ALIGNMENT OF DO-NOT-RESUSCITATE STATUS WITH PATIENTS' LIKELIHOOD OF FAVORABLE NEUROLOGICAL SURVIVAL AFTER IN-HOSPITAL CARDIAC ARREST

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ABSTRACT

After patients survive an in-hospital cardiac arrest, discussions should occur about preferences for future resuscitative efforts. Given the value patients generally place on possessing normal neurological function, these discussions should take into account a patient's prognosis for survival with good neurocognitive function to ensure autonomy and quality of life. Whether patients' decisions to become Do-Not-Resuscitate (DNR) after a successful resuscitation are aligned with the likelihood of favorable neurological survival is unknown.

Within Get With the Guidelines-Resuscitation, a prospective, observational, multicenter registry of U.S. patients with in-hospital cardiac arrest, we identified 26,327 patients who achieved return of spontaneous circulation (ROSC) after arrest between April 2006 and September 2012. Using the previously validated Cardiac Arrest Survival Post-Resuscitation In-hospital (CASPRI) tool, each patient's likelihood of meaningful survival without severe neurological disability (Cerebral Performance Category score $\leq$2; full recovery, mild or moderate disability) was calculated. We described the proportion of patients made DNR within each CASPRI score decile and calculated measures of association

between DNR status adoption and the CASPRI score as a continuous variable using the point-biserial correlation coefficient. A multivariable logistic regression model was constructed using the CASPRI score variables to predict favorable neurological survival within this study cohort. Individual risk estimates were evaluated and the predictive performance of the model was verified using the c-statistic. Finally, we correlated DNR status adoption with actual favorable neurological survival.

The 5,944 (22.6%) patients made DNR were older, with higher rates of comorbidities (all $P < 0.05$). The c-statistic for the CASPRI score in this cohort was 0.762. Among those with the best prognostic CASPRI scores (decile 1), 7.1% were made DNR and 64.7% had favorable neurological survival. In contrast, in decile 10 (worst prognosis), 36.0% were made DNR and 4.0% had favorable neurological survival (*P* for both trends <0.001). While the rate of favorable neurological survival among all non-DNR patients was 30.5%, it was only 1.8% in patients made DNR, and was low (7.1%) even in patients with the best prognosis who were made DNR (decile 1). The point-biserial correlation coefficient for DNR status adoption and continuous CASPRI score was 0.206 ($p<0.001$), implying low correlation.

Decisions to adopt DNR status after in-hospital cardiac arrest were generally aligned with patients' likelihood of favorable neurological survival. Nevertheless, nearly two-thirds of patients with the worst prognosis were not made DNR, and few of these survived to discharge with a favorable neurological status. Prospective use of the CASPRI tool may better inform patients, families, and clinicians regarding prognosis, and better support shared decision-making about DNR status after in-hospital cardiac arrest.

APPROVAL PAGE

The faculty listed below, appointed by the Dean of the School of Medicine, have examined a thesis titled "Alignment of Do-Not-Resuscitate Status with Patients' Likelihood of Favorable Neurological Survival after In-Hospital Cardiac Arrest," presented by Timothy James Fendler, candidate for the Master of Science degree, and certify that in their opinion it is worthy of acceptance.

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CHAPTER 1

INTRODUCTION

Among patients in US hospitals, it is widely-recommended that clinicians elicit patients' preferences for resuscitation upon admission.[1] Options for resuscitation orders, often referred to as code status, include "Full-Code," which indicates that a patient would receive all available therapeutic interventions if they experience cardiac arrest or respiratory failure (including cardiopulmonary resuscitation [CPR] and mechanical ventilation), and "Do-Not-Resuscitate" (DNR), which indicates that patients would decline CPR in the event of a cardiac arrest (Figure 1). DNR status is often chosen by patients (or their loved ones or health care proxies, if the patients are incapacitated) whose prognosis is poor, whether due to terminal disease, frailty, or advanced age, especially if they may also be at high risk for mechanical trauma from chest compressions.[2]

Full Code	All available therapeutic interventions would be administered.
Do Not Resuscitate (DNR)	Cardiopulmonary resuscitation (CPR) would not be initiated.
Do Not Intubate (DNI)	Mechanical ventilation would not be initiated.
DNR/DNI	Neither CPR nor mechanical ventilation would be initiated.
Comfort Care (aka Hospice, Palliation)	De-escalation of care; only therapy for comfort/quality of life, not treatment/prolongation of life.

* Patients can tailor treatment further based on personal preferences (i.e., use of intravenous medications to maintain adequate blood pressure, decisions to undergo invasive testing, etc.)

Figure 1: Code Status Options for Resuscitation Preferences

One such example of a clinical scenario that imparts poor prognosis is in-hospital cardiac arrest, which occurs in about 200,000 patients in the US annually, with rates of favorable neurological survival (i.e., survival without severe cognitive disability) estimated at < 20%.[3] Accordingly, this poor prognosis frequently prompts discussions about DNR status among resuscitated patients and their families.[4] However, the likelihood of favorable neurological survival is variably influenced by many factors, including patients' age, illness severity, comorbidities, and arrest characteristics.[5-9] It therefore remains unknown if real-world decisions to adopt DNR status after successful resuscitation from in-hospital cardiac arrest are aligned with patients' likelihood of favorable survival.

Discussions between clinicians, patients and their families regarding such issues as code status, resuscitation preferences, and goals of care are vital to patient understanding of prognosis after a traumatic and life-threatening event such as in-hospital cardiac arrest. These, in turn, help to support informed, shared decision-making between all involved parties. If there were discordance between DNR status adoption and prognosis for favorable neurological survival among survivors of in-hospital cardiac arrest, such discussions would represent important, modifiable opportunities to improve the quality of care and physician-patient communication. Clarity and understanding in the realm of resuscitation preferences, especially after a traumatic event like cardiac arrest, become paramount in honoring the wishes of patients, respecting the decision-making authority of their loved ones, and observing ethical boundaries that surround physician involvement in life-and-death decisions, even if the chosen option is not synchronous with or reflective of prognosis.

Certainly, it is well-established that while patients want to discuss code status in-hospital,[10] whether initially on admission or in response to course-altering events, these discussion are difficult for all parties involved.[11] As a result, patients' code status preferences are not always concordant with physician perceptions or orders,[12] and this often leads to inappropriate administration or withholding of CPR.[13] Furthermore, adequate documentation of the timing, content and outcomes of code status discussions are often sorely lacking from the medical record.[14] Accordingly, addressing this gap in knowledge regarding alignment of DNR status adoption and likelihood of meaningful neurological survival could lead to future efforts in fostering more open communication and documentation to improve patient decision-making and outcomes.

A critical challenge in making decisions about DNR status in this clinical setting has been the lack of a tool to quantify a patient's prognosis after initial resuscitation from an in-hospital cardiac arrest. Recently in 2012, the Cardiac Arrest Survival Post-Resuscitation In-hospital (CASPRI) score was developed and validated in 42,957 patients successfully resuscitated from in-hospital cardiac arrest, using the multicenter American Heart Association's (AHA) Get With The Guidelines®-Resuscitation (GWTG-R) registry of in-hospital cardiac arrest. The CASPRI score was shown to strongly predict one's likelihood of favorable neurological survival (c-statistic 0.802).[15] With its ability to define which patients have a high or low probability of meaningful survival, the CASPRI score provides a unique opportunity to examine whether decisions about DNR status among patients who have experienced an in-hospital cardiac arrest are aligned with their evidence-based prognosis. While the CASPRI score is relatively new, it offers the opportunity to examine practices for assigning DNR status against an estimate of a favorable prognosis after initial resuscitation and can, thus, provide unique insights into the current practice patterns of assigning DNR status after cardiac arrest.

To better understand current practice patterns for adopting DNR status in this clinical setting, we leveraged the GWTG-R registry of in-hospital cardiac arrest. Given its large sample size, minimal exclusion criteria, and topicality, this registry provides the ideal cohort to study for real-world application of results surrounding the association between DNR status and favorable neurological survival. Our specific aims were as follows:

Specific Aim 1: Examine the frequency of early DNR status adoption and favorable neurological survival after resuscitation from in-hospital cardiac arrest, and describe differences between patients made DNR and not made DNR after survival from cardiac arrest.

Specific Aim 2: Evaluate the likelihood of favorable neurological survival in individual survivors of in-hospital cardiac arrest.

Specific Aim 3: Evaluate alignment between DNR status adoption and prognosis/likelihood of favorable neurological survival, as estimated by the CASPRI score, among survivors of in-hospital cardiac arrest.

CHAPTER 2

METHODOLOGY

Study Design

Sponsored by the AHA, the GWTG-R registry is a large, multi-center, observational, prospective registry of patients who experienced in-hospital cardiac arrests at U.S. hospitals and were followed until discharge. GWTG-R was begun in 2000 and presently continues to collect data (Figure 2). Hospital participation in the registry is voluntary, and thus the number of participating hospitals is variable at any given time. Hospitals are charged an annual fee for data support and report generation for hospital-specific quality improvement, which is the primary reason for the registry's existence, in addition to the creation of evidence-based guidelines for inpatient CPR through observational research utilizing the registry's data. Participating hospitals are asked to characterize their facilities, staff, patients and resuscitation services. No specific patient identifiers are transmitted to the central database repository, and Institutional Review Board (IRB) approval is not required for each participating site, given the focus on quality improvement.[16]

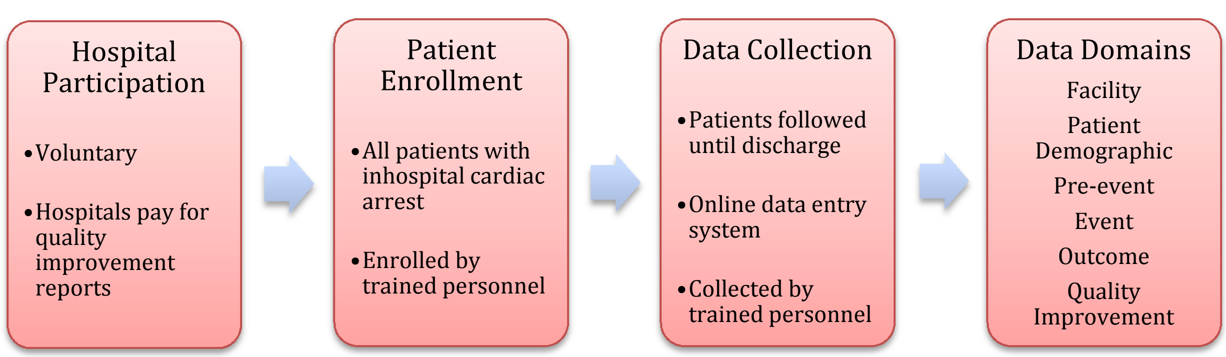


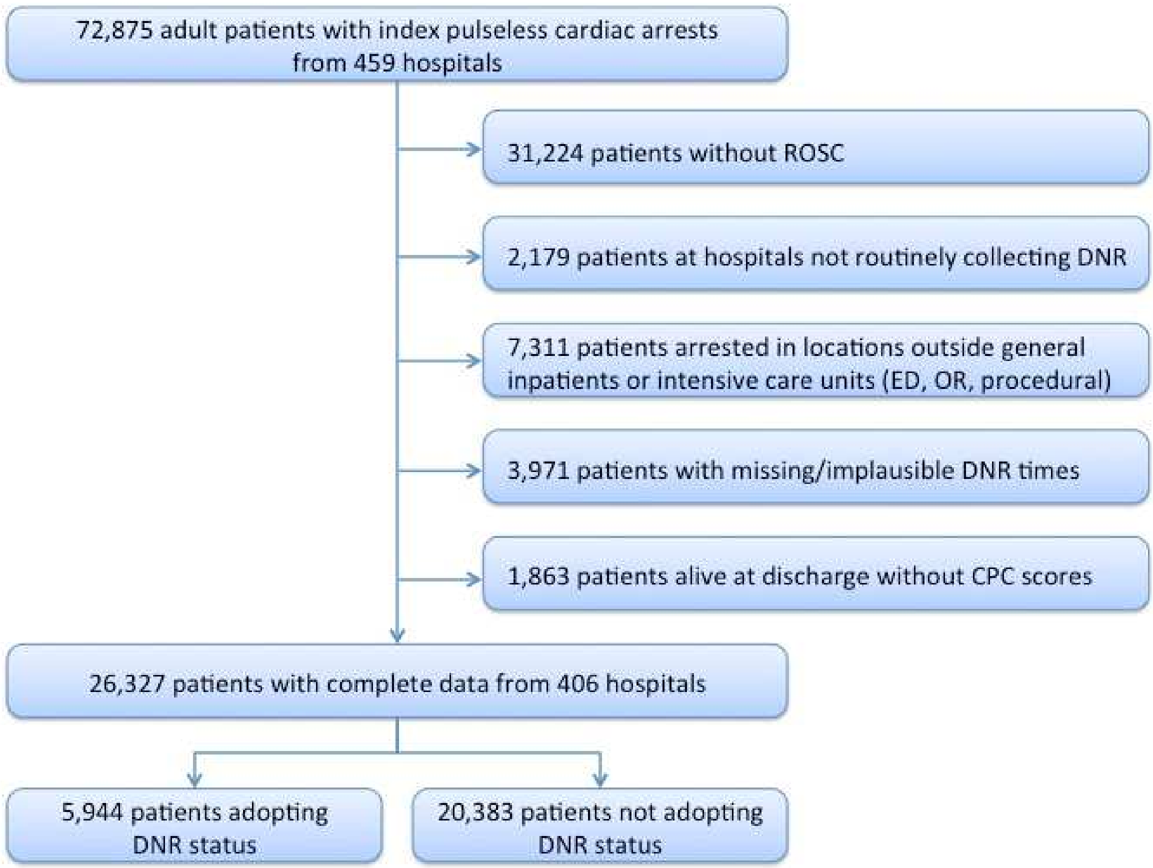
Figure 2: Get With the Guidelines-Resuscitation Registry Workflow

Trained research personnel at each participating hospital identify and enroll all patients with in-hospital cardiac arrest (defined as unresponsiveness, apnea, and absence of a palpable central pulse), without prior DNR orders, and who have undergone cardiopulmonary resuscitation (CPR). This is accomplished through multiple sources of case identification, including medical records including patients' charts and cardiac arrest forms, centralized cardiac-arrest flow sheets, hospital paging-system logs, code cart checks, pharmacy tracer drug records, and hospital billing charges for use of resuscitation medications.[7,16] Variables are collected prospectively and divided into 6 major categories: facility data, patient demographic data, pre-event data, event data, outcome data, and quality improvement data.[16] Standardized data collection methods, including Utstein consensus definitions for all variables and outcomes, and strict oversight across all participating centers, ensure accuracy, uniformity and completeness of the data.[9,17,18] The Utstein 1995 Symposium allowed experts in the field to use pre-exiting literature to set required variables for collection, and their set definitions, in the realm of in-hospital cardiac arrest, for both intrahospital and interhospital comparisons.[17] Outcome, A Quintiles Company, is the data collection coordination center for the American Heart Association/American Stroke Association Get With The Guidelines® programs, and provides the online, interactive system for data collection and feedback, called the Patient Management Tool.

The IRB of the Mid-America Heart Institute approved this study and waived the requirement for informed consent, as all data from GWTG-R was de-identified.

Study Population

Information on DNR status after return of spontaneous circulation (ROSC) was introduced into the data collection form of GWTG-R in April of 2006. Thus, our original cohort consisted of 72,875 patients from 459 hospitals who were 18 years or older and had a documented pulseless in-hospital cardiac arrest between April 2006 and September 2012 (Figure 3). If patients had more than 1 in-hospital cardiac arrest (n=7,186), we included only the index event. For the purposes of this study, in which we assessed decisions about DNR status after successful resuscitation from in-hospital cardiac arrest, we excluded 31,224 patients who died during the acute resuscitation (i.e., did not achieve ROSC). We also excluded 2,179 patients from hospitals that did not routinely collect information on DNR status after a successful resuscitation. To focus on patients who arrested in either general inpatient or intensive care units (a more homogenous group with respect to causes and characteristics of cardiac arrests), we also excluded 7,311 patients who experienced in-hospital cardiac arrest in the emergency department, operating room, procedural and post-procedural areas. Additionally, we excluded patients with missing data on neurological status if alive at discharge (1,863 patients), as this variable comprised one of our study outcomes. Finally, we excluded 3,971 patients for whom we could not calculate timing of DNR decisions due to missing or implausible times. For the group of patients with missing data, we found that there were no significant differences in baseline characteristics when compared with those of the study cohort (Supplemental Table 1). Our final cohort comprised 26,327 patients from 406 hospitals who were successfully resuscitated after in-hospital cardiac arrest.



ROSC, return of spontaneous circulation; DNR, do not resuscitate; ED, emergency department; OR, operating room; CPC, Cerebral Performance Category

Figure 3: Patient Cohort Exclusion Flow Chart

Definition of Variables

Categories of baseline data collected for all patients included demographics (age, sex, and race), pre-existing conditions (baseline CPC scores), and various arrest event characteristics (timing and location of arrest, interventions in place at the time of arrest, first recorded cardiac rhythm during arrest, and length of arrest from first recorded time to ROSC or death).

Our study examined the relationship between adoption of DNR status early after initial resuscitation from in-hospital cardiac arrest and a patient's likelihood of favorable neurological survival. Since many patients who eventually die become DNR closer to the time of death, and as we were interested in examining whether decisions to become DNR correlated with prognosis, we defined DNR status—our independent variable—as a patient for whom a DNR order was placed *within 12 hours* after achieving ROSC from an in-hospital cardiac arrest. Successfully resuscitated patients without any DNR orders at any time during their admission or those with a DNR order placed more than 12 hours after successful resuscitation were defined as non-DNR. To further investigate the impact of using a threshold of 12 hours to define DNR status, we conducted a sensitivity analysis in which DNR status was instead defined as any patient for whom a DNR order was placed *within 24 hours* after achieving ROSC from an in-hospital cardiac arrest.

Favorable neurological survival was defined as survival to hospital discharge without severe neurological disability. Neurological disability in GWTG-R was measured by Cerebral Performance Category (CPC) scores, wherein a CPC of 1 was assigned to patients at discharge with little to no neurological disability, 2 with moderate disability, 3 with severe disability, and 4 for those in a persistent coma or vegetative state (Figure 4). Based on prior work, favorable neurological survival was defined as alive at hospital discharge with a CPC score of 1 or 2,[15] referring to patients with no deficits or those who can still perform independent activities of daily living.[19]

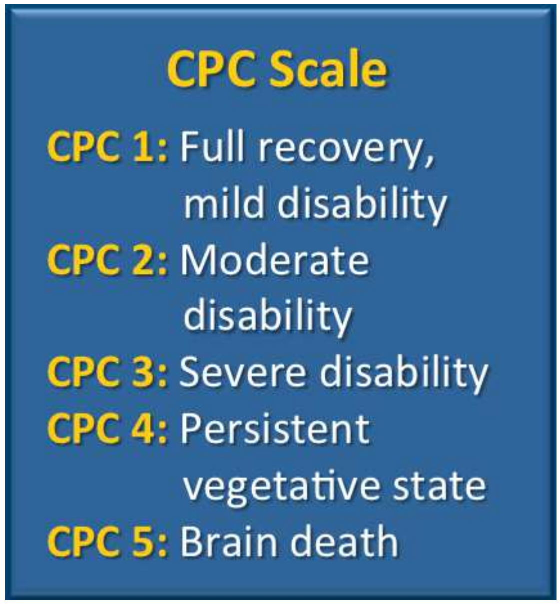


Figure 4: Cerebral Performance Category (CPC) Scale Levels

Our dependent variable, likelihood of favorable neurological survival, was defined by each individual patient's CASPRI score. Briefly, this score was derived and validated previously within GWTG-R using data from 42,957 patients. A final parsimonious model with excellent discrimination (c-statistic of 0.802) and calibration identified the following 11 significant predictors of favorable neurological survival among patients successfully resuscitated from an in-hospital cardiac arrest: age, initial cardiac arrest rhythm, pre-arrest neurological disability, hospital location of arrest, duration of cardiopulmonary resuscitation, requirement for mechanical ventilation at the time of cardiac arrest, and the presence of renal insufficiency, hepatic insufficiency, sepsis, malignant disease and hypotension at the time of cardiac arrest. CASPRI scores range from 0 to 50, with higher scores indicating a lower likelihood of favorable neurological survival.

Statistical Analysis

Because of the large study sample size, baseline differences between patients who did and did not adopt DNR were compared using standardized differences, which can account for this sample size of compared groups. The equation for standardized differences divides the difference between the means of the two groups (patients who did and did not adopt DNR) by the pooled standard deviation to better conceptualize the size of the between-groups vs. within-groups variation, and is less sensitive to large sample sizes that can easily yield statistically significant, but not clinically meaningful differences between groups using traditional significance testing such as chi-squared and student's t tests. Based on prior work, a standardized difference of greater than 10% was considered a significant and meaningful difference for the purposes of this study.[20]

To evaluate whether a patient's decision to adopt DNR status was aligned with their prognosis, we first calculated each patient's likelihood of favorable neurological survival using the previously validated CASPRI score.[15] Then, for the purposes of this study, we replicated the predictive model that was previously validated using a different subset of the database that we currently use.[15] (Namely, in the original CASPRI study, the analytic cohort was derived from the GWTG-R registry during a different time period between January 2000 and October 2009, and did not exclude patients with missing or implausible DNR times or hospitals that did not routinely collect DNR data.) A multivariable logistic regression model using the 11 variables included in the original CASPRI score[15] was constructed to evaluate the predictive performance of the model for favorable neurological survival, and the individual risk estimates for each of the 11 variables included in the model. The model's discrimination between those with and without actual favorable neurological survival (observed vs. predicted rates of outcome) was assessed using the c-statistic.

Next, to assess the alignment of decision-making for DNR status with patients' prognoses, we stratified the cohort into deciles of CASPRI scores and used crosstabs to compare rates of DNR, as well as actual favorable neurological survival, within each CASPRI decile. Furthermore, the degree to which these measures were associated with each other was quantified by calculating the point-biserial correlation coefficient between the dichotomous DNR status and the continuous CASPRI score variable.

For all analyses, the null hypothesis was evaluated at a two-side significance level of 0.05 with 95% confidence intervals (CIs). All analyses were conducted using SPSS Statistics 22 (Supplemental Figure 1).

CHAPTER 3

RESULTS

Within the study cohort of 26,327 patients, 5,944 (22.6%) adopted DNR status within the first 12 hours after ROSC, while 20,383 (77.4%) did not. Table 1 compares characteristics of patients who did and did not adopt DNR status. Patients adopting DNR status were older, more frequently of white race, and had higher rates of baseline neurological disability (CPC > 1). In addition, they had higher rates of pre-existing conditions including hypotension, respiratory insufficiency, renal insufficiency, hepatic insufficiency, metabolic/electrolyte abnormalities, and pneumonia. Finally, patients who adopted DNR status had higher rates of cardiac arrest rhythms associated with lower overall survival (e.g., pulseless electrical activity) and longer resuscitation times prior to achieving ROSC.

Table 1: Baseline Characteristics of Study Participants

	DNR (n = 5944)	Non-DNR (n = 20383)	Standardized Differences (%)
Demographics			
Age, median (IQR)	71 (59, 81)	66 (54, 76)	28.5
Female, no. (%)	2775 (46.7)	8663 (42.5)	8.5
Race, no. (%)			
White	4310 (73.6)	13697 (68.3)	11.8
Black	1165 (19.9)	4726 (23.6)	8.9
Other	381 (6.5)	1644 (8.2)	6.5
Pre-existing conditions, no. (%)			
Heart failure this admission	996 (16.8)	3783 (18.6)	4.7
Heart failure prior to admission	1225 (20.6)	4279 (21.0)	1.0
Myocardial infarction/ischemia, this admission	809 (13.6)	2814 (13.8)	0.6
Myocardial infarction/ischemia, prior to admission	851 (14.3)	2974 (14.6)	0.8
Arrhythmia	1867 (31.4)	6447 (31.6)	0.5
Hypotension	2065 (34.7)	5003 (24.5)	22.5
Respiratory insufficiency	2963 (49.8)	8864 (43.5)	12.8
Renal insufficiency	2499 (42.0)	7501 (36.8)	10.7
Hepatic insufficiency	661 (11.1)	1622 (8.0)	10.8
Metabolic/electrolyte abnormality	1264 (21.3)	3096 (15.2)	15.8
Diabetes mellitus	1807 (30.4)	7040 (34.5)	8.9
Baseline depression in central nervous system function	820 (13.8)	2159 (10.6)	9.8
Acute stroke	275 (4.6)	767 (3.8)	4.3
Acute central nervous system, non-stroke event	455 (7.7)	1354 (6.6)	3.5
Pneumonia	983 (16.5)	3112 (15.3)	14.2
Septicemia	1447 (24.3)	3779 (18.5)	3.8
Major trauma	200 (3.4)	832 (4.1)	17.4
Metastatic/hematologic malignancy	1014 (17.1)	2250 (11.0)	4.7
Interventions in place, no. (%)			
Mechanical ventilation	2428 (40.8)	6365 (31.2)	20.1
Pacemaker	334 (5.6)	1321 (6.5)	18.6
Dialysis	254 (4.4)	789 (4.0)	6.4
Event characteristics, no. (%)			
Night	2197 (37.1)	6543 (32.4)	10.0
Weekend	1776 (29.9)	5824 (28.6)	2.9

Table 1: Baseline Characteristics of Study Participants (continued)

	DNR (n = 5944)	Non-DNR (n = 20383)	Standardized Differences (%)
Location, no. (%)			
Intensive care unit	3896 (65.5)	11985 (58.8)	13.9
Monitored unit	1273 (21.4)	5706 (28.0)	15.3
Non-monitored unit	775 (13.0)	2692 (13.2)	0.5
Initial cardiac rhythm, no. (%)			
Asystole	2028 (34.1)	6888 (33.8)	0.7
Pulseless electrical activity	3457 (58.2)	10781 (52.9)	10.6
Ventricular fibrillation (VF)	423 (7.1)	2539 (12.5)	18.0
Ventricular tachycardia (VT)	36 (0.6)	175 (0.9)	3.0
Time to ROSC or death (minutes), median (IQR)	12 (6, 21)	10 (5, 19)	12.5
Cerebral Performance Category (CPC) on admission, no. (%)			
CPC 1	2436 (50.7)	9802 (58.8)	16.4
CPC 2	1244 (25.9)	4006 (24.0)	4.3
CPC 3	691 (14.4)	1895 (11.4)	9.0
CPC 4	435 (9.0)	956 (5.7)	12.7
CPC 5	1 (0.0)	5 (0.0)	0.6

When replicating the originally validated CASPRI model,[15] we found similar and significant associations with the outcome (Table 2). In short, increasing age, less organized and non-shockable initial arrest rhythms (asystole or pulseless electrical activity), higher baseline CPC scores (worse disability), arrest in a non-monitored setting, increasing duration of arrest event, and all comorbidities were significantly associated with worse odds of favorable neurological survival. Only age <50 and arrest in a monitored setting were significantly associated with increased odds of favorable neurological survival. The predictive performance of the model in this particular cohort was slightly lower than in the original work (c-statistic of 0.762 vs. 0.802).[15]

Table 2: Multivariable Predictors of Favorable Neurological Survival to Discharge, as Included in the CASPRI Score

	Odds Ratio (95% Confidence Interval)
Age group, year	
≤ 49	1.18 (1.05-1.31)
50-59	1.07 (0.96-1.19)
60-69	1 (Reference)
70-79	0.71 (0.64-0.78)
≥ 80	0.53 (0.48-0.59)
Initial arrest rhythm	
Ventricular fibrillation	1 (Reference)
Ventricular tachycardia	
Asystole	0.42 (0.37-0.46)
Pulseless electrical activity	0.39 (0.36-0.44)
Pre-arrest cerebral performance category	
1	1 (Reference)
2	0.73 (0.67-0.79)
3	0.22 (0.19-0.25)
4 or 5	0.26 (0.21-0.31)
Hospital location	
Non-monitored unit	1 (Reference)
Telemetry unit	1.50 (1.34-1.68)
Intensive care unit	1.15 (1.03-1.29)
Duration of resuscitation, min	
1	1 (Reference)
2-4	0.67 (0.57-0.81)
5-9	0.39 (0.33-0.46)
10-14	0.28 (0.23-0.33)
15-19	0.20 (0.16-0.24)
20-24	0.22 (0.18-0.27)
25-29	0.21 (0.17-0.26)
≥ 30	0.17 (0.14-0.20)
Mechanical ventilation	0.52 (0.48-0.57)
Renal insufficiency	0.70 (0.65-0.75)
Hepatic insufficiency	0.43 (0.37-0.50)
Sepsis	0.54 (0.49-0.60)
Malignant disease	0.42 (0.38-0.48)
Hypotension	0.62 (0.57-0.68)
Model C statistic	**0.762**

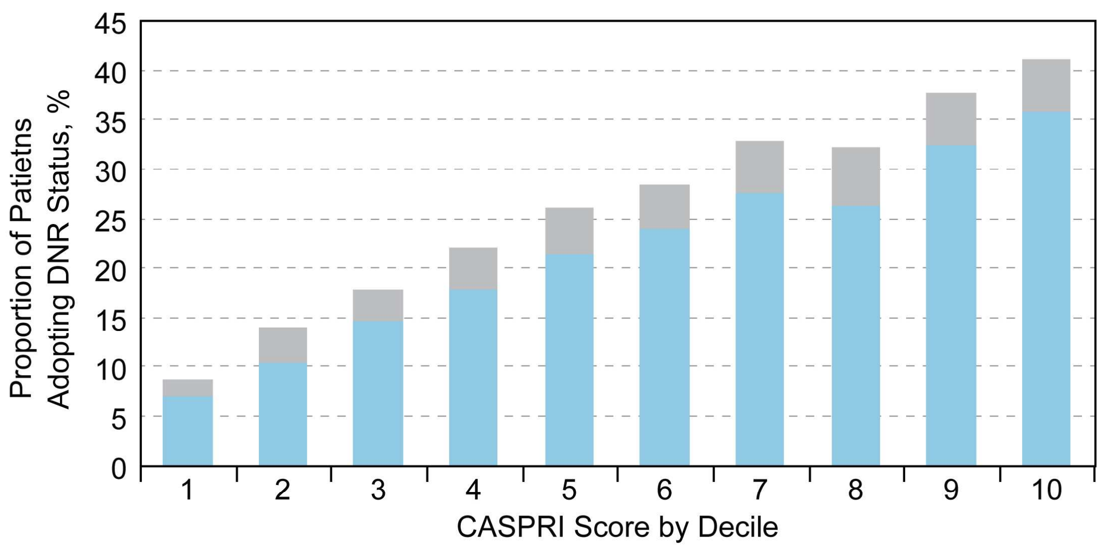
Relationship Between DNR Status and Expected Prognosis

Overall, 6,318 (24.0%) patients who achieved ROSC survived to hospital discharge with favorable neurological status (Table 3). When patients were stratified into deciles by their predicted likelihood of favorable neurological survival (i.e. CASPRI score), the actual rate of favorable neurological survival decreased uniformly with worsening CASPRI score, from 64.7% in decile 1 to 4.0% in decile 10 (P for trend <0.001), while the proportion of patients adopting DNR status increased almost uniformly as their CASPRI scores increased, from 7.1% in decile 1 (patients with the highest predicted likelihood of favorable neurological survival) to 36.0% in decile 10 (patients with the lowest predicted likelihood of favorable neurological survival; P for trend <0.001). However, these findings demonstrate that almost two-thirds (64.0%) of patients with the worst neurological prognosis (decile 10) did not adopt DNR status after resuscitation from in-hospital cardiac arrest, despite an overwhelmingly poor prognosis. In sensitivity analyses wherein we re-defined DNR status as within the first 24 hours of ROSC, we found that there were only an additional 791 (3.0%) patients who adopted DNR status between 12 and 24 hours post-ROSC, with no significant change in the relationship to CASPRI score (Figure 5). Furthermore, 50.4% of DNR patients adopted DNR status within 12 hours of ROSC, compared with 8.7% between 12 and 24 hours after ROSC, 38.7% between 1 day to 1 month after ROSC, and 2.2% greater than 1 month after ROSC (Figure 6).

Table 3: Rates of Survival* and DNR Status Adoption by CASPRI Score Decile

CASPRI Score Decile	**Overall Survival Rate*** no. (%)	**DNR Status Adoption Rate** no. (%)
Overall	**6318 (24.0)**	**5944 (22.6)**
1	1550 (64.7)	169 (7.1)
2	834 (48.3)	181 (10.5)
3	892 (35.2)	372 (14.7)
4	937 (27.9)	601 (17.9)
5	389 (20.1)	398 (21.4)
6	679 (18.4)	890 (24.1)
7	262 (15.6)	465 (27.7)
8	347 (12.2)	749 (26.4)
9	320 (9.0)	1160 (32.5)
10	108 (4.1)	959 (36.0)

* Refers to rate of favorable neurological survival (CPC 1 or 2)



	1	2	3	4	5	6	7	8	9	10
DNR ≤ 12 Hours, %	7.05	10.49	14.67	17.89	21.43	24.08	27.68	26.37	32.48	35.96
DNR 12-24 Hours, %	1.8	3.59	3.28	4.23	4.74	4.36	5.3	5.99	5.32	5.13

Figure 5: Rates of DNR Status Adoption at 12 vs. 24 Hours After Arrest, Stratified by CASPRI Score Decile

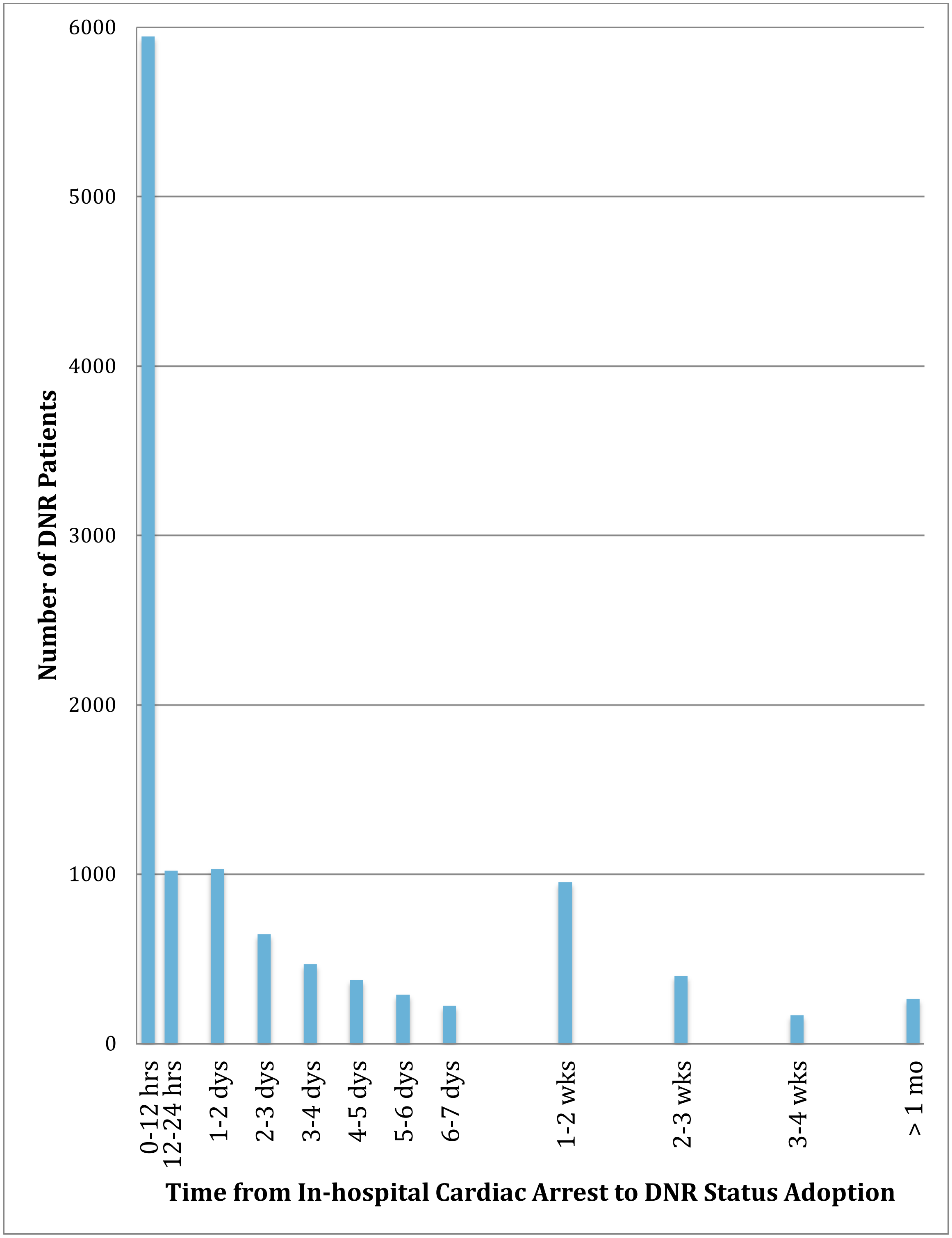


Figure 6: Distribution of Time to DNR Status Adoption after ROSC

Relationship Between DNR Status and Actual Outcomes

Among the 5,944 patients who adopted DNR status after resuscitation from in-hospital cardiac arrest, only 105 (1.8%) survived to discharge with favorable neurological status. This rate remained relatively low regardless of CASPRI score decile, including those with a high-predicted likelihood of favorable neurological survival (e.g., 7.1% and 6.1% rates for DNR patients in deciles 1 and 2, respectively) (Figure 7). In contrast, 6,213 (30.5%) of the 20,383 patients who did not adopt DNR status experienced favorable neurological survival, with substantially higher rates in the lower CASPRI deciles (e.g., 69.1% in decile 1 vs. 6.3% in decile 10). The point-biserial correlation coefficient for DNR status adoption and CASPRI score as a continuous variable was 0.206 ($p<0.001$), implying a low correlation.

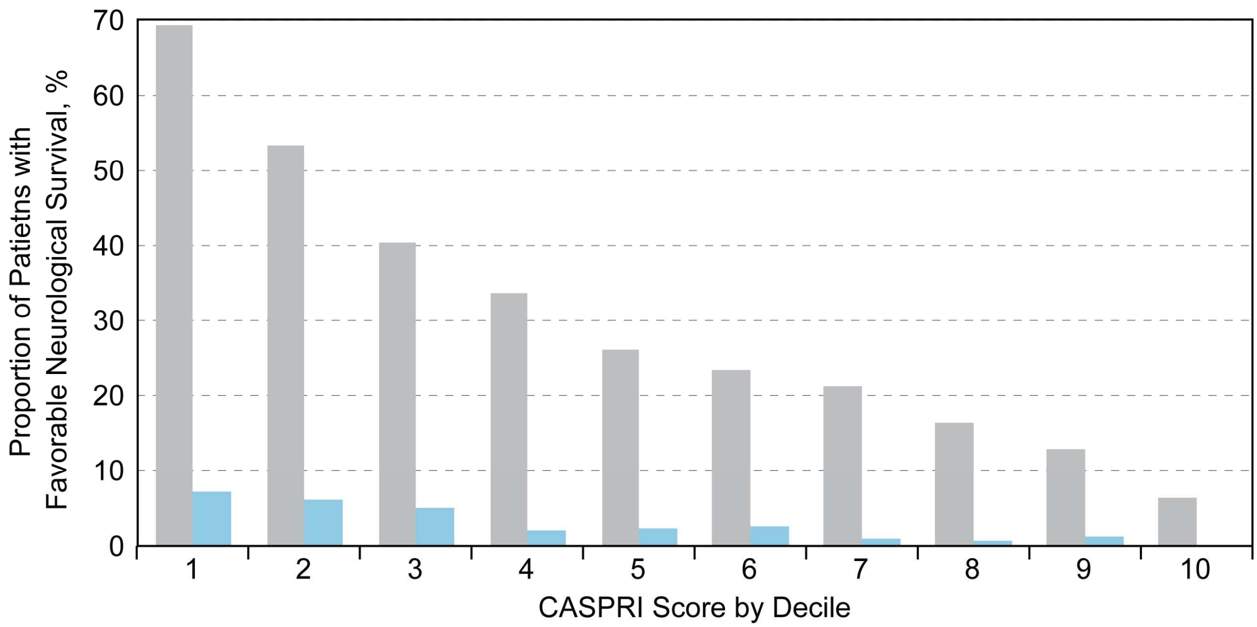


Figure 7: Rates of Favorable Neurological Survival Among DNR and Non-DNR Patients, Stratified by CASPRI Score Decile

CHAPTER 4

DISCUSSION

In this large, national in-hospital cardiac arrest registry, we found that decisions to adopt DNR status after successful resuscitation were generally aligned with patients' likelihood for favorable neurological survival, statistically represented by low to moderate correlation value. Among patients with the best prognosis for favorable neurological survival, 7.1% became DNR within the first 12 hours after achieving ROSC. This rate became successively higher as a patient's likelihood to survive without neurological disability decreased, peaking at a rate of 36% in those with the worst prognosis. Nonetheless, almost two-thirds of patients with the worst prognosis were not made DNR, even though only 6.3% of these non-DNR patients within the decile with the worst prognosis survived with favorable neurological status.

These findings highlight an important opportunity to further improve DNR decisions after in-hospital cardiac arrest, especially among patients with a low likelihood of favorable neurological survival. The decision not to adopt DNR status may have been motivated by many factors, including inaccurate clinician prognostication, inadequate communication, poor understanding of the prognosis among patients and families, family influence, or patients' personal beliefs, goals, and priorities. Within GWTG-R, we were not able to assess the role of patients', their families' and clinicians' preferences in DNR decision-making, or their understanding of prognosis. It is also the case that DNR status is not the appropriate choice for all patients with a very poor prognosis. However, our findings suggest that DNR decision-making can be better aligned with a patient's expected prognosis, and decision tools such as the CASPRI score have the potential to provide a platform for shared, informed decision-making and support rational use of DNR status in those with the poorest prognoses.

Several studies have also reported variable rates of DNR status adoption in patients hospitalized with other disease conditions, ranging from 9% in acute myocardial infarction,[21] to 13-22% in acute stroke,[22,23] to 22% in community-acquired pneumonia,[24] While these prior studies reported overall rates of DNR, they did not assess whether code status decision-making was aligned with a patient's prognosis. To our knowledge, this is the first study to analyze the association between DNR decision-making and expected prognosis.

It should also be noted that nearly 1 in 10 patients with the best prognosis in our cohort still became DNR soon after ROSC. The survival rate of 7.1% among DNR patients in this decile, however, differed markedly from non-DNR patients (69.1%) with a similar CASPRI score profile. Whether the actual survival difference between DNR and non-DNR patients with the best expected rate for favorable neurological survival reflects less aggressive care in DNR patients, patients' preferences, clinician miscalculation of prognosis, or factors not measured even in the CASPRI tool (despite its high C-statistic) remains unknown and an area of future research. Nevertheless, the fact that some patients with the best CASPRI score were made DNR is consistent with our belief that the CASPRI score should not be used in isolation to create standard thresholds for making patients DNR. Rather, the CASPRI tool should inform both physicians and patients in shared decision-making regarding DNR status after successful resuscitation from in-hospital cardiac arrest.

Our model performed similarly to that of *Chan et al* in regard to strength of association between the 11 predictor variables included in the CASPRI score and favorable neurological survival at discharge. [15] This is to be expected, as both studies utilized the

GWTG-R registry for analysis and these variables represent those most significantly associated with the outcome, which is how they came to be included in the CASPRI score. However, our c-statistic (model discrimination) was slightly lower. We hypothesize this may be due to patient selection, as our cohort was both from a later time period with only partial overlap (~2006-2009), and was also restricted to hospitals routinely collecting DNR data and patients without missing or implausible DNR orders and order times. Under the assumption that study personnel might be less likely to record DNR status in patients who do *not* adopt DNR, and given our results showing some alignment between worse DNR status adoption and poorer prognosis, our smaller cohort may be biased towards including patients with worse outcomes.

Our study should be interpreted in the context of certain limitations. First, the occurrence, frequency and content of clinician-patient discussions about DNR status were not measured in GWTG-R, and cannot be known. Therefore, we could not determine the reasons why some patients in the deciles with the best prognosis were made DNR while others with the worst prognosis were not made DNR. Future studies are needed to assess the extent to which this is due to patients' beliefs and preferences or discordance between physicians' perceptions of patients' prognoses and those of the CASPRI tool. Second, although the CASPRI score is based on a validated model with excellent discrimination, it is likely that some decisions regarding DNR status may reflect unmeasured patient characteristics that were not measured by the components of the CASPRI prediction tool. This is an especially germane limitation in regard to those patients with very good neurological prognosis who nevertheless adopted DNR status. Third, despite a wealth of evidence that DNR status adoption is associated with mortality in a number of clinical settings in addition to our findings here among survivors of in-hospital cardiac arrest (intensive care unit admissions,[25,26] acute heart failure,[27] and intracranial hemorrhage,[28,29]), it is not established whether patients' DNR status is a marker or mediator of survival. Delineation of the exact nature of this relationship merits further study.

In conclusion, we found that decisions to become DNR among successfully resuscitated patients after in-hospital cardiac arrest were generally aligned with patients' likelihood of favorable neurological survival. Nonetheless, we found that nearly 2 in 3 patients with the worst prognosis for favorable neurological survival were not made DNR within the first 12 hours after successful resuscitation. These findings suggest that systematic use of a prognostication tool, such as the CASPRI score, may help inform and optimize decisions about DNR status in patients after in-hospital cardiac arrest.

APPENDIX

Table A-1. Baseline characteristics of patients with missing data vs. final analytic cohort

	Missing (n = 8013)	**Non-missing (n = 26327)**	**Standardized Differences (%)**
Demographics			
Age, median (IQR)	67 (56, 78)	67 (55, 77)	4.0
Female, no. (%)	3476 (43.4)	11438 (43.4)	0.1
Race, no. (%)			
White	5523 (70.0)	18007 (69.5)	1.2
Black	1596 (20.2)	5891 (22.7)	6.1
Other	770 (9.8)	2025 (7.8)	6.9
Pre-existing conditions, no. (%)			
Heart failure this admission	1321 (16.5)	4779 (18.2)	4.4
Heart failure prior to admission	1530 (19.1)	5504 (20.9)	4.5
Myocardial infarction/ischemia, this admission	991 (12.4)	3623 (13.8)	4.1
Myocardial infarction/ischemia, prior to admission	935 (11.7)	3825 (14.5)	8.5
Arrhythmia	2231 (27.8)	8314 (31.6)	8.2
Hypotension	1915 (23.9)	7068 (26.8)	6.8
Respiratory insufficiency	3445 (43.0)	11827 (44.9)	3.9
Renal insufficiency	2978 (37.2)	10000 (38.0)	1.7
Hepatic insufficiency	657 (8.2)	2283 (8.7)	1.7
Metabolic/electrolyte abnormality	1135 (14.2)	4360 (16.6)	6.6
Diabetes mellitus	2469 (30.8)	8847 (33.6)	6.0
Baseline depression in central nervous system function	944 (11.8)	2979 (11.3)	1.5
Acute stroke	367 (4.6)	1042 (4.0)	3.1
Acute central nervous system, non-stroke event	611 (7.6)	1809 (6.9)	2.9
Pneumonia	1324 (16.5)	4095 (15.6)	2.6
Septicemia	1470 (18.3)	5226 (19.9)	3.8
Major trauma	375 (4.7)	1032 (3.9)	3.7
Metastatic/hematologic malignancy	1057 (13.2)	3264 (12.4)	2.4
Interventions in place, no. (%)			
Mechanical ventilation	2493 (31.1)	8793 (33.4)	4.9
Pacemaker	454 (5.7)	1655 (6.3)	2.6
Dialysis	317 (4.0)	1043 (4.1)	0.1

Table A-1. Baseline characteristics of patients with missing data vs. final analytic cohort (continued)

	Missing (n = 8013)	**Non-missing (n = 26327)**	**Standardized Differences (%)**
Event characteristics, no. (%)			
Night	2568 (32.4)	8740 (33.4)	2.2
Weekend	2338 (29.2)	7600 (28.9)	0.7
Location			
Intensive care unit	4595 (57.3)	15881 (60.3)	6.1
Monitored unit	2367 (29.5)	6979 (26.5)	6.8
Non-monitored unit	1051 (13.1)	3467 (13.2)	0.2
Initial cardiac rhythm			
Asystole	2759 (34.4)	8916 (33.9)	1.2
Pulseless electrical activity	4359 (54.4)	14238 (54.1)	0.6
Ventricular fibrillation (VF)	832 (10.4)	2962 (11.3)	2.8
Ventricular tachycardia (VT)	63 (0.8)	211 (0.8)	0.2
Time to ROSC or death (minutes), median (IQR)	11 (5, 20)	10 (5, 20)	2.4
Cerebral Performance Category (CPC) on admission, no. (%)			
CPC 1	2554 (55.0)	12238 (57.0)	4.0
CPC 2	1192 (25.7)	5250 (24.5)	2.8
CPC 3	598 (12.9)	2586 (12.0)	2.6
CPC 4	295 (6.4)	1391 (6.5)	0.5
CPC 5	2 (0.0)	6 (0.0)	0.8

Figure A-1. SPSS program syntax delineating code for analyses

Tests of Normality for Continuous Variables

```
EXAMINE VARIABLES=AGE_ADM evt2rend BY DNARnew
  /PLOT BOXPLOT HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /PERCENTILES(5,10,25,50,75,90,95) HAVERAGE
  /STATISTICS DESCRIPTIVES EXTREME
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.
```

Table 1 Data

Parametric Tests

```
CROSSTABS
  /TABLES=SEX racegrp ADM_CPC pec_hfad pec_hfpr pec_miad pec_mipr pec_arr
pec_hypo pec_resp pec_ren
    pec_hep pec_meta pec_dm pec_dcns pec_astr pec_acns pec_pneu pec_sept pec_trau
pec_mali IPA_VENT
    IPA_PACE IPB_DIAL EVT_LOC RHYCARD1 night weekend BY DNARnew
  /FORMAT=AVALUE TABLES
  /STATISTICS=CHISQ
  /CELLS=COUNT
  /COUNT ROUND CELL.
```

Nonparametric Tests

```
NPTESTS
  /INDEPENDENT TEST (AGE_ADM evt2rend) GROUP (DNARnew)
  /MISSING SCOPE=ANALYSIS USERMISSING=EXCLUDE
  /CRITERIA ALPHA=0.05  CILEVEL=95.

SORT CASES  BY DNARnew.
SPLIT FILE LAYERED BY DNARnew.

FREQUENCIES VARIABLES=AGE_ADM evt2rend
  /NTILES=4
  /STATISTICS=MEDIAN
  /ORDER=ANALYSIS.

SPLIT FILE OFF.
```

Recode variables into Groups for Risk Score Model

```
DATASET ACTIVATE DataSet1.
RECODE AGE_ADM (60 thru 69=1) (Lowest thru 49=2) (50 thru 59=3) (70 thru 79=4) (80
thru Highest=5)
    INTO AGE_GRP.
VARIABLE LABELS  AGE_GRP 'Age Group'.
EXECUTE.

RECODE RHYCARD1 (4=3) (1=2) (8 thru 9=1) INTO RHYTH_GRP.
VARIABLE LABELS  RHYTH_GRP 'Initial Rhythm Groups'.
EXECUTE.

RECODE ADM_CPC (1=1) (2=2) (3=3) (4 thru 5=4) INTO CPC_GRP.
VARIABLE LABELS  CPC_GRP 'CPC Groups'.
EXECUTE.

RECODE evt2rend (Lowest thru 1=1) (2 thru 4=2) (5 thru 9=3) (10 thru 14=4) (15 thru
19=5) (20 thru
    24=6) (25 thru 29=7) (30 thru Highest=8) INTO TIME_GRP.
VARIABLE LABELS  TIME_GRP 'Resuscitation Time Groups'.
EXECUTE.
```

Logistic Regression Model

```
LOGISTIC REGRESSION VARIABLES survfns
  /METHOD=ENTER AGE_GRP RHYTH_GRP CPC_GRP location TIME_GRP
IPA_VENT pec_ren pec_hep pec_sept
    pec_mali pec_hypo
  /CONTRAST (AGE_GRP)=Indicator(1)
  /CONTRAST (CPC_GRP)=Indicator(1)
  /CONTRAST (TIME_GRP)=Indicator(1)
  /CONTRAST (IPA_VENT)=Indicator(1)
  /CONTRAST (pec_hep)=Indicator(1)
  /CONTRAST (pec_ren)=Indicator(1)
  /CONTRAST (pec_hypo)=Indicator(1)
  /CONTRAST (pec_mali)=Indicator(1)
  /CONTRAST (pec_sept)=Indicator(1)
  /CONTRAST (RHYTH_GRP)=Indicator(1)
  /CONTRAST (location)=Indicator(1)
  /SAVE=PRED
  /CLASSPLOT
  /PRINT=GOODFIT CI(95)
  /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).
```

C Statistic calculation

```
ROC PRE_1 BY survfns (1)
  /PLOT=CURVE(REFERENCE)
  /PRINT=SE COORDINATES
  /CRITERIA=CUTOFF(INCLUDE) TESTPOS(LARGE) DISTRIBUTION(FREE) CI(95)
  /MISSING=EXCLUDE.
```

Crosstabs for Descriptive Correlation, Primary and Secondary Analysis

```
SORT CASES  BY riskscore_deciles.
SPLIT FILE LAYERED BY riskscore_deciles.

CROSSTABS
  /TABLES=DNARnew DNARnew24 BY survfns
  /FORMAT=AVALUE TABLES
  /CELLS=COUNT ROW COLUMN
  /COUNT ROUND CELL.

SPLIT FILE OFF.
```

Correlation Coefficient

```
GRAPH
  /SCATTERPLOT(BIVAR)=DNARnew WITH riskscore
  /MISSING=LISTWISE.
```

Chart Builder

```
GGRAPH
  /GRAPHDATASET NAME="graphdataset" VARIABLES=DNARnew riskscore
MISSING=LISTWISE REPORTMISSING=NO
  /GRAPHSPEC SOURCE=INLINE.
BEGIN GPL
  SOURCE: s=userSource(id("graphdataset"))
  DATA: DNARnew=col(source(s), name("DNARnew"), unit.category())
  DATA: riskscore=col(source(s), name("riskscore"))
  DATA: id=col(source(s), name("$CASENUM"), unit.category())
  GUIDE: axis(dim(1), label("DNAR <=12hrs"))
  GUIDE: axis(dim(2), label("riskscore"))
  SCALE: linear(dim(2), include(0))
  ELEMENT: schema(position(bin.quantile.letter(DNARnew*riskscore)), label(id))
END GPL.
```

Correlation Coefficient, Secondary Analysis

```
CORRELATIONS
  /VARIABLES=riskscore DNARnew24 DNARnew
  /PRINT=TWOTAIL NOSIG
  /MISSING=PAIRWISE.
```

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VITA

Timothy Fendler was born on October 10th, 1979 in Kansas City, Missouri and lived there with his parents and siblings until graduating from Rockhurst High School in 1998. He attended Saint Louis University from 1998 to 2003 and obtained bachelor of arts degrees in English and secondary education, followed by two years spent teaching high school English in the greater Saint Louis area. He returned to Kansas City and completed a post-baccalaureate, pre-medicine program of study at Rockhurst University, and subsequently enrolled in the University of Kansas School of Medicine, Kansas City, Kansas, in 2006.

After finishing medical school in 2010, he began internal medicine residency at Barnes Jewish Hospital, Washington University in Saint Louis, Missouri. He completed his residency in 2013 and moved back to Kansas City for an NIH-sponsored, T32 cardiovascular outcomes research fellowship at Saint Luke's Mid America Heart Institute, University of Missouri-Kansas City. Here he served as part-time faculty to the internal medicine residency program. During this research fellowship, he pursued a Master of Science in bioinformatics, with an emphasis in clinical research, at the University of Missouri-Kansas City.

Upon completion of his research fellowship and master degree requirements, Dr. Fendler will begin consecutive cardiovascular disease and advanced heart failure and transplant fellowships at the University of Missouri-Kansas City. Following these clinical fellowships, Dr. Fendler plans on a career in both clinical heart failure cardiology and cardiovascular outcomes research.

Dr. Fendler is a member of the American College of Cardiology, the American Heart Association, the American Medical Association, and is certified by the American Board of Internal Medicine.