

Clinical Prediction Rule for Patient Outcome after In-Hospital CPR

Satyam Merja¹, Ryan H. Lilien¹ and Hilary F. Ryder^{2,3*}

¹Department of Computer Science, University of Toronto, Toronto, Ontario, Canada

²Department of Medicine and The Dartmouth Institute, Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire

³Section of Hospital Medicine, Dartmouth-Hitchcock Medical Center, Lebanon

*Corresponding author: Hilary F. Ryder, M.D., Department of Medicine and The Dartmouth Institute, Dartmouth Medical School, One Medical Center Drive, NH, 03756, Lebanon, Tel: (603) 650-8380; Fax: (603) 653-6110; E-mail: Hilary.F.Ryder@Dartmouth.edu

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Abstract

Background: Physicians and patients frequently overestimate likelihood of survival after in-hospital cardiopulmonary resuscitation (CPR). Discussions and decisions around resuscitation after in-hospital cardiopulmonary arrest often take place without adequate or accurate information.

Methods: We conducted a retrospective chart review of 470 instances of resuscitation after in-hospital cardiopulmonary arrest. Individuals were randomly assigned to a derivation cohort and a validation cohort. Logistic Regression and Linear Discriminant Analysis were used to perform multivariate analysis of the data. The resultant best performing rule was converted to a weighted integer tool and thresholds of survival and non-survival were determined with an attempt to optimize sensitivity and specificity for survival.

Results: A 10-feature rule, using thresholds for survival and non-survival, was created; the sensitivity of the rule on the validation cohort was 42.7%, and specificity was 82.4%.

Conclusions: Utilizing information easily obtainable on admission, our clinical prediction tool, the Dartmouth Score, provides physicians individualized information about their patients' probability of survival after in-hospital cardiopulmonary arrest. The Dartmouth Score may become a useful addition to medical expertise and clinical judgment in evaluating and communicating an individual's probability of survival after in-hospital cardiopulmonary arrest after it is validated by other cohorts. Methodologically, because LDA outperformed LR in the creation of this clinical prediction rule, it may be an approach for others to more frequently consider when performing similar analysis.

Keywords: In-hospital CPR; Clinical prediction rule; Cardiopulmonary resuscitation

Introduction

Cardiopulmonary Resuscitation (CPR) was introduced in 1960 to revive victims of acute insult in otherwise good physiological condition [1]. In the past fifty years, CPR evolved from unorganized actions by untrained staff to synchronized teamwork, and has become a fundamental part of medical care for all hospitalized patients in cardiac arrest. Despite these changes, survival from CPR to hospital discharge declined from 24% in 1961 to 14% in 1981 [2]. Since 2000, the national average of survival from in-hospital cardiac arrest to hospital discharge has remained around 18% [3].

In the 1980s, responding to demands for patient autonomy, many hospitals began instituting "Do Not Resuscitate" (DNR) policies allowing patients or their families to determine that no resuscitation be attempted in the event of a cardiac arrest. However, less than 25% of seriously ill patients discuss preferences for resuscitation with their physicians [4-6]. Less than 50% of in-patients who prefer not to receive CPR have DNR orders written [7-9]. A known obstacle to the conversation is physician reluctance to discuss the issue [10,11].

Despite being asked to predict the future frequently by patients, most physicians avoid prognostication, largely because they believe they do not have sufficient information to estimate outcomes [12]. When physicians do engage in this conversation, they overestimate the likelihood of survival to hospital discharge after in-hospital CPR by as much as 300%, and they predict a success rate that is twice that actually observed [13]. This optimism strongly influences the choices of their patients. Accurate information about the probability of survival to discharge after CPR significantly alters patients' DNR preferences [14,15] and might be helpful to patients and their physicians in deciding whether to forego this intervention.

A tool, or clinical prediction rule, utilizing pre-arrest data to estimate an individual's risk of not surviving CPR, could empower physicians to prognosticate more accurately, increase frequency of code status discussions and thereby promote patient autonomy. In the late 1980s and early 1990s, three morbidity scores, Pre-Arrest Morbidity score (PAM) [16,19], Prognosis After Resuscitation score (PAR) [20], and Modified PAM Index (MPI) [21] attempted to predict survival after resuscitation based on univariate meta-analysis (PAR), literature review (MPI) or stepwise logistic regression (PAM). However, changes in CPR algorithms, a changing and ageing population and advances in medical science in the past twenty years have led to a need to update these tools. In addition, advances in the

use of computational sciences allow increasingly sophisticated multivariate and multidimensional analysis of data.

Since the creation of the “Utstein template” defining variables and outcomes essential for documenting in-hospital cardiac arrest, it has been possible to gather data in a standardized fashion. Recent studies [16-18], availing themselves of Utstein template and data collection methods, have focused on intra-arrest characteristics that are predictive of survival, but such data is not helpful to the physician or patient attempting to make a preemptive decision about use of CPR.

This study uses primary CPR data gathered retrospectively at a single center and analyzed by both linear discriminant analysis and logistic regression to attempt to determine variables predictive of non-survival after cardiac arrest and in-hospital resuscitation and to create a score that can be clinically useful to physicians and their patients.

Methods

Setting

We retrospectively reviewed medical and nursing records of all adult in-patient CPR attempts at our institution between January 2003 and December 2005. The center is a 389-bed tertiary care hospital affiliated with Dartmouth Medical School with average yearly admission of 20,000 patients.

Patient selection

Individuals were identified retrospectively from the CPR committee log of in-hospital cardiopulmonary arrests. Cardiac arrest was defined "the cessation of cardiac mechanical activity, confirmed by the absence of a detectable pulse, unresponsiveness, and apnea" [22]. The study cohort consisted of all consecutive patients aged 18 years and older with an in-hospital cardiac arrest and attempted resuscitation. Syncope, seizures, and primary respiratory arrests were excluded. Multiple arrests by the same individual were excluded. Patients whose resuscitation began outside of the hospital were excluded.

Assuming unequal groups (based on previous statistics, we predicted a 20% survival rate after cardiac arrest), 308 enrolled patients were needed for the study to have a statistical power of 80% to detect a significant difference with respect to history of congestive heart failure or renal failure (the only parameters with adequate published data) with a 2-sided α level of 0.05.

Data collection

A single trained chart abstractor reviewed each medical record. Admission variables were recorded on a structured data collection sheet designed for this study. We used admission variables (values obtained within 24 hours of admission) because we expect conversations about CPR and therefore the use of our rule, to take place on admission. We pre-specified all variables by developing a list of variables identified in the literature as varying significantly between survivors and non-survivors. All features were defined precisely (Appendix) prior to data collection. These criteria were adapted when possible from those used in previous investigations [23]. To minimize bias associated with the unavailability of data in patient subgroups, we imputed a value of normal when a physiologic value was missing.

The primary outcome measured was non-survival to hospital discharge. The study protocol was approved by the institutional review board of Dartmouth College.

Development of the clinical prediction rule

Two different techniques, linear discriminant analysis (LDA) and logistic regression (LR), were considered. Both techniques are established methods of generating prediction rules. The slight differences in the techniques allow each to occasionally outperform the other. In theory, if the feature covariance matrices for each of two sets of patients are unequal, there may be a slight advantage to using LR over LDA. However, empirical evidence suggests that this covariance matrix test is not always predictive [24,25]. We therefore computed clinical prediction rules using both LDA and LR, and compared their performance.

To remain consistent with previous work, we defined a positive outcome as not surviving to discharge [26]. A true positive is a patient who does not survive to discharge who was predicted not to survive. The specificity measures the percentage of patients who lived that were predicted to live. The sensitivity measures the percentage of patients who did not survive who were predicted to not survive. We maximized specificity.

The dataset consisting of 470 patients was divided into derivation and validation cohorts. A random sample of 330 patients was assigned to the derivation cohort, which was used for developing the prediction rule (Figure 1). After we constructed the model, we evaluated its performance on the validation cohort.

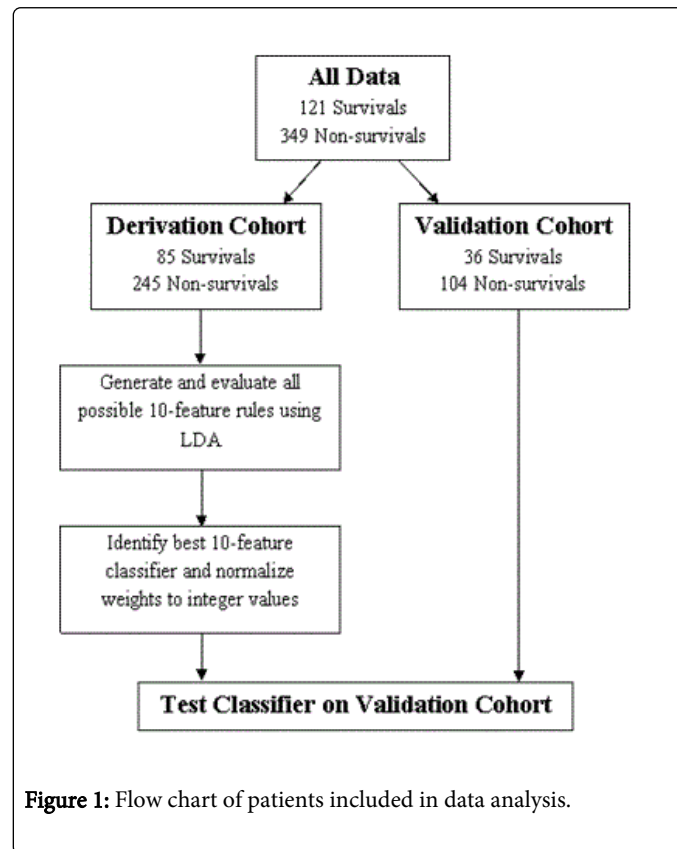


Figure 1: Flow chart of patients included in data analysis.

Twenty-six of thirty initially collected features were used with LDA to create the clinical prediction rule. S3 gallop and abnormal PaCO₂

were excluded due to insufficient data. Independence or dependence with ADLs were removed after analysis revealed that the act of assessing ADL status, not the status itself, was predictive of survival. Using the derivation cohort, a search over all possible 10-feature combinations of the 26 features (approximately 5.3 million combinations) was performed. Each set of 10-features was evaluated by performing 1000 splits of the derivation cohort into a training set containing 90% of the patients in the cohort and a testing set containing the remaining 10%. For each split, LDA was used to generate significance weights for each feature and a temporary threshold was chosen to identify all survivors on the training set. The choice to identify all survivors compromised sensitivity but resulted in a desired low false-positive rate. The average performance over the 1000 randomly chosen test sets was used as a criterion to rank each set of 10 features.

The best performing 10-feature rule was identified and normalized to create an integer classifier with all feature weights falling between 0 and 5 (inclusive). To increase the usability and adaptability of the tool by the healthcare team, all initially negative weights were converted to positive weights by replacing each feature with a negative weight with an equivalent 'absent' feature with the same weight magnitude, albeit positive (e.g., angina pectoris had an initial weight of -4, so we added a feature "no angina pectoris" with a weight of +4). This weight inversion required that the thresholds be shifted by an equivalent amount. The final thresholds reported in this study (≤ 7 and ≥ 9) were manually selected. Patients with a score of 7 or lower are likely to survive to discharge, patients with a score of 9 or above are not likely to survive to discharge, and no prediction is made for patients who score between the thresholds. The performance of this rule was

evaluated against the validation cohort and the results were compared against other clinical prediction rules.

We also considered the technique of LR. The entire dataset was analyzed with the logistic regression functions as implemented in the statistical computing software R [27]. The binomial logit model was used and calculations took four Fisher Scoring iterations. Four features were identified with p-values less than 0.05. The classifier was normalized to integer weights and thresholds were manually selected to optimize sensitivity and specificity. Since the data was not divided into derivation and validation cohorts, the performance of LR was judged using the entire dataset. Given that we are trying to optimize specificity, it is most fair to compare the LDA model to an LR model with threshold chosen to approximately match the specificity of the LDA-derived rule.

Results

Characteristics of the study population

A total of 470 individual attempts at CPR after cardiopulmonary arrest were reviewed. Overall, 25.7% survived to hospital discharge. In the derivation cohort, the mean age was 67.2 years (Standard Deviation, 14.8 years); 58.5% were men; and 85 of 330 or 25.8% survived to hospital discharge. In the validation cohort, the mean age was 67.0 (Standard Deviation, 15.7 years); 51.4% were men; and 36 of 140 or 25.7% survived to hospital discharge. No significant differences in baseline characteristics between the two cohorts were observed (Table 1).

Characteristic	Number of Patients		% of Patients		P-Value	Chi-Square Score
	Derivation Cohort	Validation Cohort	Derivation Cohort	Validation Cohort		
Male Sex	193	72	58%	51%	0.158	1.99
Age >70	148	67	45%	48%	0.549	0.359
Independent ADLs	160	76	48%	54%	0.25	1.323
Not-Completely-Independent ADLs	128	47	39%	34%	0.285	1.145
PMH CVA	37	15	11%	11%	0.875	0.025
CRI/ ESRD	71	29	22%	21%	0.846	0.038
Angina Pectoris	102	36	31%	26%	0.258	1.279
CHF (III or IV)	98	36	30%	26%	0.382	0.765
PMH MI	73	24	22%	17%	0.223	1.487
Cancer	82	32	25%	23%	0.645	0.212
Cirrhosis	9	6	3%	4%	0.379	0.773
Dementia	13	4	4%	3%	0.566	0.33
Respiratory Insufficiency	114	47	35%	34%	0.839	0.041
Immunocompromised	8	4	2%	3%	0.786	0.074
Sepsis	25	9	8%	6%	0.661	0.193
Pneumonia	46	19	14%	14%	0.916	0.011

Recent MI	90	41	27%	29%	0.656	0.198
CVA	14	8	4%	6%	0.49	0.477
Coma	13	3	4%	2%	0.326	0.965
Ventilation	145	71	44%	51%	0.178	1.817
Hypotension	94	35	28%	25%	0.439	0.599
S3 Gallop	1	0	0%	0%	0.514	0.425
Oliguria	4	2	1%	1%	0.848	0.037
Pulmonary Edema	73	37	22%	26%	0.313	1.017
Abnl BUN	48	23	15%	16%	0.602	0.272
Abnl Cr	136	51	41%	36%	0.333	0.939
Abnl pH	75	28	23%	20%	0.513	0.427
Abnl PaCO ₂	95	38	29%	27%	0.717	0.131
Abnl PaO ₂	23	11	7%	8%	0.734	0.115
Abnl Bicarb	31	11	9%	8%	0.593	0.285
Deceased	245	104	74%	74%	0.992	0

Table 1: Baseline characteristics of the derivation and validation cohorts.

In chi-square univariate analysis of the derivation cohort, the presence of angina pectoris, hypotension, abnormal pH, and abnormal bicarbonate were the only characteristics that had a statistically significant difference between patients who survived to discharge and those who did not (Table 2). Angina pectoris was found to be

protective while hypotension, abnormal pH, and abnormal bicarbonate were significant risk factors for non-survival to hospital discharge. There was no significant association between mortality and the other variables.

Characteristic	Number of Patients		% of Patients		P-Value	Chi-Square Score
	Survived	Deceased	Survived	Deceased		
Male Sex	57	136	67%	56%	0.063	3.466
Age >70	34	114	40%	47%	0.297	1.088
Independent ADLs	41	119	48%	49%	0.957	0.003
Not-Completely-Independent ADLs	38	90	45%	37%	0.194	1.689
PMH CVA	9	28	11%	11%	0.832	0.045
CRI/ ESRD	22	49	26%	20%	0.255	1.293
Angina Pectoris	38	64	45%	26%	0.001	10.205
CHF (III or IV)	32	66	38%	27%	0.063	3.466
PMH MI	19	54	22%	22%	0.952	0.004
Cancer	20	62	24%	25%	0.744	0.107
Cirrhosis	1	8	1%	3%	0.308	1.038
Dementia	4	9	5%	4%	0.673	0.178
Respiratory Insufficiency	36	78	42%	32%	0.079	3.086
Immunocompromised	3	5	4%	2%	0.442	0.591

Sepsis	5	20	6%	8%	0.493	0.469
Pneumonia	12	34	14%	14%	0.956	0.003
Recent MI	24	66	28%	27%	0.817	0.053
CVA	1	13	1%	5%	0.104	2.649
Coma	2	11	2%	4%	0.383	0.761
Ventilation	35	110	41%	45%	0.551	0.355
Hypotension	16	78	19%	32%	0.022	5.246
S3 Gallop	0	1	0%	0%	0.555	0.348
Oliguria	0	4	0%	2%	0.236	1.405
Pulmonary Edema	19	54	22%	22%	0.952	0.004
Abnl BUN	11	37	13%	15%	0.626	0.237
Abnl Cr	34	102	40%	42%	0.792	0.069
Abnl pH	9	66	11%	27%	0.002	9.606
Abnl PaCO ₂	24	71	28%	29%	0.896	0.017
Abnl PaO ₂	2	21	2%	9%	0.052	3.764
Abnl Bicarb	3	28	4%	11%	0.031	4.626

Table 2: Univariate analysis of clinical characteristics and survival in the derivation cohort.

The four features in bold demonstrated a statistically significant difference between patients that did and did not survive (via chi-square analysis at the 0.05 level).

Description of the clinical prediction rule

We define the Dartmouth Score as the best ten-feature clinical prediction rule generated using LDA (Table 3). The rule includes both

protective features and those indicative of non-survival. It achieves a specificity of 82.4% and a sensitivity of 42.7% on the validation cohort. In contrast, the LR derived rule obtained when the threshold is set to approximate the same specificity (83%) achieves a lower sensitivity and a higher false negative rate than the Dartmouth Score (Table 4).

Clinical feature	Weighted score
Age>70	2
No Angina Pectoris	4
No Dementia	1
No Respiratory Insufficiency	2
CVA	5
Hypotension	3
Abnl PaO ₂	3
Abnl Bicarb	3
Coma	2
Cancer	1

Table 3: The Dartmouth Score ten feature clinical prediction rule.

Performance of logistic regression classifier	
Specificity	0.83
Sensitivity	0.33
FNrate	0.67
LRP	1.99
LRN	0.8
PPV	0.85
NPV	0.3
FNrate: False Negative Rate, LRP: Likelihood ratio of a positive result, LRN: Likelihood ratio of a negative result, PPV: Positive Predictive Value, NPV: Negative Predictive Value	

Table 4: Test characteristics of Logistic Regression Analysis classifier.

In the Dartmouth Score, the features of age (greater than 70 years of age), history of cancer, previous cardiovascular accident or CVA, presence of coma, hypotension, abnormal PaO₂, and abnormal bicarbonate were identified as the best predictors of non-survival. Angina, dementia, and chronic respiratory insufficiency were selected as protective features.

Development of thresholds for utilization

Setting the survival threshold at ≤7 and the non-survival threshold at ≥9 allowed us to predict the outcome in 88% of patients in our validation cohort. For 12% of the patients there was insufficient information, given the clinical features, to make a prediction. In these instances, rather than force a prediction, the rule states that the outcome is uncertain.

Comparison with other scores

We compared our rule's performance to the performance of previously published clinical prediction rules (PAM [19], PAR [20],

MPI [21]) on our testing cohort (Table 5). Compared with previously published rules, our score achieves the highest sensitivity, and is most predictive, having the highest positive and negative prediction values, while maintaining relatively similar specificity and false negative rates. Interestingly, the previously published morbidity scores PAM, PAR, MPI do not show a statistically significant difference between the scores of those who survive to hospital discharge and those who do not (P-values for χ^2 for MPI 0.10, PAM 0.38, PAR 0.55). There is a statistically significant correlation between the Dartmouth Scores (DS) of patients who are discharged alive and those who are not (P-value for χ^2 for DS is 0.01). It is important to note that despite our use of separate derivation and validation cohorts, one would reasonably expect our rule to outperform previous rules on our dataset given that our patient demographics are likely slightly different from those used to create previous rules. Follow-up studies will be informative with respect to how well our rule generalizes.

		Test
PAM	Specificity	0.78
	Sensitivity	0.3
	FN rate	0.7
	LRP	1.34
	LRN	0.9
	PPV	0.8
	NPV	0.28
	P-value	0.382
PAR	Specificity	0.86
	Sensitivity	0.18
	FN rate	0.82

	LRP	1.32
	LRN	0.95
	PPV	0.79
	NPV	0.27
	P-value	0.548
MPI	Specificity	0.89
	Sensitivity	0.24
	FN rate	0.76
	LRP	2.16
	LRN	0.86
	PPV	0.86
	NPV	0.29
	P-value	0.099
DS Cutoff 7, 9	Specificity	0.82
	Sensitivity	0.43
	FN rate	0.57
	LRP	2.42
	LRN	0.7
	PPV	0.86
	NPV	0.35
	P-value	0.01

FN rate: False Negative Rate, LRP: Likelihood ratio of a positive result, LRN: Likelihood ratio of a negative result, PPV: Positive Predictive Value, NPV: Negative Predictive Value, P-value: chi-square p-value for clinical prediction vs. actual outcome.

Table 5: Comparison of test characteristics The Dartmouth Score with other published scores.

Discussion

Discussion of code status has become a routine part of many hospital admissions, but is still performed without sufficient discussion of or knowledge about the patient's chance of surviving resuscitation. We used two statistical techniques to create a simple but clinically useful prediction tool. The Dartmouth Score uses information easily obtainable on admission to provide physicians and their patient's individualized information about their probability of survival after in-hospital cardiopulmonary arrest and attempted resuscitation.

Our dataset is the largest to date used to develop a clinical prediction rule for non-survival after in-hospital cardiac arrest. We used standardized definitions of medical diagnoses, physical findings and laboratory tests to determine each individual's features. We combined our comprehensive retrospective chart review with rigorous computational methods to create a relatively sensitive and specific score with a statistically significant correlation between predicted and actual outcomes. We attempted to maximize specificity since most physicians would prefer to attempt several unsuccessful resuscitations

rather than risk withholding resuscitation from a single patient in whom it would be successful. Our two-threshold prediction rule is more sensitive than other previously published scores. Our prediction rule has the additional advantage that it can indicate when there is insufficient information to make a prediction. Given the complexity of many patients' medical state, the identification of a 'grey zone' is clinically reasonable.

As mentioned above, our study population (derivation plus validation cohorts), had an average of 25.7% of patients survive CPR to hospital discharge. The Dartmouth Score was able to provide more patient-specific information about chances of surviving to hospital discharge. Patients with a score of 7 or lower on the Dartmouth Score had a 38.5% chance of surviving to hospital discharge after CPR, while those patients with a score of 9 or higher had a less than 15% chance of surviving to hospital discharge after CPR. This information may be helpful to clinicians when attempting to translate a patient's Dartmouth Score into actionable information for a patient and their family.

Our prediction rule has reasonable face validity in addition to our successful empirical validation. The multifaceted nature of the relevant

medical phenomena makes it difficult to fully rationalize the inclusion of each clinical variable into our prediction rule. In the next few paragraphs we propose potential medical justification to support our rule's inclusion of several clinical variables. These ideas are intended to spur discussion and are not meant as definitive explanations.

Many of the features of our prediction rule (age>70 years, angina pectoris, dementia, CVA, cancer, comatose state and hypotension) are included as risk factors in previous mortality scores (Table 6). Angina

pectoris is included as a risk factor in PAM and MPI but is a protective factor in our study. This difference may be because of how angina pectoris was defined; we were more rigorous in our definition of angina pectoris and did not include unstable angina as a feature. Chronic, stable angina pectoris may be a surrogate marker for VT arrest, which is known to lead to better survival rates than other forms of cardiac arrest [28].

Comparison of Dartmouth Score (DS) with PAM, PAR and MPI scores				
	DS	PAM	PAR	MPI
Age >70	2		2	1
Angina Pectoris		1		1
No Angina Pectoris	4			
Dementia				2
No Dementia	1			
Respiratory Insufficiency				
No Respiratory Insufficiency	2			
CVA	5	1		2
Hypotension	3	3		3
Abnl PaO ₂	3			
Abnl Bicarb	3			
Coma	2	1		1
Cancer	1	3		2
Metastatic Cancer			10	
Non-Metastatic Cancer			3	
Homebound		3	5	2
Heart Failure		1		1
Cirrhosis		1		
Sepsis		1	5	1
Pneumonia		3	3	2
Acute MI		1	-2	1
Ventilated		1		1
Gallop		1		1
Oliguria		1		1
Abnl Creatinine		3	3	2
<i>Cutoff</i>	≤7 and ≥9	>6	>7	>6

Table 6: Comparison of the Dartmouth Score (DS) with previously published decision rules.

Dementia is included as a risk factor in MPI but is protective in our study. Our study had far fewer patients with dementia than expected (3.6% of the patients in our sample had dementia, compared to a

national prevalence of dementia in the elderly of 13.9% [29]). We suspect that our finding reflects that only a subsection of healthier demented patients undergo CPR as increased use of advanced

directives and living wills prevent resuscitation in patients with end-stage dementia.

Chronic respiratory insufficiency is unique to our score. Patients with respiratory insufficiency are more likely to be exposed to theophylline and beta-adrenergic agonists, which can cause ventricular ectopy including ventricular tachycardia. In addition, COPD is associated with prolonged QT which can degenerate into torsades de pointes. Increased survival after CPR for patients with chronic respiratory insufficiency may reflect these more treatable arrhythmias.

Abnormal laboratory results of partial pressure of oxygen in arterial blood (PaO₂) and serum bicarbonate are also unique to our score. Review of patients with abnormal PaO₂ found hypoxia significant enough to require ventilation, and is therefore in line with prior scores use of indicators of acute respiratory insufficiency (ventilator-dependent and pneumonia) as risk factors for non-survival. Review of patients with abnormal serum bicarbonate indicated that 91% of patients with abnormal levels suffered from severe acidemia, with the remaining patients having chronic respiratory acidosis. Low serum bicarbonate may thus be a proxy for organ infarction (lactic acidosis), diabetic ketoacidosis, renal failure, or fatal toxic ingestions.

Poor functional status has been shown to correlate with poor outcomes in other studies. We had hoped to incorporate functional status in our score, but the lack of data reflecting functional status in the sicker, intensive-care based population, prevented us from doing so.

Our rule was derived using data from a patient population that underwent CPR. Patients with DNR orders who did not undergo CPR were not captured in our study. Hence, our rule is biased towards patients who opted against a DNR order.

The Dartmouth Score was developed based on data collected at a rural, academic, tertiary-care center serving a largely Caucasian population. Differences in survival after CPR based on location and size of hospital as well as race have been documented [3]. The Dartmouth Score should be evaluated outside our institution. The score was based on data collected retrospectively and validated with an independent validation cohort. Due to the rarity of in-hospital cardiopulmonary arrest, prospective validation of the tool is impractical. Validation retrospectively at multiple centers would provide further evidence as to the accuracy and clinical utility of The Dartmouth Score. Our score may be clinically useful after it is validated by other cohorts.

The complex physiologic process of cardiac arrest, resuscitation, and recovery makes it unlikely that a handful of features will be able to predict outcomes with extremely high accuracy. However, the Dartmouth Score may be a useful addition to medical expertise and clinical judgment in evaluating and communicating an individual's probability of survival after in-hospital cardiopulmonary arrest. Our model may provide helpful information to guide physicians and patients in shared decision making on this important subject.

Acknowledgements

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