MORTALITY RISK AMONG PATIENTS WHO PRESENT TO HOSPITALS WITH OUT-OF-HOSPITAL CARDIAC ARREST AND ST-ELEVATION MYOCARDIAL INFARCTION

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ABSTRACT

In the emergent setting of an ST-elevation myocardial infarction (STEMI) presenting with an out-of-hospital cardiac arrest (OHCA), decisions for immediate coronary angiography are made when the likelihood of survival is highly variable and unknown. A simple prognostic tool that can identify patients with a very high mortality risk upon hospital presentation may inform decision-making regarding emergent procedures.

Within the Cardiac Arrest Registry to Enhance Survival (CARES), I included adult patients with OHCA and STEMI who presented from January 2013 to December 2019. Using multivariable logistic regression, I developed a predictive model and risk score for in-hospital mortality.

Of 13,444 hospitalized patients with OHCA and STEMI (median age 64 [IQR 55-74], 31.6% female, 56.6% white), 8141 (60.6%) died. Higher age, non-shockable cardiac arrest rhythm, not having sustained return of spontaneous circulation upon hospital arrival, and total resuscitation time on scene were most predictive of mortality (*C*-statistic, 0.86). An integer risk score (range: 0-7) derived from this model estimated that patients with STEMI and OHCA have an in-hospital mortality from 15% to nearly 100%, with the odds of in-

hospital mortality more than doubling for each additional point (odds ratio, 2.64; 95% CI, 2.55–2.73; $p<0.001$; *C*-statistic, 0.85).

STEMI patients with OHCA have highly variable mortality risk. I created a simple prediction model comprised of four prehospital characteristics to estimate this risk. Further work is needed to define how this model can support procedural decision-making and better risk-adjustment for mortality-based quality measures in this high-risk population.

APPROVAL PAGE

The faculty listed below, appointed by the Dean of the School of Medicine has examined this research proposal titled, “Mortality Risk Among Patients Who Present to Hospitals with Out-Of-Hospital Cardiac Arrest and ST-Elevation Myocardial Infarction” presented by Andy Tran, candidate for the Master of Science Bioinformatics, and certify that in their opinion it is worthy of acceptance.

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CHAPTER 1

INTRODUCTION

An estimated 5% of patients with ST-segment elevation myocardial infarction (STEMI) present with out of hospital cardiac arrest (OHCA), and these patients have a 10-fold higher mortality rate as compared with STEMI patients not having an OHCA.[1] Consensus guidelines recommend emergent coronary angiography for OHCA patients with STEMI.[2-4] Despite a meta-analysis of observational studies that showed better outcomes in patients with STEMI and OHCA who undergo early coronary angiography,[5] the mortality rate of these patients remains very high, at approximately 27-30% compared to the mortality rate of 3-4% in STEMI without OHCA.[1, 6]

For patients with STEMI and OHCA, decisions for emergent coronary angiography are typically made upon hospital arrival to maximize the potential benefits of revascularization. However, such decisions can be difficult as clinicians may intuitively determine that some patients have a very low chance of survival. Determining the potential advantages of an invasive management strategy should drive decision-making, however, this is complicated by national benchmarking of an operator's procedural mortality rate for percutaneous coronary intervention (PCI) as a quality metric. Although current benchmarking adjusts for the presence of cardiac arrest[7, 8] it is not entirely clear that adjustment for cardiac arrest as a dichotomous variable fully captures mortality risk as there is likely substantial heterogeneity in mortality risk among patients who present with OHCA and STEMI.

Accordingly, within a national registry of OHCA, the Cardiac Arrest Registry to Enhance Survival (CARES) registry, I developed a mortality risk score for patients presenting with STEMI complicated by OHCA. This risk score can give operators a more accurate, evidence-based estimate of mortality to inform their clinical-making processes and can inform risk-adjustment for national benchmarking of mortality rates for coronary angiography and PCI.

CHAPTER 2

REVIEW OF LITERATURE

Challenges of Acute Myocardial Infarction in Out-of-Hospital Cardiac

Out-of-hospital cardiac arrest (OHCA) affects almost 400,000 adults each year in the United States and is a leading cause of mortality and morbidity worldwide.[9-11] Moreover, the majority of patients successfully resuscitated from out-of-hospital cardiac arrest die in the hospital with a mortality rate of 90% nationally.[10-12]

Recent guidelines suggest on improving post-resuscitation survival rate through targeted temperature management and coronary angiography.[12-14] However, coronary angiography after out-of-hospital cardiac arrest remains challenging because it is invasive and resource intensive, with no definite causal link to improved outcomes.[14]

Epidemiology of Coronary Artery Disease in Out-of-Hospital Cardiac

Among patients with out-of-hospital cardiac arrest, coronary artery disease is often diagnosed at autopsy, and coronary artery disease is a common cause of out-of-hospital cardiac arrest without other evidence of noncardiac cause.[15] Close to one-half of all patients who die of coronary artery disease in the hospital have out-of-hospital cardiac arrest, and about 10% of patients who present with coronary artery disease have out-of-hospital cardiac arrest as their initial presentation.[15]

In a landmark clinical study,[16] immediate coronary angiography was performed on 84 consecutive patients with out-of-hospital cardiac arrest and without apparent noncardiac cause. These patients did not have ST-segment elevation which the investigators reported to be presented in about 40% of the patients.[16] The findings revealed obstructive coronary artery disease was present in 60 patients (71%) and acute coronary occlusion was present in 40 patients (47%). Further follow ups showed that successful percutaneous coronary intervention was associated with 5-fold higher odds of hospital survival.[16]

Clinical Studies of Coronary Artery Disease in Out-of-Hospital Cardiac

Further observational studies of patients with out-of-hospital cardiac arrest who received coronary angiography have shown a similar 70% prevalence of obstructive coronary artery disease with approximately 50% of patients having acute coronary occlusion (angiographic culprit arteries requiring percutaneous coronary intervention).[17-19] Multi-vessel obstructive coronary artery disease was also reported in greater than 50% of out-of-hospital cardiac arrest patients in a recent study.[19]

Most interestingly, OHCA patients who had coronary angiography often differed significantly from those who did not.[20-22] Early coronary angiography (within 24 hour of hospital arrival) and percutaneous coronary intervention (PCI) are associated with improved survival outcomes after OHCA. However, only early PCI was associated with a significant benefit after statistical adjustment, and thus, this finding would potentially lead to ascertainment bias regarding the prevalence of coronary artery disease as the prevalence is influenced by patient selection for coronary angiography. Regardless, those clinical studies that used a more systematic approach to coronary angiography in less selected populations still demonstrated a high frequency of coronary artery disease.[18, 19]

Consensus Guidelines of Out-of-Hospital Cardiac

In summary, consensus guidelines recommend emergent coronary angiography for out-of-hospital cardiac arrest patients with ST-elevation myocardial infarction.[2-4] Early coronary angiography and percutaneous coronary intervention after out-of-hospital cardiac arrest has been associated with lower mortality in some studies,[20-22] yet the survival rate for out-of-hospital cardiac arrest remains low. In the emergent setting of ST-elevation myocardial infarction when decisions for immediate coronary angiography must be made upon hospital arrival, it is unclear if there are patients who would have a very low chance of survival despite having survived an out-of-hospital cardiac arrest to hospital admission in the setting of a ST-elevation myocardial infarction. These are likely patients who are elderly, with prolonged EMS times in the field, non-shockable out-of-hospital cardiac arrest rhythms, and no return of spontaneous circulation upon hospital admission.

Research Objectives

A national registry of OHCA, the Cardiac Arrest Registry to Enhance Survival (CARES) registry, was employed to develop a mortality risk score for patients presenting with STEMI complicated by OHCA. This risk score is developed to give operators a more accurate, evidence-based estimate of mortality to inform their clinical-making processes and to inform risk-adjustment for national benchmarking of mortality rates for coronary angiography and PCI.

CHAPTER 3

METHODOLOGY

Data Source and Study Design

The Cardiac Arrest Registry to Enhance Survival (CARES) is a prospective, multicenter registry of patients with out-of-hospital cardiac arrest (OHCA) in the U.S. established by the Centers for Disease Control and Emory University for public health surveillance and communities benchmark for continuous quality improvement. The design of the registry has been previously described.[23, 24] Briefly, all patients with a confirmed OHCA (defined as pulselessness, apnea, and unresponsiveness) and for whom resuscitation is attempted are identified and followed by Emergency Medical Service (EMS) systems, representing a catchment area of approximately 152 million U.S. residents or approximately 46% of the US population. Data are collected from three sources that comprehensively define the continuum of emergency cardiac care: 911 dispatch centers, EMS agencies, and receiving hospitals. Standardized international Utstein definitions for specifying clinical variables and outcomes are used to ensure uniformity.[25] A CARES analyst reviews every record for completeness and accuracy.[24]

The Cardiac Arrest Registry to Enhance Survival contains patient-level data on demographics (age, sex, and race/ethnicity), location of cardiac arrest, initial cardiac arrest rhythms, and whether the arrest was witnessed. Additionally, information as to whether bystander cardiopulmonary resuscitation (CPR) or defibrillation with an automated external defibrillator was administered prior to EMS arrival and cardiac arrest etiology (presumed cardiac, respiratory, drug overdose and other) is collected, as well as times to EMS arrival and duration of EMS treatment. The study was approved by Saint Luke's Mid America Heart Institute, which waived the requirement for informed consent because the analysis included only deidentified data.

Study Population and Primary Outcome

I performed a retrospective cohort analysis of all OHCA patients using data from CARES database between January 1, 2013 and December 31, 2019. I identified 457,621 patients with an OHCA during this period. I excluded 12,679 children age <18 years. I then restricted our cohort to patients who were transported alive to the emergency department, excluding 150,842 patients who died in the field. As our focus was on patients with STEMI, I excluded 208,310 patients without a STEMI, 71,229 with unavailable data on STEMI, and 1,068 patients who were transferred to another facility. Our study cohort included 13,493 patients with STEMI and OHCA (Figure 1). The primary endpoint for the study was in-hospital mortality.

Statistical Analysis

I compared baseline characteristics between patients who died and survived to hospital discharge using chi-square tests for categorical variables and Student's t-tests for continuous variables when normally distributed or Wilcoxon's rank sum tests when not normally distributed.

Model Development and Derivation of Risk Score

To determine the mortality risk for patients who initially presented to the emergency room with OHCA and STEMI, I constructed a multivariable logistic regression model using pre-hospital patient and cardiac arrest variables. These variables included age, female, arrest at home/residence, unwitnessed arrest, bystander CPR, bystander AED applied, non-shockable rhythm cardiac arrest rhythm, non-sustained ROSC, presumed arrest etiology, and EMS time on scene. The candidate variables were all pre-hospital patient-level data obtained directly by EMS; thus, these data are readily accessible while enroute to the hospital. These predictors were chosen by utilizing all variables that were available in the CARES registry while also considering existing evidence for predictors of OHCA in general. In 2015, the American College of Cardiology Interventional Council published 10 unfavorable resuscitation features that were overall predictive of nonhospital survivorship,[26] and Harhash and colleagues also looked at these 10 unfavorable features and examine which features are most impactful in predicting prognosis for cardiac arrest survivors.[27] According to the author, the presence of the three strongest risk factors: age more than 85 years, time to ROSC of more than 30 minutes, and non-shockable initial rhythm together predict less than 10% chance of survival to discharge,[27] and these, likewise, were accounted in our models. As tests for non-linearity for continuous variables were significant, age and time on scene were categorized by 10-year intervals and 5-minute intervals, respectively, to facilitate clinical interpretation.

From an initial full model, to support the clinical utility of using the model in routine care, I created a parsimonious model according to Harrell's method.[28] Using the predicted values from the full model, I ranked all predictors by their R^2, and variables with the smallest contribution to the model were sequentially eliminated until removal resulted in more than a 5% loss in model prediction as compared with the initial full model (i.e., the reduced model and would retain 95% of the predictive power of the full model). I then derived a mortality risk score with the variables in the reduced model using the model's β coefficients, which were re-scaled and rounded to integers.[29] With this mortality risk model, I evaluated the diagnostic performance of the score on a continuous scale using the area under the receiver-operating characteristic curve (AUC), or C-statistic. To evaluate risk of overfitting, I performed internal bootstrap validation.[30] Calibration of the observed versus predicted probabilities was also assessed over bootstrapped samples.

Early Coronary Angiography Rates

Finally, to examine the extent to which decisions for early coronary angiography in routine practice aligns with patients' mortality risk, I examined rates of early coronary angiography (within 2 hours of hospital presentation) stratified by patients' mortality risk score. Furthermore, to highlight mortality differences in the highest-risk group, I compared their characteristics and outcomes of patients with a model-estimated mortality risk of >90% stratified by whether they underwent early coronary angiography, delayed angiography during the hospitalization, or no angiography.

Missing Data

In our study cohort, 6.6% of patients had missing data: 1 (<0.01%) patient had missing data on witnessed arrest status, 1 (<0.01%) on initial rhythm type, 1 (<0.01%) on bystander CPR, 46 (0.3%) on hospital outcome, and 837 (~6.2%) with time on scene. Before development of the models, time on scene was imputed with random forest imputation[31] (missForest package version 1.4 in R) given its higher missing data rate, while cases (Cases with missing data = 49) with remaining missing data were excluded given their very low missing rate.

All tests are 2-tailed, and an alpha level of 0.05 was considered statistically significant. All analyses were conducted using R statistical software version 4.0.5 (R Project for Statistical Computing).

CHAPTER 4

RESULTS

Baseline Characteristics

Of 13,444 patients with out-of-hospital cardiac arrest (OHCA) and STEMI who survived to the emergency department, 8141 (60.6%) died during the hospitalization. Median age was 64 [IQR 55-74], 4255 (31.6%) patients were female and 7592 (56.6%) were white. Overall, 8820 (65.6%) had their OHCA at home, 3174 (23.6%) had an unwitnessed cardiac arrest, 6197 (46.1%) had an initial non-shockable rhythm, and 3101 (23.1%) did not have sustained return of spontaneous circulation (ROSC) upon hospital arrival. The bystander cardiopulmonary resuscitation (CPR) rate was 49.7%, and bystander automated external defibrillator (AED) rate was 16.7%. A comparison of patients who survived and died is provided in Table 1. Patients who died were older, more often female and of non-white race, and were more likely to have an OHCA at home, an unwitnessed arrest, or initial non-shockable cardiac arrest rhythm; not receive CPR or be evaluated with an AED by a bystander; not have sustained ROSC at the time of hospital arrival; and have a longer time on scene before EMS transport.

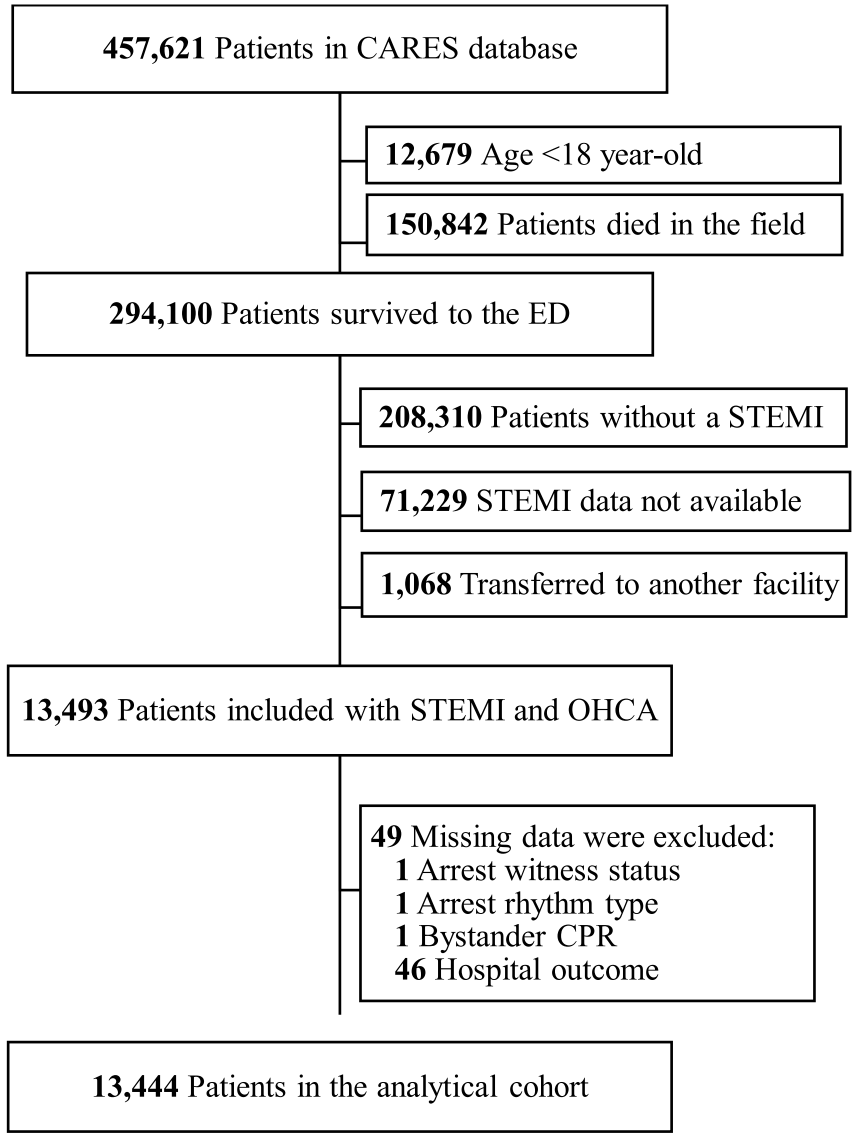


Figure 1. Diagram of Analytical Cohort
CARES indicates Cardiac Arrest Registry to Enhance Survival; CPR, cardiopulmonary resuscitation; ED, emergency department; OHCA, out-of-hospital cardiac arrest; STEMI, ST-Elevation Myocardial Infarction.

Table 1. Baseline Characteristics of Study Cohort, Stratified by In-Hospital Mortality

	Alive (N=5304)	**Died** (N=8141)	**Total** (N=13444)	***P*-value**
Age, year	60 [52-68]	67 [58-78]	64 [55-74]	<.001
Female	1259 (23.7)	2996 (36.8)	4255 (31.6)	<.001
Race/Ethnicity				<.001
White	3200 (60.3)	4392 (53.9)	7592 (56.5)	
Black	601 (11.3)	1329 (16.3)	1930 (14.4)	
Hispanic	243 (4.6)	520 (6.4)	763 (5.7)	
Asian	87 (1.6)	189 (2.3)	276 (2.1)	
Other/Unknown	1172 (22.1)	1711 (21)	2883 (21.4)	
Arrest at Home/Residence	3031 (57.2)	5789 (71.1)	8820 (65.6)	<.001
Unwitnessed	738 (13.9)	2436 (29.9)	3174 (23.6)	<.001
Bystander CPR Rate*	2088 (61.0)	2260 (42.5)	4348 (49.7)	<.001
Bystander AED Rate†	326 (21.6)	112 (10.1)	438 (16.7)	<.001
Non-shockable Rhythms	829 (15.6)	5368 (65.9)	6197 (46.1)	<.001
Non-sustained ROSC	356 (6.7)	2745 (33.7)	3101 (23.1)	<.001
Arrest Etiology				<.001
Presumed Cardiac	5153 (97.2)	7614 (93.5)	12767 (95)	
Respiratory/Asphyxia	98 (1.8)	348 (4.3)	446 (3.3)	
Drug Overdose	28 (0.5)	84 (1)	112 (0.8)	
Other	24 (0.5)	95 (1.2)	119 (0.9)	
Time to Arrival, mins	7 [5-9.7]	7.4 [5.4-10]	7.2 [5.2-10]	<.001
Time on Scene, mins	19 [14-25]	25 [19-33]	22 [16-30]	<.001
Transport Time, mins	11 [7-17]	10 [7-16]	11 [7-16]	<.001
Total Response Time, mins	39 [32-49]	46 [37-57]	43 [34-54]	<.001

Values are median [25^{th} – 75^{th} interquartile range] or n (%).
* Bystander CPR rate was calculated from a total N of 8740 after excluding 911 responder witnessed events as well as those that occurred in a nursing home/healthcare setting.
† Bystander AED rate was calculated from a total N of 2622 after excluding 911 responder witnessed events as well as those that occurred in a nursing home/healthcare and home/residence setting.
Abbreviations: AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; IQR, inter-quartile range; ROSC, return of spontaneous circulation.

Selection of the Final Model

In the full multivariable model, I identified several predictors of in-hospital mortality (Table 2). These included higher age, female sex, arrest at home, unwitnessed arrest, initial non-shockable rhythm, non-sustained ROSC upon hospital arrival, and longer time on scene. The full model had excellent discrimination and calibration (C-statistic, 0.87; Figure A-1). In the reduced model that retained 95% of the full model's predictive power (Table 2), four key variables were retained to predict in-hospital mortality and included older age, non-shockable cardiac arrest rhythm, no sustained ROSC upon hospital arrival, and time on scene. Model performance was similar with excellent discrimination (C-statistic, 0.86; Figure A-2).

Table 2. Full and Reduced Multivariable Models for In-hospital Mortality

Characteristic	Full Model			Reduced Model		
	OR	95% CI	*P*-value*	OR	95% CI	*P*-value*
Age by 10 years			<0.001			<0.001
60 to ≤70	REF	—		REF	—	
18 to ≤30	0.56	0.37, 0.85		0.66	0.45, 0.99	
30 to ≤40	0.49	0.38, 0.62		0.54	0.43, 0.68	
40 to ≤50	0.56	0.48, 0.65		0.58	0.49, 0.67	
50 to ≤60	0.68	0.60, 0.76		0.69	0.61, 0.77	
70 to ≤80	1.58	1.39, 1.81		1.60	1.40, 1.82	
80 to ≤90	2.37	1.99, 2.82		2.42	2.04, 2.88	
>90	3.15	2.16, 4.68		3.33	2.30, 4.95	
Female	1.18	1.07, 1.30	0.001	*removed*		
Arrest at Home/Residence	1.22	1.10, 1.35	<0.001	*removed*		
Unwitnessed	2.13	1.91, 2.39	<0.001	*removed*		
Bystander CPR	1.00	0.91, 1.10	>0.9	*removed*		
Bystander AED Applied	0.59	0.48, 0.73	<0.001	*removed*		
Non Shockable Rhythms	6.76	6.13, 7.47	<0.001	7.36	6.70, 8.10	<0.001
Non Sustained ROSC	6.71	5.87, 7.68	<0.001	6.37	5.58, 7.28	<0.001
Arrest Etiology			0.14	*removed*		
Presumed Cardiac	REF	—				
Respiratory/Asphyxia	0.77	0.60, 1.02				
Drug Overdose	1.27	0.77, 2.15				
Other	1.32	0.79, 2.27				
Time on scene by 5 mins			<0.001			<0.001
15 to ≤20	REF	—		REF	—	
0 to ≤5	0.62	0.36, 1.06		0.59	0.35, 0.99	
5 to ≤10	0.62	0.50, 0.78		0.58	0.46, 0.72	
10 to ≤15	0.89	0.76, 1.03		0.86	0.74, 0.99	
20 to ≤25	1.39	1.22, 1.59		1.47	1.29, 1.68	
25 to ≤30	2.71	2.34, 3.14		2.96	2.56, 3.43	
30 to ≤35	2.91	2.44, 3.49		3.15	2.64, 3.76	
35 to ≤40	3.65	2.92, 4.57		4.01	3.22, 5.01	
40 to ≤45	4.07	3.08, 5.42		4.49	3.41, 5.96	
45 to ≤50	5.54	3.76, 8.33		5.86	4.01, 8.72	
50 to ≤55	6.37	3.76, 11.3		6.96	4.13, 12.3	
55 to ≤60	4.97	2.85, 9.05		5.43	3.12, 9.87	
>60	9.83	5.99, 16.9		10.7	6.53, 18.3	
***C* statistic**	0.87			0.86		

*Global P-value. Abbreviations: AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; REF, reference; ROSC, return of spontaneous circulation.

Association of In-Hospital Mortality

An integer risk score was developed from these 4 variables based on strength of association of their β coefficients in the reduced model. Risk score ranged from 0 to a maximum score of 7 points. The score components included: 1 point for age greater than or equal to 70, 2 points each for non-shockable rhythms or non-sustained ROSC, and 1 or 2 points for time on scene greater than 20 or 40 minutes, respectively (Figure 3). Patients with a risk score of 0 (comprising 17.5% of the study cohort) had a predicted mortality risk of 15.4%, whereas those with a risk score of 4 or more (comprising 29.2% of the study cohort) had a predicted mortality risk of 93.5% or higher (Table 3), and the predicted mortality risks were similar to the observed mortality in the cohort (Figure 2). The odds of in-hospital mortality more than doubled for each 1-unit score increase when the score was evaluated as a continuous measure with minimal loss to model discrimination (odds ratio, 2.64; 95% CI, 2.55–2.73; $p<0.001$; C-statistic, 0.85). The final risk score model calibration was excellent as predicted vs. observed mortality were similar with a slope of near 1.000 (Figures A-3). Findings for the model were upheld in the internal bootstrap validation, with an optimism-corrected AUC of 0.85.

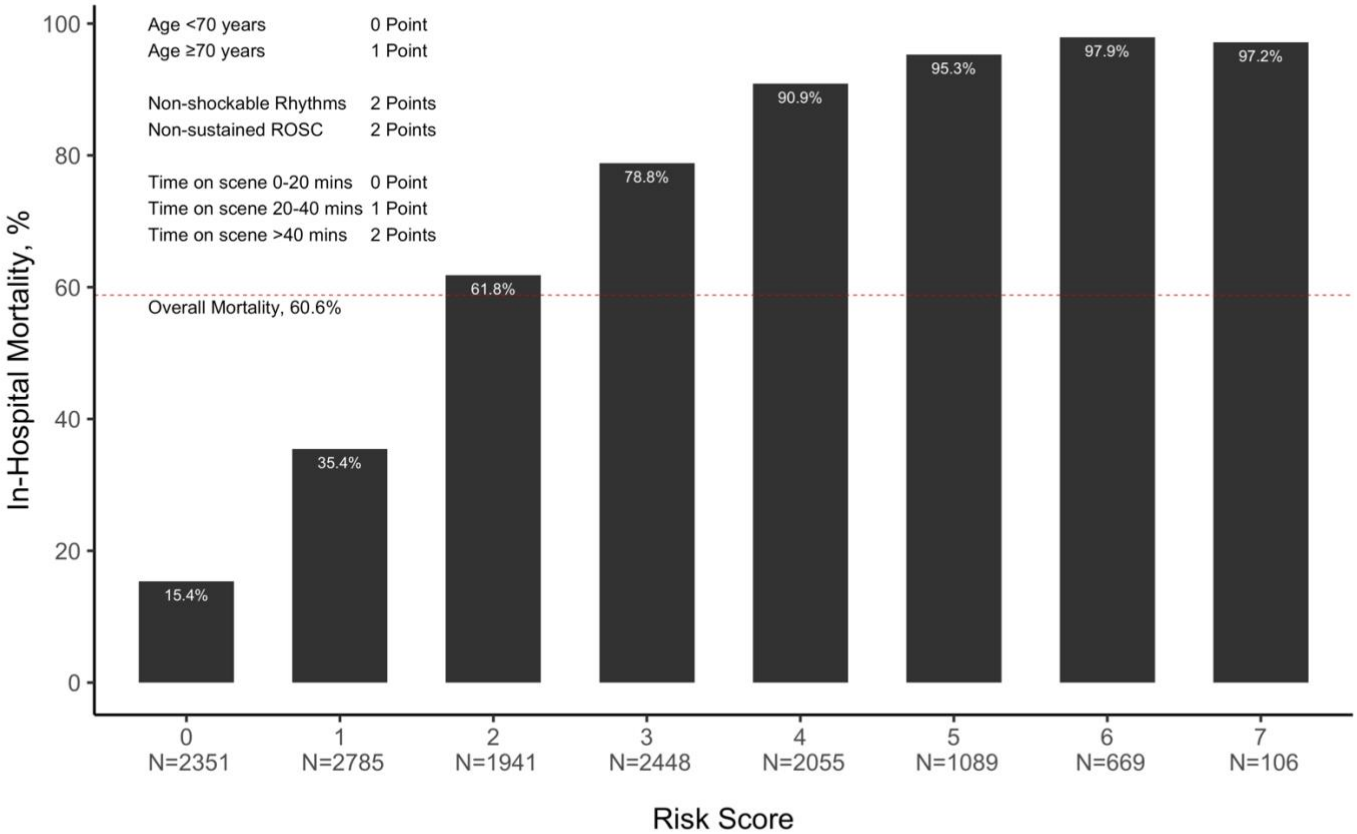


Figure 2. Observed In-Hospital Mortality Rate by Risk Score.
ROSC indicates return of spontaneous circulation.

Letter	Clinical Characteristic	Points
A	Age ≥70	1
N	Non-shockable rhythms	2
N	Non-sustained ROSC	2
T	Time on scene >20 or >40 minutes	1 or 2
	Maximum Risk Score	**7**

ROSC = return of spontaneous circulation

	A-2N-T Score		In-Hospital Mortality Rate
LOW RISK 0-1 Point	0	=	15.4%
	1	=	35.4%
INTERMEDIATE RISK 2-3 Points	2	=	61.8%
	3	=	78.8%
HIGH RISK 4 or More Points	4	=	90.9%
	5	=	95.3%
	6	=	97.9%
	7	=	97.2%

Figure 3. A-2N-T Mortality Risk Scoring for Survivors of Out-of-Hospital Cardiac Arrest with ST-Elevation Myocardial Infarction

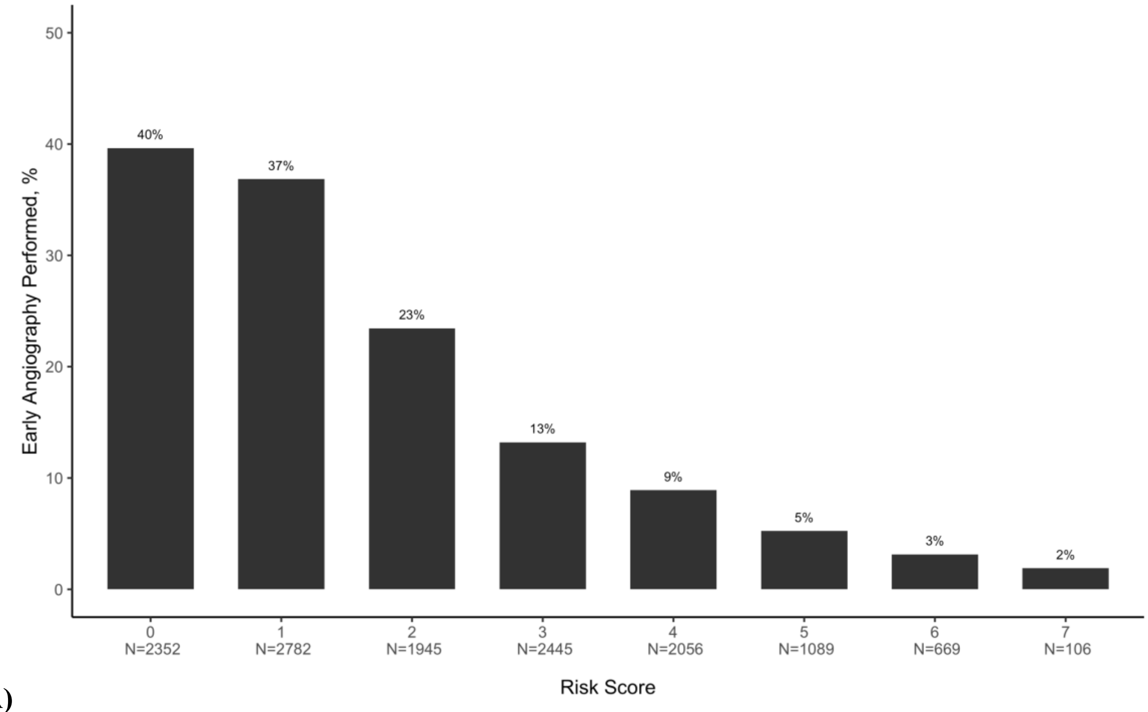
Table 3. In-Hospital Mortality Risk Score and Risk Category by Early Coronary Angiography

	Total (N=13,444)	**Not Early Aniography** (N=10,445)	**Early Angiography** (N=2999)	***P*-value**	**Survived to Discharge** (N=5303)	**Died in Hospital** (N=8141)	***P*-value**
Risk Score				<.001			<.001
0	2351	1419 (60.4)	932 (39.6)		1990 (84.6)	361 (15.4)	
1	2785	1760 (63.2)	1025 (36.8)		1798 (64.6)	987 (35.4)	
2	1941	1486 (76.6)	455 (23.4)		741 (38.2)	1200 (61.8)	
3	2448	2124 (86.8)	324 (13.2)		518 (21.2)	1930 (78.8)	
4	2055	1872 (91.1)	183 (8.9)		188 (9.1)	1867 (90.9)	
5	1089	1032 (94.8)	57 (5.2)		51 (4.7)	1038 (95.3)	
6	669	648 (96.9)	21 (3.1)		14 (2.1)	655 (97.9)	
7	106	104 (98.1)	2 (1.9)		3 (2.8)	103 (97.2)	
Risk Category (Score)				<.001			<.001
Low (0-1)	5136	3179 (61.9)	1957 (38.1)		3788 (73.8)	1348 (26.2)	
Intermediate (2-3)	4389	3610 (82.3)	779 (17.7)		1259 (28.7)	3130 (71.3)	
High (4+)	3919	3656 (93.3)	263 (6.7)		256 (6.5)	3663 (93.5)	

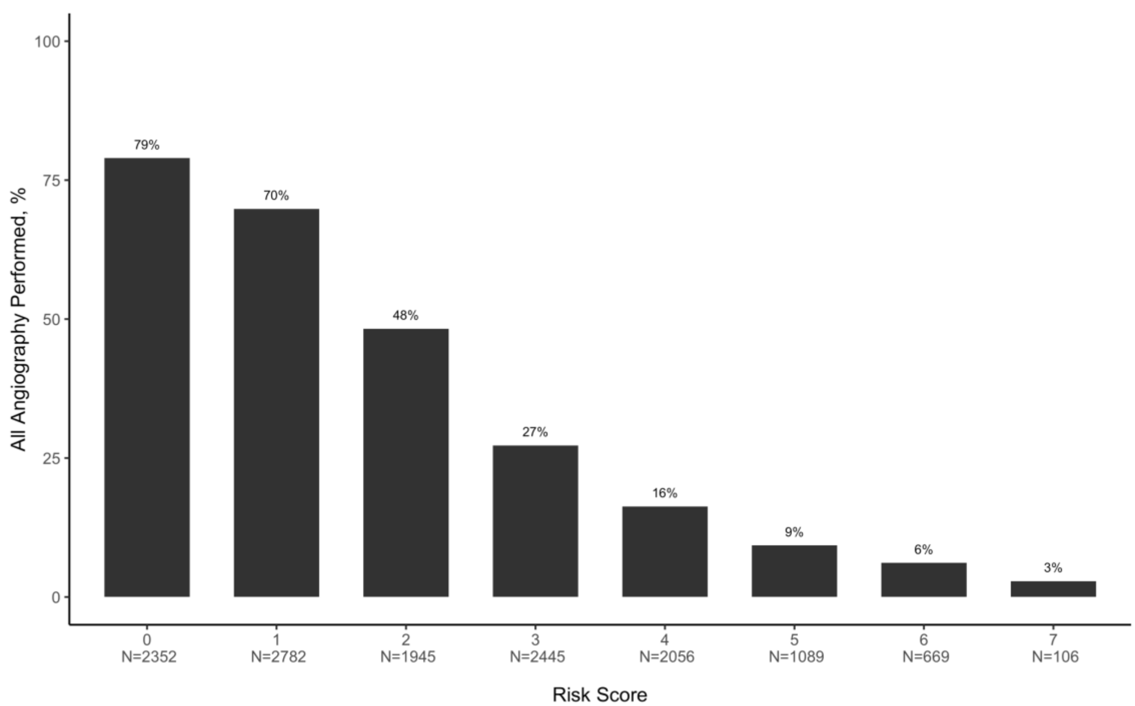
Values are n or n (%). Early angiography is defined as angiography performed within 2 hours from hospital arrival. Not early angiography is defined as angiography performed more than 2 hours from hospital arrival, no angiography performed, or unknown.

Early Coronary Angiography Performed

Overall, 2999 (22.3%) of the initial cohort of 13,444 patients underwent early coronary angiography within the first 2 hours of hospital arrival. Table 3 and Figure 4 summarize the proportion of patients who underwent early coronary angiography stratified by their mortality risk as estimated by our score. Among the 38.2% of patients with the lowest low risk (score of 0 or 1), 1957 of 5136 (38.1%) underwent early coronary angiography with an observed mortality rate of 26.2%. Conversely, among the 3,919 (29.2%) highest risk patients with a risk score of 4 or greater, the mortality rate was 93.5%. In this highest mortality group, 263 (6.7%) underwent early angiography within the first 2 hours, 217 (5.5%) underwent coronary angiography later during the hospitalization, and 3439 (87.8%) did not undergo coronary angiography. The mortality rate of the early and late angiography patients in this highest risk score group were 78.7% and 74.7%, respectively, whereas it was 95.8% for those who did not undergo angiography at all (Table A-1).



(A)



(B)

Figure 4. Coronary Angiography Performed by Risk Score
A) Early coronary angiography and B) All coronary angiography performed.

CHAPTER 5

DISCUSSION

In a large, multi-site registry of out-of-hospital cardiac arrest (OHCA) patients, I derived a model to predict mortality risk among patients presenting concurrently with a STEMI and who survived to hospitalization. I found that 3 in 5 patients died overall, but that there was substantial heterogeneity in mortality risk. I identified four variables as key predictors of in-hospital mortality for patients with OHCA and STEMI and developed a mortality risk score that can stratify the risk of in-patient mortality from 15% in those with a score of 0 to over 90% in those with scores of 4 or greater. Moreover, I found that in current practice that 22.3% of patients presenting with a STEMI in the setting of OHCA are treated with an early invasive treatment strategy, and early angiography was rarely performed in the highest risk patients with scores ≥4. Collectively, our findings underscore that patients with OHCA and STEMI have a high and wide range of mortality risk, but a simple score can identify patients with a high likelihood of surviving to discharge or dying during their hospitalization.

Although OHCA risk models predicting mortality from the time of the initial arrest or hospital admission have been developed,[32-34] model to estimate mortality risk in the setting of STEMI based on pre-hospital factors only are lacking. While OHCA risk models not involving STEMI have identified similar variables as predictors—higher age, non-shockable cardiac arrest rhythm, no sustained ROSC upon hospital arrival, and total resuscitation time on scene—our model is unique as it was developed in patients with concurrent STEMI who have a higher overall survival rate for OHCA and in whom decisions regarding early and emergent coronary angiography need to be made within the first half-hour of hospital arrival. Thus, our study extends the work of prior models by creating a simple-to-calculate risk score in an OHCA patient with STEMI in whom information on immediate clinical decision-making is invaluable and can assist clinicians and patients and families in shared decision-making regarding proceeding to immediate coronary angiography.

Although consensus guidelines recommend emergent coronary angiography for patients who have STEMI complicated by OHCA,[2-4] substantial heterogeneity in whether patients undergo emergent coronary angiography was fairly concordant with patients' mortality risks. Among patients with a relatively favorable prognosis, (scores of 0 or 1), 38.1% underwent angiography, as compared with only 6.7% of those with a 90% higher risk of in-hospital mortality (risk score of 4 or greater). Whether or not a larger proportion of patients with lower risk of dying should be considered for acute reperfusion or if it is truly futile to attempt such treatment in higher-risk patients will require future investigation.

Clinical Implications

In contemporary practice, although current consensus guidelines recommend emergent coronary angiography for patients who have STEMI complicated by OHCA,[2-4] I found substantial heterogeneity in whether patients undergo emergent coronary angiography, which was fairly concordant with patients' mortality risks. Among patients with a relatively favorable prognosis (scores of 0 or 1), 38.1% underwent early angiography, as compared to 6.7% of those with a higher than 90% risk of in-hospital mortality (risk score of 4 or greater). Notably, patients with the highest risk of mortality who underwent early vs.

later coronary angiography had high and comparable crude mortality rates of 74-78%. Whether or not a larger proportion of patients with lower risk of dying ought to be considered for acute reperfusion deserves future investigation.

Besides rapid estimation of patients' mortality risk at the bedside, our risk score underscores a potentially important role to inform ongoing national quality improvement efforts for public reporting of operator mortality rates for coronary angiography. Currently, risk-adjustment for cardiac arrest in calculating these publicly reported rates involves solely controlling for whether a patient had an OHCA or not. Our study underscores that this risk adjustment is likely inadequate and incomplete, given that patients' predicted mortality risks can be as low as 15% and as high as nearly 100%. As a result, it is possible that physicians may forego emergent coronary angiography in patients with STEMI and OHCA they perceive to be at very high mortality risk to avoid being penalized for public reporting if the model does not account for this heterogeneity in mortality risk. To avoid this scenario, the American Heart Association and the Society of Cardiac Angiography and Interventions published scientific and position statements to suggest separate reporting of procedural mortality rates for OHCA and STEMI.[7, 8] An alternate approach would be to conduct more granular risk adjustment for the presence of OHCA in patients with STEMI using our mortality risk model to facilitate more thorough adjustment for the presence of OHCA in public reporting of operator mortality rates. Accomplishing more complete risk adjustment for STEMI patients with OHCA would help support both physicians and ongoing national efforts for procedural benchmarking.

Limitations

This study should be considered in the context of the following potential limitations. First, the Cardiac Arrest Registry to Enhance Survival (CARES) registry does not fully collect clinical information on patients (limited information on comorbidities as past medical history is collected but an optional field, no hemodynamic information or frailty) that may affect mortality risk. Additionally, both STEMI and coronary angiography data are optional elements and were only collected on approximately 75-80% of the cases. Nonetheless, even without these variables, our risk score model discrimination for in-hospital mortality was excellent at 0.85; therefore, additional patient variables would have had only a modest impact on predicting in-hospital mortality. Second, I did not conduct a comparative effectiveness assessment of the benefits of emergent coronary angiography for patients with OHCA and STEMI. This is because our study objective was to evaluate the range of mortality risk for OHCA patients with STEMI driven by prehospital cardiac arrest variables. Moreover, substantial unmeasured indication bias exists as to who undergoes emergent angiography, limiting inferences from such comparative effectiveness analyses.

Conclusions

STEMI patients with OHCA have highly variable mortality risk. I created a simple prediction model comprised of four prehospital characteristics to estimate this risk. Further work is needed to define how this model can support procedural decision-making and better risk-adjustment for mortality-based quality measures in this high-risk population.

APPENDIX

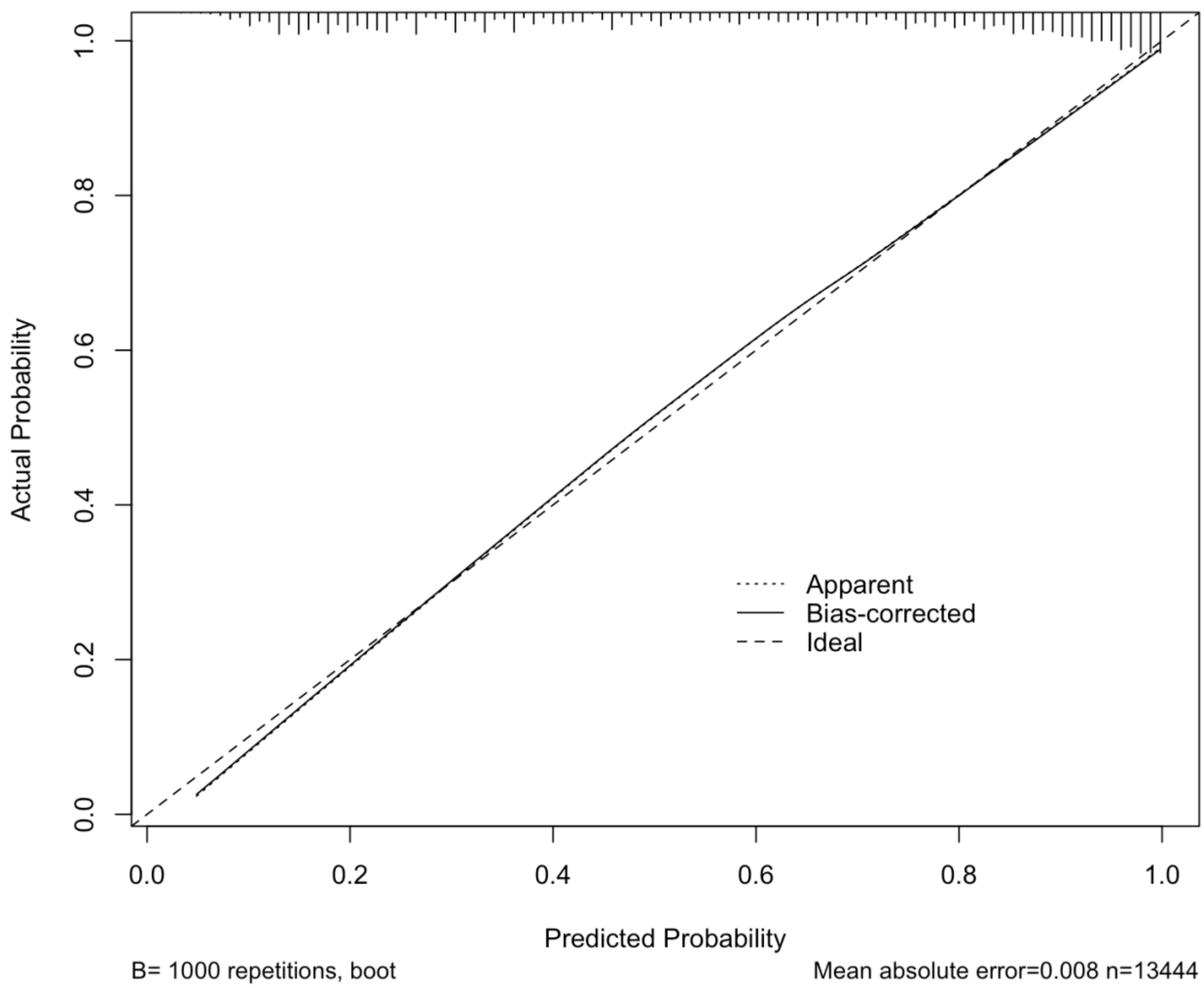


Figure A-1. Model Calibration with Bootstrapping for Full Model
Resampling model calibration using 1000 bootstrap samples. The concordance statistic is 0.8650 based on the original sample. The correction (i.e., optimism) derived from the internal validation is 0.0027. This indicates that the corrected concordance statistic is 0.8641, which is very similar to the original concordance statistic.

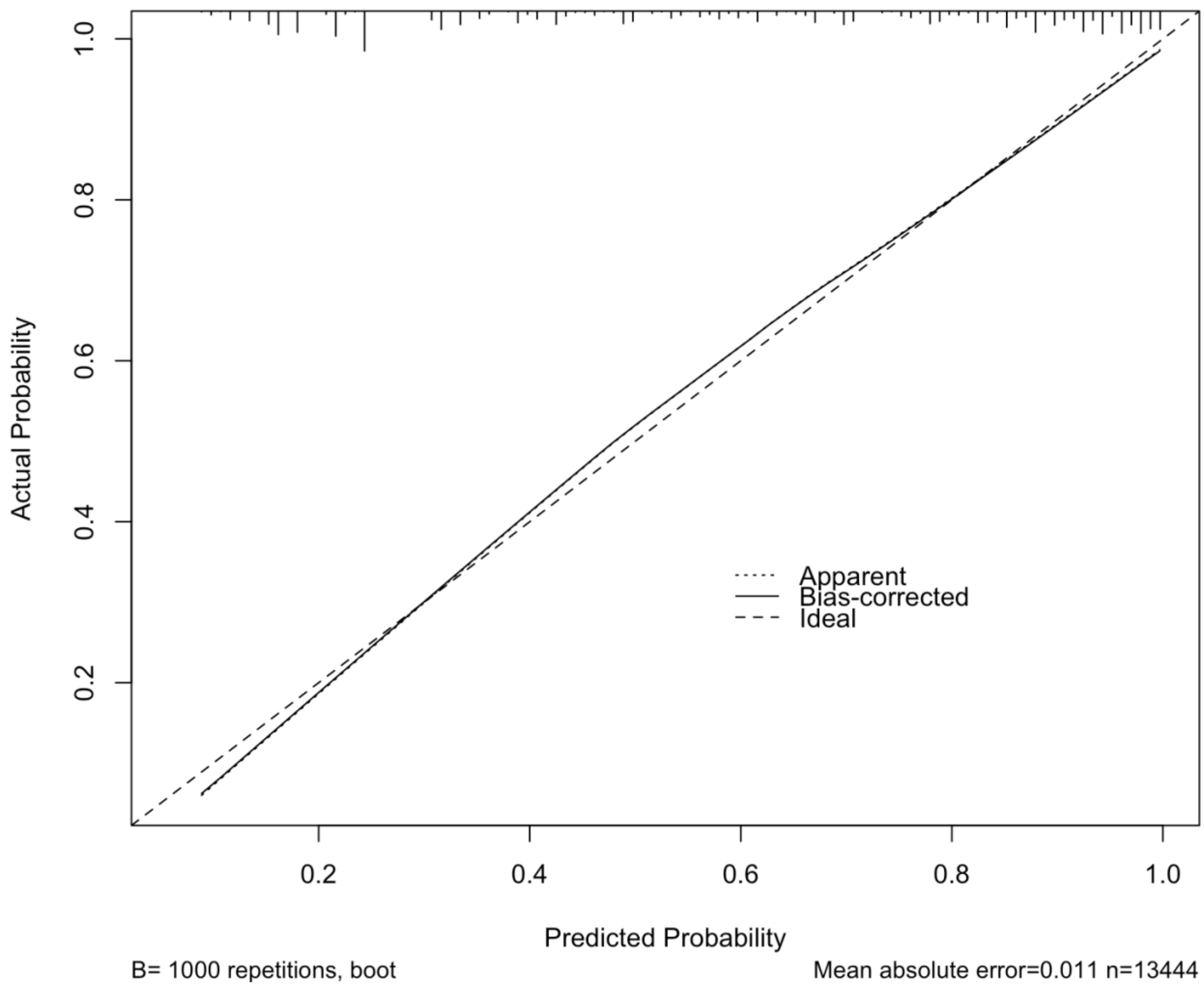


Figure A-2. Model Calibration with Bootstrapping for Reduced Model
Resampling model calibration using 1000 bootstrap samples. The concordance statistic is 0.8589 based on the original sample. The correction (i.e., optimism) derived from the internal validation is 0.0016. This indicates that the corrected concordance statistic is 0.8581, which is very similar to the original concordance statistic.

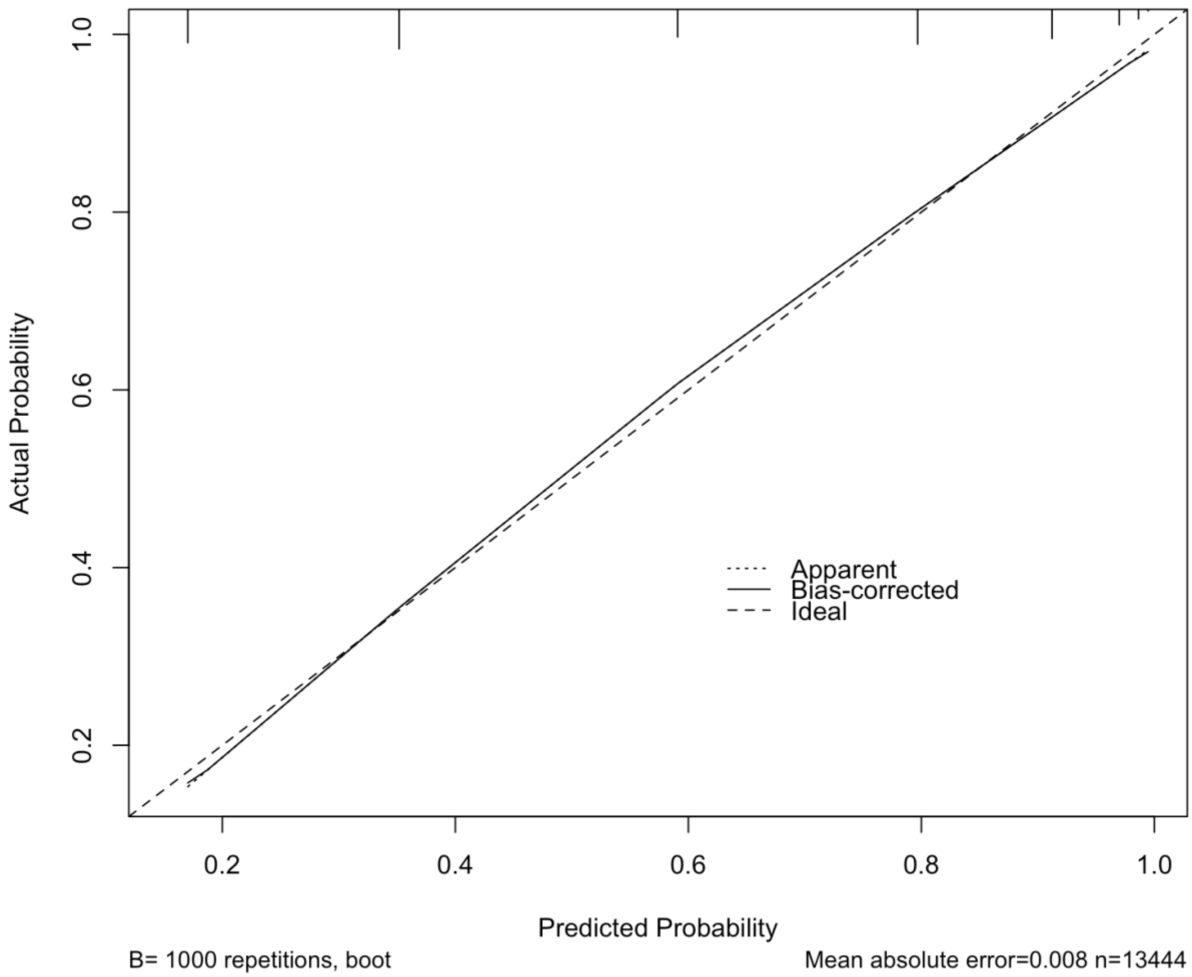


Figure A-3. Model Calibration with Bootstrapping for Risk Score Model
Resampling model calibration using 1000 bootstrap samples. The concordance statistic is 0.8458 based on the original sample. The correction (i.e., optimism) derived from the internal validation is 0.0002. This indicates that the corrected concordance statistic is 0.8457, which is very similar to the original concordance statistic.

Table A-1. Characteristics and Outcomes Among High-Risk Patients, Stratified by Coronary Angiography Performed

	Total	Early	Late	No/Unknown	*P*-Value
	N=3919	N=263	N=217	N=3439	
Age, year	74 [63-82]	73 [61-80]	73 [60-78]	74 [63-82]	0.007
Female	1612 (41.1)	88 (33.5)	75 (34.6)	1449 (42.1)	0.003
Race/Ethnicity					0.001
White	2069 (52.8)	167 (63.5)	104 (47.9)	1798 (52.3)	
Black	756 (19.3)	42 (16)	32 (14.7)	682 (19.8)	
Hispanic	236 (6)	12 (4.6)	20 (9.2)	204 (5.9)	
Asian	98 (2.5)	8 (3)	6 (2.8)	84 (2.4)	
Other/Unknown	760 (19.4)	34 (12.9)	55 (25.3)	671 (19.5)	
Arrest at Home	2843 (72.5)	201 (76.4)	167 (77)	2475 (72)	0.096
Unwitnessed	1170 (29.9)	78 (29.7)	53 (24.4)	1039 (30.2)	0.195
Bystander CPR	1172 (29.9)	89 (33.8)	75 (34.6)	1008 (29.3)	0.092
Bystander AED Applied	166 (4.2)	7 (2.7)	7 (3.2)	152 (4.4)	0.295
Non-shockable Rhythms	3646 (93)	224 (85.2)	182 (83.9)	3240 (94.2)	<.001
Non-sustained ROSC	2319 (59.2)	116 (44.1)	110 (50.7)	2093 (60.9)	<.001
Arrest Etiology					0.423
Presumed Cardiac	3630 (92.6)	239 (90.9)	208 (95.9)	3183 (92.6)	
Respiratory/Asphyxia	215 (5.5)	19 (7.2)	6 (2.8)	190 (5.5)	
Drug Overdose	27 (0.7)	2 (0.8)	2 (0.9)	23 (0.7)	
Other	47 (1.2)	3 (1.1)	1 (0.5)	43 (1.3)	
Time on Scene, minute	28 [22-38]	31 [24-43]	27 [22-40]	28 [22-37]	<.001
Risk Score*					<.001
4	2055 (52.4)	183 (69.6)	152 (70)	1720 (50)	
5	1089 (27.8)	57 (21.7)	44 (20.3)	988 (28.7)	
6	669 (17.1)	21 (8)	20 (9.2)	628 (18.3)	
7	106 (2.7)	2 (0.8)	1 (0.5)	103 (3)	
TTM†					<.001
Yes	708 (18.1)	131 (49.8)	111 (51.2)	466 (13.6)	
No	883 (22.5)	128 (48.7)	103 (47.5)	652 (19)	
Not Applicable	2307 (58.9)	4 (1.5)	1 (0.5)	2302 (66.9)	

	Total	Early	Late	No/Unknown	*P*-Value
Missing	21 (0.5)	0 (0)	2 (0.9)	19 (0.6)	
In-Hospital Mortality‡	3663 (93.5)	207 (78.7)	162 (74.7)	3294 (95.8)	<.001

Values are median [25th – 75th interquartile range] or n (%).
*P-value=0.92 when compared early vs. late subgroup.
†P-value=0.29 when compared early vs. late subgroup.
‡P-value=0.35 when compared early vs. late subgroup.
Abbreviations: AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; IQR, inter-quartile range; ROSC, return of spontaneous circulation; TTM, targeted temperature management

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VITA

Andy Tran was born on June 30th, 1987 in a rural village of Bac Lieu, Vietnam. At 10 years of age and not knowing any English, he immigrated to the United States and grew up in Orange County, CA. After successfully completing English as a Second Language (ESL) courses and Cypress High School in 2005, he attended undergraduate at the University of California, Los Angeles (UCLA) and completed his bachelor's degree in Microbiology, Immunology and Molecular Genetics with College Honors in 2010. He went to complete his medical school at the Midwestern University, Arizona College of Osteopathic Medicine in Glendale, AZ and obtained his medical degree in 2015.

After completing his medical school training, Dr. Andy Tran started internal medicine residency at the University of Missouri-Columbia (MU)/University Hospital and Harry S. Truman Memorial Veterans' Hospital. Following completion of residency in 2018, he was appointed faculty and remained at MU as an academic hospitalist for one year. While trying to understand how to generate new evidence to improve care especially in the practice of evidence-based medicine and the cost-effectiveness of patient-focused care, he pursued and was accepted in a 2-year NIH-funded T32 Cardiovascular Outcomes Research Fellowship Program at Saint Luke's Mid America Heart Institute, which he also enrolled in the Master of Science in Bioinformatics program at the University of Missouri-Kansas City (UMKC). Upon completion of his outcomes research fellowship and graduating from UMKC, Dr. Tran aspires and has strong interest in building an academic career that involves medical education, outcomes research and quality clinical care.

Dr. Tran is currently a fellow in training member of the American College of Cardiology, a member in the American Heart Association and the American College of Physicians.