Risk Stratification for In-Hospital Mortality in Acutely Decompensated Heart Failure

Classification and Regression Tree Analysis

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Context Estimation of mortality risk in patients hospitalized with acute decompensated heart failure (ADHF) may help clinicians guide care.

Objective To develop a practical user-friendly bedside tool for risk stratification for patients hospitalized with ADHF.

Design, Setting, and Patients The Acute Decompensated Heart Failure National Registry (ADHERE) of patients hospitalized with a primary diagnosis of ADHF in 263 hospitals in the United States was queried with analysis of patient data to develop a risk stratification model. The first 33 046 hospitalizations (derivation cohort; October 2001-February 2003) were analyzed to develop the model and then the validity of the model was prospectively tested using data from 32 229 subsequent hospitalizations (validation cohort; March-July 2003). Patients had a mean age of 72.5 years and 52% were female.

Main Outcome Measure Variables predicting mortality in ADHF.

Results When the derivation and validation cohorts are combined, 37 772 (58%) of 65 275 patient-records had coronary artery disease. Of a combined cohort consisting of 52 164 patient-records, 23 910 (46%) had preserved left ventricular systolic function. In-hospital mortality was similar in the derivation (4.2%) and validation (4.0%) cohorts. Recursive partitioning of the derivation cohort for 39 variables indicated that the best single predictor for mortality was high admission levels of blood urea nitrogen (≥43 mg/dL [15.35 mmol/L]) followed by low admission systolic blood pressure (<115 mm Hg) and then by high levels of serum creatinine (≥2.75 mg/dL [243.1 μmol/L]). A simple risk tree identified patient groups with mortality ranging from 2.1% to 21.9%. The odds ratio for mortality between patients identified as high and low risk was 12.9 (95% confidence interval, 10.4-15.9) and similar results were seen when this risk stratification was applied prospectively to the validation cohort.

Conclusions These results suggest that ADHF patients at low, intermediate, and high risk for in-hospital mortality can be easily identified using vital sign and laboratory data obtained on hospital admission. The ADHERE risk tree provides clinicians with a validated, practical bedside tool for mortality risk stratification.

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Heart failure causes considerable morbidity and mortality and is responsible for a tremendous burden on the health care system in the United States.[1] It accounted for approximately 1 million hospital discharges in 2001, an increase of 164% since 1979, and is associated with an overall annual cost of nearly $29 billion.[1] Reported in-hospital mortality ranges from as low as 2.3% among patients enrolled in clinical trials to 19% in referral hospital series.[2,3]

Despite this dramatic increase in the public health burden of hospitalization for heart failure, models for the risk stratification of patients during admission for acute decompensated heart failure (ADHF) are not well established. Clinical risk prediction tools may be helpful in guiding medical decision making. Patients estimated to be at a lower risk may be managed with less intensive monitoring and therapies available on a telemetry unit or hospital ward, whereas a patient estimated to be at a higher risk may require more intensive management in an intensive

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or coronary care unit. Previous studies, generally based on outpatients with chronic heart failure, have identified a number of variables that are associated with increased mortality, including etiology,[4] patient age,[5] clinical assessment at the time of hospitalization,[4] cardiothoracic ratio,[5,6] peak oxygen consumption,[6] left ventricular ejection fraction,[6] serum sodium concentration,[5] serum creatinine concentration,[4,5] and B-type natriuretic peptide concentration.[7]

In contrast, several factors have limited the development of similar models in patients with ADHF. Lack of a consistent definition of ADHF, different nomenclature to describe its clinical features, incomplete data available in administrative data sets, and varying statistical methods have hindered the development of risk stratification tools.[8-10] Consequently, unlike acute coronary syndromes, in which several systems have been developed for risk stratification,[11-17] no clinically practical method of risk stratification exists for patients hospitalized with ADHF.

The objective of the present analysis was to develop and validate a practical and user-friendly method of risk stratification for in-hospital mortality among patients admitted with ADHF that could be applicable to routine clinical practice. Data used to model risk were taken from the Acute Decompensated Heart Failure National Registry (ADHERE).[18,19] This registry collects detailed hospitalization data from initial presentation in the hospital or emergency department until discharge, transfer, or in-hospital death.[19] As an observational database, these data reflect current real-world treatment patterns and in-hospital clinical outcomes for patients hospitalized with ADHF.

METHODS

The ADHERE registry contains data on patients hospitalized with ADHF in 263 community, tertiary, and academic centers from all regions of the United States.[20] For the purpose of the registry, ADHF is defined as new-onset decompensated heart failure or decompensation of chronic, established heart failure with symptoms sufficient to warrant hospitalization. The design, methods, and patient characteristics in the ADHERE registry have been described previously.[20] Briefly, medical records are reviewed by trained abstractors at participating study sites and data from consecutive eligible male and female patients aged 18 years or older at the time of hospitalization are entered into the registry using an electronic case report form incorporating real-time validity checking.[19,20] These data include demographic information, medical history, baseline clinical characteristics, initial evaluation, treatment received, procedures performed, hospital course, and patient disposition.[18-20] Standardized definitions are used for all patient-related variables, clinical diagnoses, and hospital outcomes.[21]

Institutional review board approval is required for all participating centers; however, informed consent of individuals is not required for registry entry.[19,20] To preserve patient confidentiality, direct patient identifiers are not collected. Data are reported only in aggregate format. Therefore, registry entries reflect individual hospitalization episodes, not individual patients, and multiple hospitalizations of the same patient may be entered into the registry as separate records.

The current analysis is based on the initial 65 275 patient-records entered into the registry. For this analysis, predictors of in-hospital mortality were determined from an initial derivation cohort consisting of data from October 2001 to February 2003 (33 046 hospitalizations). These data were subjected to classification and regression tree (CART) analysis to identify the best predictors of in-hospital mortality and develop the risk stratification model. The validity of this model was then independently assessed using data from the second validation cohort, consisting of the subsequent 32 229 hospitalization episodes (March 2003 to July 2003).

Admission and/or medical staff recorded race/ethnicity, usually as the patient was registered, using hospital-defined race/ethnicity. Patients were assigned to only 1 race/ethnicity category. Prior studies in patients hospitalized with heart failure have suggested different mortality risk based on race/ethnicity. Race/ethnicity was also a significant univariate predictor of in-hospital mortality in the ADHERE derivation cohort. Race/ethnicity was thus included as one of the 39 variables for CART and logistic regression analysis.

Model Development

The CART method is an empirical, statistical technique based on recursive partitioning analysis.[22-24] Unlike multivariable logistic regression, it is well suited to the generation of clinical decision rules.[23,24] Furthermore, because it does not require parametric assumptions, it can handle numerical data that are highly skewed or multimodal and categorical predictors with either an ordinal or nonordinal structure.[23,24] The CART method involves the segregation of different values of classification variables through a decision tree composed of progressive binary splits. Every value of each predictor variable is considered as a potential split, and the optimal split is selected based on impurity criterion (the reduction in the residual sum of squares due to a binary split of the data at that tree node). When missing values are encountered in considering a split, they are ignored and the probability and impurity measures are calculated from the nonmissing values of that variable. Each parent node in the decision tree produces 2 child nodes, which in turn can become parent nodes producing additional child nodes. This process continues with both tree building and pruning until statistical analysis indicates that the tree fits without overfitting the information contained in the data set.[23] As a result, CART analysis produces decision trees that are simple to interpret and may be applied at the bedside.

An open-source adaptation of the CART algorithm (tree library in S-PLUS, version 6.0, Insightful Corp, Seattle, Wash) was used to analyze 39 potential clinical variables of interest in the

derivation cohort (TABLE 1). These variables were selected from 80 variables collected in the ADHERE registry by virtue of predicting in-hospital mortality on univariate analysis or having been identified in previous published studies as risk factors for mortality. Nodes in the CART tree were constrained to have a minimum size of 800 records in parent nodes and 400 records in final child nodes. A 10-fold cross-validation was used to assess the predictive ability of the tree model. Mortality was calculated for each of the terminal nodes in the CART tree and used to generate the risk stratification model. The predictive value of this model was then assessed by determination of mortality odds ratios (ORs) and 95% confidence intervals (CIs) between risk groups.

Table 1. Variables Tested for Their Predictive Potential for In-Hospital Mortality

Variable	Records in Derivation Data Set With Missing Data, %
Demographics	
Age	0
Sex	0
Height	47.6
Weight	15.1
Race/ethnicity	0
Primary insurance*	0.8
Heart failure history	
Prehospital	0
Ischemic etiology	0
Baseline NYHA class	91.7
NYHA class at presentation	90.1
Medical history	
Coronary artery disease	0
Prior myocardial infarction	0
Prior revascularization	0
Atrial fibrillation	0
Congestion (first x-ray)	10.1
Chronic obstructive pulmonary disease	0
Chronic renal insufficiency	0
Diabetes	0
Duration of symptoms	19.3
Fatigue	0
Hyperlipidemia	0
Hypertension	0
Peripheral edema	0
Peripheral vascular disease	0
Rales	0
Stroke/transient ischemic attack	0
Ventricular tachycardia/ventricular fibrillation	0
Laboratory values	
B-type natriuretic peptide	81.9
Blood urea nitrogen†	2.2
Cardiac enzymes	44.6
Creatinine†	2.1
Dyspnea at rest	0
Hemoglobin	4.0
QRS duration >120 ms	16.2
Qualitative LVEF: prehospital or initial evaluation	20.1
Sodium	2.2
Initial vital signs	
Diastolic blood pressure	0.5
Systolic blood pressure†	0.8
Heart rate	0.7

Abbreviations: LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
*Main insurance company covering the patient's hospital admission (eg, Medicare, Medicaid, commercial [fee for service], health maintenance organization, Veterans Administration, self-pay).
†Strongest predictors of in-hospital mortality.

Model Validation

The ability of the derived risk tree to identify ADHF patients at low, intermediate, and high risk for in-hospital mortality was tested. The patients from the validation cohort were classified into risk groups based on the CART tree. Mortality for these risk groups and the mortality ORs and 95% CIs between risk groups were determined and these data were compared with those of the derivation cohort.

Finally, a multivariate logistic regression model was constructed from the derivation cohort (logistic procedure in SAS version 8.2, SAS Institute Inc, Cary, NC), tested in the validation cohort, and the accuracy of the CART and logistic regression models was compared using area under receiver operating characteristic curves in the derivation and validation cohorts.

RESULTS

Baseline characteristics and main outcomes of the 33 046 hospitalization episodes used to develop the model (derivation cohort) and the 32 229 hospitalization episodes used to test the model (validation cohort) are shown in TABLE 2 and TABLE 3. The derivation and validation cohorts were similar with respect to age at admission; sex distribution; heart failure history; medical history; and clinical symptoms, vital signs, and laboratory values (Table 2). Clinical outcomes were also similar between the 2 cohorts (Table 3).

Of the 39 variables evaluated, the CART method identified blood urea nitrogen (BUN) level of 43 mg/dL or higher (≥15.35 mmol/L) at admission as the best single discriminator between hospital survivors and nonsurvivors. The next best predictor of in-hospital mortality in both the higher and lower BUN

nodes was systolic blood pressure (SBP) at a discrimination level of less than 115 mm Hg. For the node with patients having a BUN level of 43 mg/dL or higher (≥15.35 mmol/L) and SBP of less than 115 mm Hg, a serum creatinine level of 2.75 mg/dL or higher (≥243.1 µmol/L) provided additional prognostic value. FIGURE 1 depicts the final tree generated by the CART analysis along with the mortality data for each child node of this tree. These branch points permit patient stratification into 5 risk groups: high risk (BUN level ≥43 mg/dL [≥15.35 mmol/L], SBP <115 mm Hg, and creatinine level ≥2.75 mg/dL [≥243.1 µmol/L]), intermediate risk 1 (BUN level ≥43 mg/dL [≥15.35 mmol/L], SBP <115 mm Hg, and creatinine level <2.75 mg/dL [<243.1 µmol/L]), intermediate risk 2 (BUN level ≥43 mg/dL [≥15.35 mmol/L] and SBP ≥115 mm Hg), intermediate risk 3 (BUN level <43 mg/dL [<15.35 mmol/L] and SBP <115 mm Hg), and low risk (BUN level <43 mg/dL [<15.35 mmol/L] and SBP ≥115 mm Hg). TABLE 4 summarizes the clinical characteristics of patients in these 5 risk groups. The mortality OR between the high- and low-risk groups was 12.9 (95% CI, 10.4-15.9), with statistically significant differences in mortality risk detected between all risk groups except intermediate risk groups 2 and 3 (TABLE 5). Although additional risk nodes involving additional variables could be generated, they offered little incremental risk discrimination.

The decision tree generated by CART analysis of the derivation cohort was tested for its ability to risk stratify patients in the validation cohort. This risk tree was able to stratify patients into high, intermediate, and low risk (FIGURE 2). The mortality OR between the high- and low-risk groups was 10.4 (95% CI, 8.4-13.0), with statistically significant differences detected between all risk groups except intermediate risk groups 2 and 3 (Table 4). These absolute mortality rates, as well as the clinical characteristics and mortality ORs between risk groups, were similar to those of the derivation cohort (Table 4 and Table 5)

Table 2. Demographic and Clinical Characteristics*

	Derivation Cohort	Validation Cohort
	(n = 33 046)	(n = 32 229)
Age, mean (SD), y	72.5 (13.9)	72.5 (14.0)
Female	17 204 (52)	16 584 (51)
Current smoker	4202 (13)	4162 (13)
Heart failure history	25 368 (77)†	24 027 (75)
Severity of ADHF‡		
Mild	7352 (22)	7635 (24)
Moderate	15 208 (46)	14 828 (46)
Severe	10 486 (32)	9766 (30)
Clinical symptoms		
Dyspnea	29 908 (91)	28 707 (89)
Peripheral edema	22 042 (67)	21 347 (66)
Rales	22 896 (69)	21 566 (67)
Blood pressure, mean (SD), mm Hg		
Systolic	143.7 (32.6)	144.7 (32.5)
Diastolic	77.3 (20.0)	78.4 (20.2)
Laboratory values, mean (SD)		
Blood urea nitrogen, mg/dL	32.2 (21.6)	31.5 (20.8)
Creatinine, mg/dL	1.8 (1.7)	1.8 (1.7)
Sodium, mEq/L	138.0 (5.0)	138.3 (4.8)
Hemoglobin, g/dL	12.5 (2.8)	12.4 (2.6)
QRS duration, ms	111.1 (50.2)	115.1 (42.3)
Medical history		
Coronary artery disease	19 584 (59)	18 188 (56)
Renal insufficiency	9513 (29)	9603 (30)
Atrial fibrillation	10 129 (31)	9776 (30)
Diabetes	14 522 (44)	14 296 (44)
Hypertension	23 602 (71)	23 355 (72)
Hyperlipidemia	11 320 (34)	10 995 (34)
Peripheral vascular disease	5561 (17)	5834 (18)
COPD/asthma	10 132 (31)	9967 (31)
LVEF ≥40%§	11 689 (44)	12 221 (47)
	(n = 33 029)	(n = 32 197)
Long-term medication use		
ACE inhibitor	13 661 (41)	13 165 (41)
Angiotensin receptor blocker	3666 (11)	3815 (12)
Anti-arrhythmic	3717 (11)	3553 (11)
Aspirin	12 235 (37)	11 988 (37)
β-Blocker	14 814 (45)	15 353 (48)
Calcium channel blocker	7560 (23)	7369 (23)
Clopidogrel	2795 (8)	3305 (10)
Digoxin	9736 (29)	8807 (27)
Diuretics	23 370 (71)	22 314 (69)
Glitazone	1411 (4)	1554 (5)
Lipid-lowering agent	9864 (30)	9998 (31)
NSAID	2047 (6)	1712 (5)
Nitrate	9148 (28)	8450 (26)
Peripheral vasodilator	1721 (5)	1522 (5)
Warfarin	7629 (23)	7556 (23)

Abbreviations: ACE, angiotensin-converting enzyme; ADHF, acute decompensated heart failure; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NSAID, nonsteroidal anti-inflammatory drug.
SI conversion factors: To convert urea nitrogen to mmol/L, multiply by 0.357; creatinine to µmol/L, multiply by 88.4.
*Values are expressed as number (percentage) unless otherwise indicated. Data are based on patients with available data for each characteristic.
†One patient did not have heart failure history, so the total No. of patients was 33 045.
‡Determined using a University of North Carolina severity score, with scores of less than 4 representing mild; 4 to 6, moderate; and more than 6, severe. The total score ranges from 0 to 9 and is calculated by adding 1 if congestion is present on the chest radiograph; 1 if rales are present; 1 if edema is present; 2 if fatigue is present; and 1, 2, 3, or 4 for unspecified dyspnea, dyspnea with moderate activity, dyspnea with minimal activity, or dyspnea at rest, respectively.
§Of 26 408 participants in derivation cohort and of 25 756 participants in validation cohort.

and comparable risk stratification occurred when the analysis was limited to the subset of validation patients with new onset heart failure (in-hospital mortality: 23.6% in the high-risk group; 20.0%, intermediate risk group 1; 5.0%, intermediate risk group 2; 5.1%, intermediate risk group 3; and 1.8%, low-risk group).

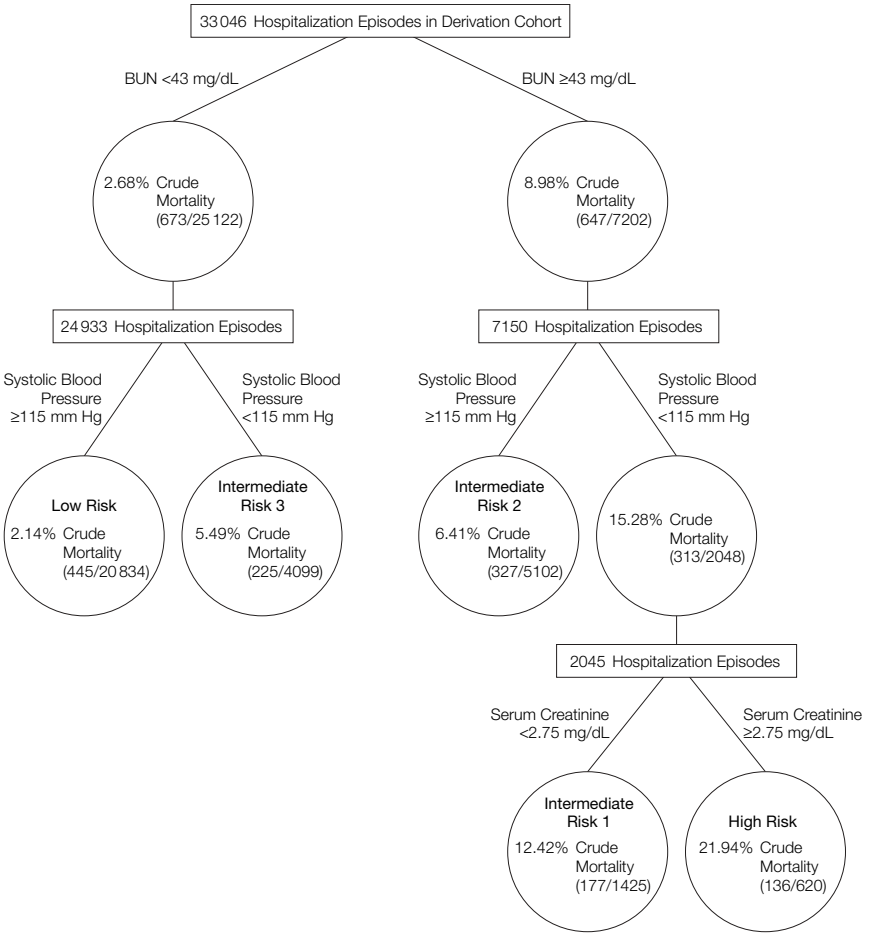
Multivariate logistic regression identified BUN level, SBP, heart rate, and age as the most significant mortality risk predictors:

log odds of mortality =
0.0212 × BUN – 0.0192 × SBP
+ 0.0131 × heart rate + 0.0288
× age – 4.72.

Table 3. Main Outcomes

	Derivation Cohort (n = 33 046)	Validation Cohort (n = 32 229)
Deaths, No. (%)	1383 (4.2)	1302 (4.0)
Length of stay, mean (SD), d		
Total hospital	5.9 (5.7)	5.8 (5.2)
Intensive or coronary care unit	4.0 (5.8)	3.7 (4.5)

Figure 1. Predictors of In-Hospital Mortality and Risk Stratification for the Derivation Cohort



Each node is based on available data from registry patient hospitalizations for each predictive variable presented. BUN indicates blood urea nitrogen. To convert BUN to mmol/L, multiply by 0.357; creatinine to μmol/L, multiply by 88.4.

The addition of 24 predictors did not meaningfully increase the accuracy of this model. FIGURE 3 compares in-hospital mortality rates in the derivation and validation cohorts based on risk groups determined by logistic regression. Based on the area under the receiver operating characteristic curves, the accuracy of the CART model (derivation cohort: 68.7%; validation cohort: 66.8%) was modestly less than that of the more complicated logistic regression model (derivation cohort: 75.9%; validation cohort: 75.7%).

COMMENT

This analysis of more than 65 000 recent ADHF hospitalizations in patients demographically and clinically similar to those seen in other large community- or Medicare-based evaluations[25-27] demonstrates that the risk of in-hospital mortality can be reliably estimated using routinely available vital signs and laboratory data obtained on hospital admission. Overall, in-hospital mortality was 4.1%, but this mortality risk varied more than 10-fold (from 2.1% to 21.9%) based on the patient's initial SBP and levels of BUN and creatinine.

Multiple evaluations of patients hospitalized for heart failure have demonstrated an association between clinical outcomes and indices of renal function and blood pressure.[28-32] In the Enhanced Feedback for Effective Cardiac Treatment study, increasing BUN levels and decreasing SBP were significant and independent predictors of both 30-day and 1-year mortality.[28] In the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure study, these same parameters were significant and independent predictors of mortality or rehospitalization.[31] Similarly, in a retrospective review of 1004 consecutive patients hospitalized for heart failure at 11 geographically diverse hospitals, worsening renal function was associated with a 7.5-fold increase (95% CI, 2.9- to 19.3-fold increase) in the adjusted risk of in-hospital mortality.[32] In a prospective

Table 4. Demographic and Clinical Characteristics of Risk Groups

		Intermediate Risk			
	High Risk*	1†	2‡	3§	Low Risk‖
		Derivation Cohort			
Total No. of patients	620	1425	5102	4099	20 834
Age, mean (SD), y	73.6 (12.4)	74.9 (12.1)	73.9 (12.8)	69.7 (15.1)	72.6 (13.9)
No. (%) of patients					
Female	187 (30)	548 (38)	2627 (51)	1761 (43)	11 608 (56)
Coronary artery disease	446 (72)	995 (70)	3365 (66)	2451 (60)	11 770 (57)
Renal insufficiency	496 (80)	720 (51)	3586 (70)	727 (18)	3704 (18)
Diabetes	312 (50)	662 (46)	3043 (60)	1377 (34)	8689 (42)
COPD	156 (25)	452 (32)	1522 (30)	1307 (32)	6420 (31)
No./total (%) of patients with systolic dysfunction¶	400/512 (78)	912/1174 (78)	2007/3906 (51)	2326/3331 (70)	8636/16 761 (52)
		Validation Cohort			
Total No. of patients	592	1270	4834	3882	20 820
Age, mean (SD), y	74.0 (12.7)	74.7 (11.6)	74.0 (13.1)	70.0 (15.2)	72.6 (14.1)
No. (%) of patients					
Female	180 (30)	488 (38)	2501 (52)	1660 (43)	11 391 (55)
Coronary artery disease	407 (69)	871 (69)	3002 (62)	2205 (57)	11 236 (54)
Renal insufficiency	479 (81)	650 (51)	3402 (70)	720 (19)	4081 (20)
Diabetes	298 (50)	590 (46)	2887 (60)	1337 (34)	8804 (42)
COPD	160 (27)	406 (32)	1466 (30)	1263 (33)	6436 (31)
No./total (%) of patients with systolic dysfunction	352/472 (75)	774/1054 (73)	1753/3641 (48)	2166/3174 (68)	8115/16 797 (48)

Abbreviation: COPD, chronic obstructive pulmonary disease.
*Defined as blood urea nitrogen level of 43 mg/dL or higher (≥15.35 mmol/L), systolic blood pressure of less than 115 mm Hg, and creatinine level of 2.75 mg/dL or higher (≥243.1 μmol/L).
†Defined as blood urea nitrogen level of 43 mg/dL or higher (≥15.35 mmol/L), systolic blood pressure of less than 115 mm Hg, and creatinine level of less than 2.75 mg/dL (<243.1 μmol/L).
‡Defined as blood urea nitrogen level of 43 mg/dL or higher (≥15.35 mmol/L) and systolic blood pressure of 115 mm Hg or higher.
§Defined as blood urea nitrogen level of less than 43 mg/dL (<15.35 mmol/L) and systolic blood pressure of less than 115 mm Hg.
‖Defined as blood urea nitrogen level of less than 43 mg/dL (<15.35 mmol/L) and systolic blood pressure of 115 mm Hg or higher.
¶Patients had a left ventricular ejection fraction of less than 40% or moderate to severe impairment.

analysis of 412 patients hospitalized at a single institution, the 6-month mortality risk increased with decreasing renal function, which was determined by the change in creatinine levels relative to baseline.[30] Renal dysfunction causes further congestion and neurohormonal activation, which are factors associated with adverse outcomes in patients with heart failure.[33]

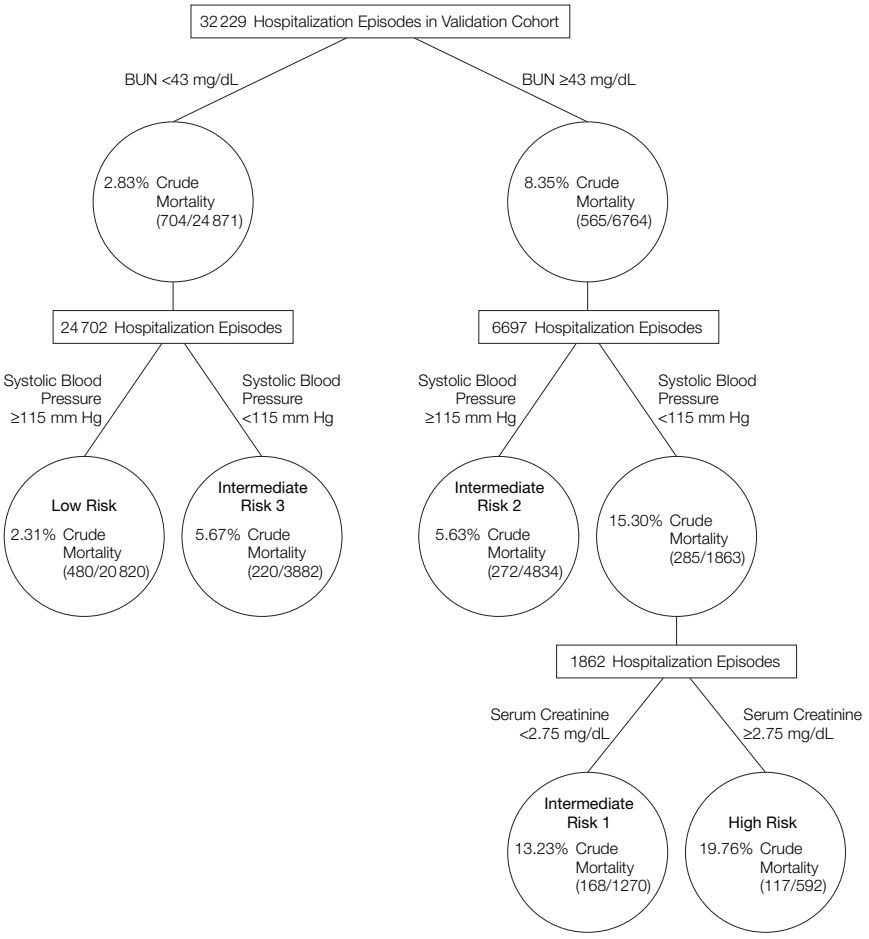
In addition to these parameters, other parameters that have been correlated with clinical outcomes in patients hospitalized with heart failure include age[3,28,29,34]; sex[34]; heart failure etiology[34,35]; history of previous heart failure hospitalizations[31]; comorbid conditions such as cerebrovascular disease, dementia, chronic obstructive pulmonary disease, hepatic cirrhosis, and cancer[28,34]; respiratory rate[28]; anemia[31,36,37]; serum sodium concentration[28]; B-type natriuretic peptide levels[38,39]; left ventricular ejection fraction[29]; and heart failure therapy.[3] Because multiple risk factors can exist in the same patient, risk factor analysis (to be meaningful) must consider factors in combination rather than isolation. Because previous evaluations tended to treat these factors as isolated entities, they have not produced a

Table 5. In-Hospital Death Between Risk Groups*

	Derivation Cohort		Validation Cohort	
Risk Group Analysis	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
High vs				
Low	12.9 (10.4-15.9)	<.001	10.4 (8.4-13.0)	<.001
Intermediate 3	4.8 (3.8-6.1)	<.001	4.1 (3.2-5.2)	<.001
Intermediate 2	4.1 (3.3-5.1)	<.001	4.1 (3.3-5.2)	<.001
Intermediate 1	2.0 (1.5-2.5)	<.001	1.6 (1.2-2.1)	<.001
Intermediate 1 vs				
Low	6.5 (5.4-7.8)	<.001	6.5 (5.4-7.8)	<.001
Intermediate 3	2.4 (2.0-3.0)	<.001	2.5 (2.1-3.1)	<.001
Intermediate 2	2.1 (1.7-2.5)	<.001	2.6 (2.1-3.1)	<.001
Intermediate 2 vs				
Low	3.1 (2.7-3.6)	<.001	2.5 (2.2-2.9)	<.001
Intermediate 3	1.2 (1.0-1.4)	.07	1.0 (0.8-1.2)	.94
Intermediate 3 vs low	2.7 (2.2-3.1)	<.001	2.5 (2.2-3.0)	<.001

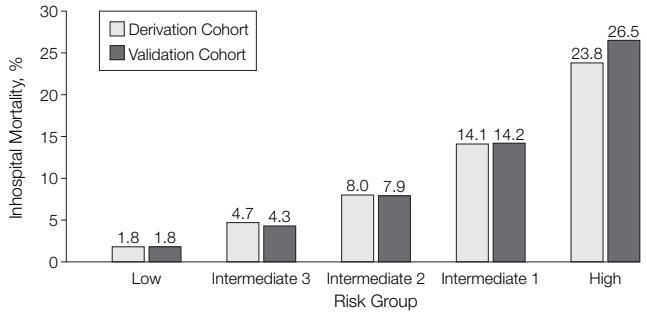
Abbreviations: CI, confidence interval; OR, odds ratio.
*See Table 4 footnotes for definitions of risk determined by blood urea nitrogen, systolic blood pressure, and creatinine.

Figure 2. Predictors of In-Hospital Mortality and Risk Stratification for the Validation Cohort



Each node is based on available data from registry patient hospitalizations for each predictive variable presented. BUN indicates blood urea nitrogen. To convert BUN to mmol/L, multiply by 0.357; creatinine to μmol/L, multiply by 88.4.

Figure 3. In-Hospital Mortality Based on the Logistic Regression Model



No. of Patients					
Derivation Cohort	20764	4087	5087	1419	617
Validation Cohort	20518	4010	4919	1370	471

Log odds of mortality was calculated for all records in the derivation cohort and risk group cut points established at percentile rankings equivalent to those of the classification and regression tree model (65th, 78th, 94th, and 98th percentiles).

clinically practical way of integrating various factors to stratify risk in heart failure patients.[40]

Unlike ADHF, several risk stratification schemes already exist for patients with acute coronary syndromes.[11-17] These schemes are typically based on multivariable analysis using logistic regression or Cox proportional hazards models. Although schemes using as few as 3[13,17] to more than 20 variables are available,[12] an acute coronary syndromes risk scoring scheme generally involves 7 to 10 variables.[11,14-16] Such clinical prediction models have been interpreted to be helpful for risk stratification and management of acute coronary syndrome patients and have been integrated into national guidelines.[11]

Although no in-hospital mortality risk stratification scheme is available for patients hospitalized with heart failure, a heart failure survival score has been developed and independently validated for ambulatory outpatients with heart failure.[40,41] This score, based on 7 variables—heart failure etiology, heart rate, blood pressure, serum sodium concentration, intraventricular conduction time, left ventricular ejection fraction, and peak oxygen consumption—stratifies patients into low (16%), medium (39%), and high (50%) mortality risk categories.[40] In addition, hospitalization data have been used to develop a risk score for heart failure readmission.[42] This risk score, which is based on 16 variables, was moderately predictive in a derivation cohort but it has not been independently validated in a second cohort.[42]

A significant disadvantage of multivariable-generated risk schemes is their complexity. The number of variables and mathematical functions involved frequently require access to a computer or an electronic calculator to generate a score and to determine risk, making them impractical for bedside assessment unless such tools are readily available. Even when converted to point scores, the tools derived from a multivariate model still require a nomogram reference to convert a point score to risk. Similar to multivariate regression tech-

niques, the CART method can detect interactions between variables.[24] Moreover, it yields a decision tree that is relatively easy to apply at the bedside, leading to its potential use in a wide variety of clinical conditions, including infections[43] and neurological,[44] oncological,[45,46] and cardiac[47] disorders.

In the current evaluation, the CART method identified 3 of 39 potential variables as significant predictors of in-hospital mortality risk. In a simple 2- to 3-step process, these variables permit identification of patients with low, intermediate, or high risk for in-hospital mortality. Furthermore, the accuracy of this model, which can be easily applied at the bedside, is close to that of the more complicated model derived from logistic regression. Alternately, if computer access or a pocket digital assistant is available at the bedside, the model derived from logistic regression may have advantages.

These validated models should aid medical decision making in patients hospitalized with ADHF. Patients judged to be at higher risk may receive higher-level monitoring and earlier, more intensive treatment for ADHF, while patients estimated to be at lower risk may be reassured and managed less intensively. In addition, these models may prove to be valuable in designing clinical trials to evaluate heart failure therapies because they permit risk to be balanced across treatment groups[45] and allow for selective inclusion criteria to enroll only patients at high risk for in-hospital mortality.

Potential limitations of the current analysis must be acknowledged. Real-world practice information can be both an advantage and a disadvantage of analyses based on registry data. Study results can be influenced by differences in disease assessment, treatment, and documentation patterns at participating institutions. The ADHERE registry reflects patients cared for by thousands of clinicians at hundreds of hospitals across the country and thus has an excellent chance to adjust for this variation and create a risk prediction model that is robust for most situations. However, this model may not apply to patients who are cared for in settings that deviate substantially from those in ADHERE. In addition, each patient's actual risk may be influenced by many factors not measured or considered in this model. The CART method favors variables available for analysis in the greatest proportion of patients. Some potential risk factors, such as B-type natriuretic peptide, were obtained in less than 25% of patients. Consequently, there may be additional variables that either were not considered or were considered and rejected because of limited data that could ultimately improve the risk discrimination if assessed in a sufficient number of patients.

Therefore, this model enhances, not replaces, physician assessment. Moreover, because the ADHERE registry does not contain specific patient identifiers, information regarding patient status following hospital discharge is not available. Thus the effects of any of the variables evaluated in this analysis on intermediate- and long-term mortality risks cannot be determined. Similarly, because of the lack of patient identifiers, the analyzed cohorts may contain multiple admissions for the same patient. However, this should not have influenced the study results because the outcome parameter, in-hospital mortality, and the identified risk factors (admission SBP and admission levels of BUN and creatinine) are specific to individual hospitalization episodes. Lastly, the derivation and validation cohorts come from periods that differ both temporally and in duration. Nonetheless, these cohorts are similar in size, baseline characteristics, and clinical outcome. Despite these potential limitations, the current CART-based analysis of the ADHERE registry has created a simple robust tool to predict in-hospital mortality that is easy to use and has good discriminative ability.

In patients hospitalized with ADHF, the risk of in-hospital mortality can be quickly and accurately determined using admission clinical and laboratory variables. Of 39 variables, BUN level of 43 mg/dL or higher (≥15.35 mmol/L), serum creatinine level of 2.75 mg/dL or higher (≥243.1 μmol/L), and SBP of less than 115 mm Hg were independent predictors of high risk for in-hospital mortality in the current CART analysis. On the basis of these 3 variables, ADHF patients can be readily stratified into groups at low, intermediate, and high risk for in-hospital mortality, with mortality risks ranging from 2.1% to 21.9%. The finding that indices of renal status are 2 of the 3 predictors providing the best mortality risk discrimination underscores the importance of renal function in ADHF patients. The continued high mortality for patients hospitalized with ADHF provides a compelling indication to apply tools, such as the risk tree derived in this study, to improve the evaluation and, potentially, management and outcomes of these patients.

Author Contributions: Dr Fonarow had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Fonarow, Adams, Abraham, Yancy.
Acquisition of data: Fonarow, Adams, Abraham, Yancy.
Analysis and interpretation of data: Fonarow, Adams, Abraham, Yancy, Boscardin.
Drafting of the manuscript: Fonarow.
Critical revision of the manuscript for important intellectual content: Adams, Abraham, Yancy, Boscardin.
Statistical analysis: Boscardin.
Administrative, technical, or material support: Abraham.
Study supervision: Fonarow, Adams, Abraham, Yancy.
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