problem. Therefore, using estimates from logistic regression to predict probability of survival is appropriate. However, for the other health problems, it may be still necessary to consider the random effect related to the different hospitals.

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