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Predictors of In-Hospital Mortality in Patients Hospitalized for Heart Failure

Insights From the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF)

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Objectives The aim of this study was to develop a clinical model predictive of in-hospital mortality in a broad hospitalized heart failure (HF) patient population.

Background Heart failure patients experience high rates of hospital stays and poor outcomes. Although predictors of mortality have been identified in HF clinical trials, hospitalized patients might differ greatly from trial populations, and such predictors might underestimate mortality in a real-world population.

Methods The OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) is a registry/performance improvement program for patients hospitalized with HF in 259 U.S. hospitals. Forty-five potential predictor variables were used in a stepwise logistic regression model for in-hospital mortality. Continuous variables that did not meet linearity assumptions were transformed. All significant variables ($p < 0.05$) were entered into multivariate analysis. Generalized estimating equations were used to account for the correlation of data within the same hospital in the adjusted models.

Results Of 48,612 patients enrolled, mean age was 73.1 years, 52% were women, 74% were Caucasian, and 46% had ischemic etiology. Mean left ventricular ejection fraction was 0.39 ± 0.18. In-hospital mortality occurred in 1,834 (3.8%). Multivariable predictors of mortality included age, heart rate, systolic blood pressure (SBP), sodium, creatinine, HF as primary cause of hospitalization, and presence/absence of left ventricular systolic dysfunction. A scoring system was developed to predict mortality.

Conclusions Risk of in-hospital mortality for patients hospitalized with HF remains high and is increased in patients who are older and have low SBP or sodium levels and elevated heart rate or creatinine at admission. Application of this risk-prediction algorithm might help identify patients at high risk for in-hospital mortality who might benefit from aggressive monitoring and intervention. (Organized Program to Initiate Lifesaving Treatment In Hospitalized Patients With Heart Failure [OPTIMIZE-HF]; NCT00344513) (J Am Coll Cardiol 2008;52:347–56) © 2008 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

CART = classification and regression tree

HF = heart failure

LVEF = left ventricular ejection fraction

LVSD = left ventricular systolic dysfunction

SBP = systolic blood pressure

SCr = serum creatinine

Acute decompensated heart failure (HF) requiring hospitalization is common and has been steadily increasing: in 2004, there were more than 1 million HF discharges in the U.S., an increase of 175% since 1979 (1). Despite the prevalence of acute HF, research efforts over the last 15 years have focused primarily on chronic HF. As a result, few studies have been conducted specifically in the hospitalized HF population, and data describing clinical characteristics and outcomes for these patients have been lacking.

The increasing incidence and associated morbidity and mortality of acute HF create an urgent need to better understand this patient population. Because risk-prediction models are useful for focusing on factors influencing clinical outcomes, several analyses have been conducted to determine mortality risk after hospitalization for HF, with both clinical trial and administrative databases (2–7). Clinical trial datasets have contributed valuable information, but their general applicability is limited because these trials reflect a select patient group and the findings of risk-prediction models generated from these databases might or might not apply to a broader population (8). Whereas administrative datasets might not adequately capture clinical variables of prognostic importance, observational registries are a useful data source for evaluating event rates and developing risk-prediction models across a representative patient spectrum. With this in mind, an analysis of the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) registry database was conducted to identify predictors of in-hospital mortality in a large, unselected sample of observed patients hospitalized with HF and to develop a practical risk-prediction tool that could be applied in routine clinical practice.

Methods

The OPTIMIZE-HF registry is a national hospital-based registry and quality-improvement program conducted in 259 hospitals across the U.S. The rationale and design have been discussed in detail elsewhere and will be summarized here (9–11). The primary objective of the program was to improve medical care and education given to HF patients by accelerating the initiation of evidence-based, guideline-recommended HF therapies. The OPTIMIZE-HF registry combined a web-based registry data collection tool with a process-of-care intervention that included standing orders, algorithms, and care paths that encouraged the use of evidence-based therapies for all eligible patients (9). The web-based registry collected data on all Joint Commission on Accreditation of Healthcare Organizations performance measures, and these data were available for sites to review and analyze in real time. The registry data coordinating center was Outcome Sciences, Inc. (Cambridge, Massachusetts).

Patients were eligible for registry enrollment if they were ≥18 years of age and the primary reason for their hospital admission was new or worsening HF or if they developed significant HF symptoms during their hospitalization, even if HF was not the reason for their initial admission but was the primary discharge diagnosis (9). The registry enrolled consecutive patients and included patients with left ventricular systolic dysfunction (LVSD), defined as a left ventricular ejection fraction (LVEF) <40% or moderate/severe left ventricular dysfunction by qualitative report; those with preserved systolic function, defined as LVEF ≥40% or qualitatively normal left ventricular function; and those without ventricular function measured. Baseline characteristics, treatment patterns, and in-hospital outcomes were collected on all patients participating in the study. Admission staff, medical staff, or both recorded race/ethnicity, usually as the patient was registered. Prior studies in patients hospitalized with HF have suggested differences in characteristics and outcomes on the basis of race/ethnicity. Automated electronic data checks were used to prevent out-of-range entry or duplicate patients. A database audit was performed, on the basis of predetermined criteria, of a random sample of 5% of the first 10,000 patients verified against source documents (10,11). The protocol was approved by each participating center's institutional review board or through use of a central institutional review board.

Statistical methods. All statistical analyses were performed independently by the Duke Clinical Research Institute, Durham, North Carolina. Data are reported as mean ± SD for continuous variables or percentages of patients with nonmissing values for categorical variables. A logistic model was developed to identify significant predictors of in-hospital mortality. Deaths beyond the first 120 days of hospitalization were censured. There were 30 patients where vital status was missing. Forty-five candidate predictor variables were considered in the model (Table 1). The final model was derived in the population of patients without missing data for any variable retained in the model (Fig. 1). These baseline clinical and treatment factors were applied with both stepwise and backward variable selection techniques with a p value of 0.05 as criteria for both entering and remaining in the model. The restricted cubic spline transformation method was used to determine the functional form for continuous variables. The most common transformation applied for modeling was piecewise linear splines. The final model was repeated with generalized estimating equations to account for the correlation of data within the same hospital in the adjusted models. The final model presented is based on the model including the hospital effect. The SAS statistical software, version 8.2 (SAS Institute Inc., Cary, North Carolina) was used for all statistical analyses.

Table 1 Candidate Predictors Considered in the Model

Baseline characteristics
Age
Female gender
Race (Caucasian, African American evaluated separately)
Medical history/comorbidities
Smoker within the previous year
Internal cardiac defibrillator
Anemia
Atrial arrhythmia
Coronary artery disease
Cerebrovascular accident or transient ischemic attack
Depression
Insulin-treated diabetes
Noninsulin-treated diabetes
Hyperlipidemia
Hypertension
Liver disease
Chronic obstructive pulmonary disease
Pulmonary hypertension
Prior myocardial infarction
Prior revascularization
Renal disease
Reactive airway disease
Peripheral vascular disease
Thyroid abnormality
Ventricular arrhythmia
Pacemaker
Vital signs/clinical characteristics (at admission)
Weight
Heart rate
Systolic blood pressure
Diastolic blood pressure
HF characteristics/history
Ischemic HF
No known prior HF
HF as primary cause of admission
LVSD
Rales
Lower extremity edema
Laboratory data
Admission serum sodium
Admission serum creatinine
Admission hemoglobin
Admission medications
ACE inhibitor
Aldosterone antagonist
Angiotensin receptor blocker
Beta-blocker
Digoxin
Statin
Diuretic

ACE = angiotensin-converting enzyme; HF = heart failure; LVSD = left ventricular systolic dysfunction.

A point scoring system, or nomogram, was developed to predict in-hospital mortality. This score was calculated from the 7 most important predictors from the multivariable logistic regression analysis. The score was determined by the regression coefficient and the range of value of each predictor (12). We used 200 bootstrap re-samples to evaluate the reliability of the regression coefficients and the C-statistic from the reduced model used to create the nomogram. Finally, a classification and regression tree (CART) analysis was performed to compare the ability of the logistic regression model to discriminate mortality compared with this alternative methodology.

Results

The OPTIMIZE-HF enrollment began in March 2003 and was completed in December 2004. A total of 48,612 patients were enrolled from 259 hospitals across all regions of the U.S. Hospitals of all sizes participated in the OPTIMIZE-HF registry, including both academic (48%) and community-based (52%) centers. Of participating centers, 14% perform heart transplantation. The mean age of the overall cohort was 73 years; 52% of the participants were women, and 74% were Caucasian. LVSD was present in 49% of those patients assessed for this variable. The in-hospital mortality rate was 3.8% (n = 1,834), providing an adequate number of events from which to evaluate predictors. Hospital characteristics, patient clinical characteristics at admission, and clinical outcomes are reported in Table 2. Of the 18 variables retained in the model, only 3 were <98% or more complete: race, missing in 2.93%; smoking status, missing in 3.59%; and left ventricular systolic function measured, missing in 15.1%. The overall model was based on complete cases of 37,548 patients and 1,217 deaths (Fig. 1).

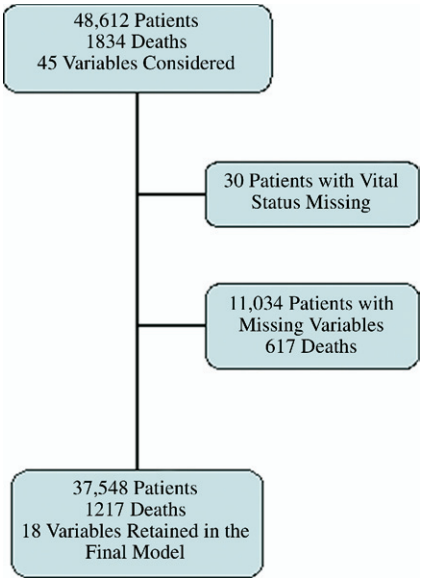

Figure 1 Cohort Derivation and Variable Retention for the Risk Model

Diagram showing number of patients, number of deaths, and variables at each stage in model development

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Univariable predictors of in-hospital mortality are shown in Table 3. On multivariable analysis, 18 of the 45 candidate variables were predictive of mortality (Table 4). The C-statistic for the final model with these variables was 0.77 before adjusting for center effects with generalized estimating equations. The patient characteristics that were most strongly predictive of in-hospital mortality included admission serum creatinine (SCr), admission systolic blood pressure (SBP), and patient age. In-hospital mortality increased 18% for every 0.3 mg/dl increase in SCr up to approximately 3.5 mg/dl; increases above 3.5 mg/dl were not associated with incremental risk. Advanced patient age, per 10-year increase, was associated with a 34% higher risk for in-hospital mortality, whereas increased SBP at admission, up to a threshold of approximately 160 mm Hg, was associated with a lower risk of in-hospital mortality: each 10-mm Hg increase up to 160 mm Hg was associated with a 17% reduction in in-hospital mortality.

Increased risk of in-hospital mortality was associated with several comorbid conditions, including liver disease, past cerebrovascular events, peripheral vascular disease, and chronic obstructive pulmonary disease. Of particular interest was the finding that hyperlipidemia was associated with a lower risk of in-hospital mortality, particularly because a statin or other lipid-lowering therapy was prescribed in only 66% of patients with hyperlipidemia at the time of admission. Diabetes, gender, and coronary artery disease were not significant predictors of mortality.

Interestingly, patients were at lower risk if HF was diagnosed for the first time during the index admission. Patients were also significantly more likely to survive the hospitalization if HF was listed as the primary cause of admission. African-American race and a history of smoking within the previous 12 months were factors associated with a lower in-hospital mortality risk.

Of note, patients taking an angiotensin-converting enzyme inhibitor or beta-blocker at the time of admission faced lower risk of in-hospital mortality, whereas other medications including digoxin, angiotensin-receptor blocker, statin, and diuretics did not significantly predict mortality.

Table 2 Hospital Characteristics, Baseline Patient Clinical Characteristics, and Clinical Outcomes

	Overall Registry	Patients Surviving Hospital Stay	Patients Dying During Hospital Stay	p Value for Surviving vs. Dying
Hospital characteristics, n (%)	n = 259			
Academic hospital	118 (48)			
Transplant hospital	34 (14)			
Intervention hospital	163 (67)			
Patient characteristics	n = 48,612	n = 46,778	n = 1,834	
Mean age, yrs (SD)	73.2 (14.0)	73.0 (14.0)	78.5 (11.8)	<0.0001*
Male, %	48	48	51	0.0284
Race, % (n = 47,189)				<0.0001
Caucasian	74	74	83	
African American	18	18	10	
Ischemic etiology, %	46	46	49	0.0067
Hypertensive etiology, %	23	23	16	<0.0001
Chronic obstructive pulmonary disease, %	28	27	32	0.0001
Insulin-treated diabetes, %	17	17	16	0.4364
Noninsulin-treated diabetes, %	25	25	24	0.1929
Smoker, % (smoking status documented, n = 46,869)	17	17	11	<0.0001
Atrial fibrillation, %	31	31	35	0.0002
LVSD, n (% of those with LVF assessed, n = 41,267)	20,118 (48.8)	19,336 (48.5)	782 (56.2)	<0.0001
Mean LVEF, % (SD) (n = 36,115)	39.0 (17.6)	39.1 (17.6)	36.3 (18.3)	<0.0001*
Rales on admission, %	64	64	68	0.0021
Dyspnea on exertion on admission, %	61	62	50	<0.0001
Dyspnea at rest, %	44	44	51	<0.0001
Mean systolic blood pressure, mm Hg (SD)	143 (32.9)	143 (32.8)	125 (30.7)	<0.0001*
Mean heart rate, beats/min (SD)	87 (21.5)	87 (21.4)	89 (22.7)	<0.0001*
Mean sodium, mEq/l (SD)	137.8 (4.7)	137.8 (4.7)	136.6 (5.7)	<0.0001*
Mean creatinine, mg/dl (SD)	1.8 (1.6)	1.7 (1.6)	2.2 (1.6)	<0.0001*
Mean hemoglobin, g/dl (SD)	12.1 (2.0)	12.1 (2.0)	11.7 (2.1)	<0.0001*
Clinical outcomes	n = 48,612	n = 46,778	n = 1,834	
Length of stay, days				0.4562*
Mean	5.7	5.7	4.1	
Median	4.0	4.0	4.0	
In-hospital mortality, %	3.8	—	—	

*Nonparametric test was used to generate p value.

LVEF = left ventricular ejection fraction; LVF = left ventricular function; other abbreviations as in Table 1.

Table 3 Univariable Predictors

Predictor	Odds Ratio	95% CI	Wald Chi-Square	p Value
Age: per 10-yr increase	1.401	1.346–1.459	269.6717	<0.0001
African American	0.512	0.439–0.597	72.6897	<0.0001
Heart rate: per 10 beats/min increase between 65 and 110 beats/min	1.094	1.062–1.127	35.5163	<0.0001
SBP: per 10-mm Hg increase up to 160 mm Hg	0.767	0.752–0.782	686.0916	<0.0001
Diastolic blood pressure: per 10-mm Hg increase up to 100 mm Hg	0.725	0.703–0.747	435.2111	<0.0001
Sodium: per 3-mEq/l decrease; above 140 mEq/l	0.811	0.749–0.879	26.3194	<0.0001
Sodium: per 3-mEq/l decrease; below 140 mEq/l	1.245	1.208–1.283	201.1702	<0.0001
SCr: per 0.3-mg/dl increase up to 3.5 mg/dl	1.168	1.150–1.186	394.9925	<0.0001
Cause of admission: HF vs. other	0.656	0.578–0.743	43.6791	<0.0001
Cerebrovascular accident/transient ischemic attack (prior)	1.328	1.179–1.495	21.8900	<0.0001
Hyperlipidemia	0.708	0.636–0.788	39.7312	<0.0001
Liver disease	1.793	1.345–2.391	15.8274	<0.0001
Smoker within past year	0.590	0.505–0.690	43.9171	<0.0001
Chronic obstructive pulmonary disease	1.233	1.115–1.363	16.5641	<0.0001
Peripheral vascular disease	1.414	1.251–1.597	30.7676	<0.0001
No known HF before this admission	0.524	0.434–0.632	45.7773	<0.0001
LVSD	1.366	1.226–1.522	32.0067	<0.0001
ACE inhibitor at admission	0.700	0.633–0.774	48.5991	<0.0001
Beta-blocker at admission	0.706	0.643–0.776	52.3759	<0.0001

CI = confidence interval; SBP = systolic blood pressure; SCr = serum creatinine; other abbreviations as in Table 1.

In-hospital mortality was evaluated by admission SCr and SBP subgroups. Mortality was lowest (2.5%) in patients with SBP readings above 100 mm Hg and SCr values below 2.0 mg/dl. The highest mortality was evident in patients with low SBP and elevated SCr (Fig. 2).

The risk-prediction nomogram generated from the multivariable model is displayed in Table 5. The risk prediction nomogram is also available at the OPTIMIZE-HF website (13). This model was based on complete cases for the 7 variables: 40,201 patients, and 1,337 fatal events. From this table or the website, one can use common variables collected for a patient at baseline. From each of these variables, a score can be calculated that is directly associated with the probability of in-hospital mortality (Fig. 3). For example, a 50-year-old patient admitted for HF with a heart rate of 82 beats/min, SBP of 91 mm Hg, serum sodium of 126 mmol/l, and SCr of 1.5 mg/dl would have a score of 9 + 2 + 14 + 7 + 7 + 0 = 39. From Figure 3, a score of 39 is associated with a probability of in-hospital mortality of 4%. This model had good discrimination and excellent reliability, as seen in Figure 4. The boot-

Table 4 In-Hospital Mortality Model

Variable	Wald Chi-Square	Odds Radio	95% CI	p Value
SCr: per 0.3-mg/dl increase up to 3.5 mg/dl	335.5	1.18	1.16–1.20	<0.0001
SBP: per 10-mm Hg increase up to 160	107.0	0.83	0.80–0.86	<0.0001
Age: per 10-yr increase	108.5	1.34	1.26–1.41	<0.0001
Heart rate: per 10 beats/min increase between 65 and 110 beats/min	55.1	1.18	1.13–1.24	<0.0001
Sodium: per 3-mEq/l decrease below 140 mEq/l	39.1	1.15	1.10–1.20	<0.0001
Sodium: per 3-mEq/l decrease above 140 mEq/l	6.63	0.87	0.78–0.97	0.0100
HF as primary cause of admission	10.7	0.72	0.60–0.88	0.0011
Liver disease	11.5	2.33	1.43–3.80	0.0007
Prior cerebrovascular accident/transient ischemic attack	18.6	1.37	1.19–1.58	<0.0001
Peripheral vascular disease	12.9	1.32	1.13–1.54	0.0003
Diastolic blood pressure: per 10-mm Hg increase up to 100 mm Hg	12.9	0.90	0.85–0.95	0.0003
Hyperlipidemia	11.1	0.80	0.71–0.91	0.0009
Smoker within past year	12.5	0.70	0.58–0.85	0.0004
No known HF before this admission	10.5	0.65	0.51–0.85	0.0012
African American	11.1	0.71	0.57–0.87	0.0009
LVSD	14.0	1.28	1.13–1.46	0.0002
Chronic obstructive pulmonary disease	6.32	1.19	1.04–1.35	0.0120
ACE inhibitor at admission	7.67	0.84	0.75–0.95	0.0056
Beta-blocker at admission	17.3	0.77	0.68–0.87	<0.0001

The model was based on complete cases of 37,548 patients and 1,217 deaths.
Abbreviations as in Tables 1 and 3.

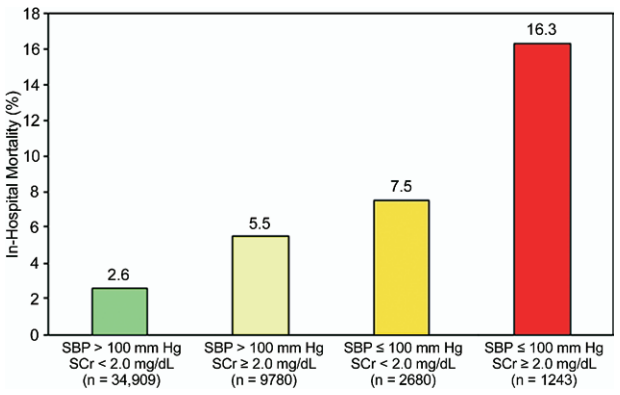

Figure 2 In-Hospital Mortality by SCr and SBP

The relationship between serum creatinine (SCr) and systolic blood pressure (SBP) as measured at hospital admission and in-hospital mortality.

strapped re-sampling indicated that discrimination remained high with a C-statistic of 0.753 (95% confidence interval: 0.741 to 0.765).

Furthermore, this nomogram was applied to admission data for patients hospitalized with acute decompensated HF and enrolled in a previously published randomized controlled trial of acutely decompensated HF, the OPTIME-CHF trial (14). There were 28 in-hospital deaths among the 937 patients included in the trial. The OPTIMIZE-HF nomogram performed well in this highly selected patient population, predicting an in-hospital mortality rate of 2.91% compared with an observed rate of 2.99%, with a C statistic of 0.756. The model was further validated with ADHERE (Acute Decompensated Heart Failure National Registry) data with 181,830 HF patient hospitalization episodes (4,649 in-hospital deaths) at 285 hospitals from October 2001 to May 2005. The OPTIMIZE-HF model performed well in this population with a C statistic of 0.746. Finally, a CART analysis was performed on the OPTIMIZE-HF data and yielded SBP, SCr, age, and heart rate as the variables most discriminative for in-hospital mortality. The C statistic of this CART model was 0.683, indicating the OPTIMIZE-HF logistic regression model and nomogram had superior capability in predicting mortality.

Discussion

These data from OPTIMIZE-HF further reinforce that patients hospitalized with worsening symptoms of HF face a high risk of mortality and provide new insight into the predictors of in-hospital mortality among a representative HF patient population. We observed both similarities and differences between our findings and those of other published risk models (Table 6). Few risk-prediction models have been developed specifically with the hospitalized HF population. With the exception of OPTIMIZE-HF and the ADHERE, the majority of these models were developed with relatively small samples and in highly selected groups of HF patients. In addition, previous data were collected in the early to late 1990s and might not accurately reflect current trends in HF management or outcomes.

The OPTIMIZE-HF registry is most comparable to the ADHERE registry in terms of its scope and temporal relevance. Although the in-hospital mortality rates for ADHERE (4%) and OPTIMIZE-HF (3.8%) are remarkably similar (15), ADHERE used the CART analytic method to determine the best predictors of in-hospital mortality and OPTIMIZE-HF used logistic regression. The 3 factors most predictive of mortality in ADHERE

Table 5 Risk-Prediction Nomogram

Age, yrs	Score	Heart Rate, beats/min	Score	SBP, mm Hg	Score	Sodium, mEq/l	Score	SCr, mg/dl	Score	Primary Cause of Admission	Score	LVSD	Score
20	0	65	0	50	22	110	13	0	0	HF	0	No	0
25	2	70	1	60	20	115	11	0.5	2	Other	3	Yes	1
30	3	75	1	70	18	120	9	1	5				
35	5	80	2	80	16	125	7	1.5	7				
40	6	85	3	90	14	130	4	2	10				
45	8	90	4	100	12	135	2	2.5	12				
50	9	95	4	110	10	140	0	3	15				
55	11	100	5	120	8	145	2	3.5	17				
60	13	105	6	130	6	150	4						
65	14	110	6	140	4	155	6						
70	16			150	2	160	8						
75	17			160	0	165	10						
80	19					170	12						
85	20												
90	22												
95	24												

The nomogram was based on 40,201 patients and 1,337 fatal events.
Abbreviations as in Tables 1 and 3.

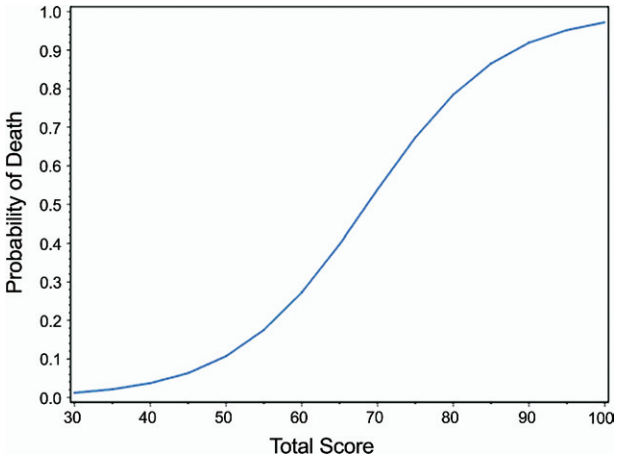

Figure 3 **Association Between Risk Prediction Score and Probability of Death**

The risk of in-hospital mortality as a function of the risk prediction nomogram score from Table 5.

were blood urea nitrogen, SBP, and SCr (16). These factors also were identified in OPTIMIZE-HF as significant predictors, with the exception of blood urea nitrogen, which was not collected in the OPTIMIZE-HF database. Several other predictors were identified as well, as noted in the preceding text.

The in-hospital mortality predictors detected in OPTIMIZE-HF are consistent with other published reports in both hospitalized patients and those with chronic stable HF. Increased SCr, older age, increased heart rate, liver disease, cerebrovascular disease, low SBP, and low serum sodium have all been associated with in-hospital mortality (2–4,6,7). The findings of the OPTIMIZE-HF model confirm the relevance of these variables as prognostic factors with a population representative of the current HF era.

Several variables were noted to have a significant difference in slope beyond certain cutoff points. Increased SCr was associated with higher mortality up to the level of 3.5 mg/dl. Beyond this level, no incremental risk was evident. A similar relationship was reported in ADHERE where patients with estimated glomerular filtration rate in the 15 to 29 ml/min/1.73 m^2 range had higher in-hospital mortality (7.6%) than patients with estimated glomerular filtration rate <15 ml/min/1.73 m^2 (6.5%) (17). A difference in slope was also noted for SBP: as SBP increased, mortality risk decreased. This finding was present up to an SBP of 160 mm Hg, and there was no incremental benefit of increases beyond this point. Our model did not detect excess risk associated with higher SBP, but the number of patients with readings above this level might not have been large enough to detect any evidence of this association. Patients hospitalized with HF and elevated SBP might have greater myocardial reserve and thus be at lower short-term mortality risk. In addition, it might be easier to stabilize and restore compensation in these patients compared with those admitted with lower SBP.

The fact that hyperlipidemia and smoking within the previous year were associated with lower in-hospital mortality risk might be considered counterintuitive. Only slightly more than one-half (66%) of patients with a diagnosis of hyperlipidemia were treated with statins or other lipid-lowering therapy at the time of hospital admission. However, a number of prior studies have demonstrated an inverse relationship between total cholesterol levels and mortality in patients with pre-existing chronic HF (18,19). This is the first study, to our knowledge, suggesting that a history of hyperlipidemia is associated with lower mortality among hospitalized HF patients. Hyperlidiemia might be a marker of less-severe HF or a potential mediator of improved outcome as previously suggested (18,19). The lipid profile at the time of the admission was not collected and, as a result the relationship between the actual lipid parameters and in-hospital mortality, could not be determined. Although cigarette smoking is clearly established as a major modifiable risk factor for cardiovascular disease, current or recent smoking has previously been reported to be associated with lower short-term mortality risk among patients hospitalized with acute myocardial infarction or stroke (the so-called smoker's paradox) (20,21). The current findings suggest that current or recent smoking might precipitate hospitalization in patients with lesser underlying HF disease severity and as a result lower in-hospital mortality risk. This finding requires replication and further analysis.

Patients with a de novo HF hospitalization were found to be at significantly lower risk for in-hospital mortality, even after adjustment for other prognostic variables. Recent studies have suggested that prior hospitalization for HF confers a significantly increased risk of subsequent death (22,23). In a large community-based study, patients with first hospitalization for HF were at lower risk for mortality and each

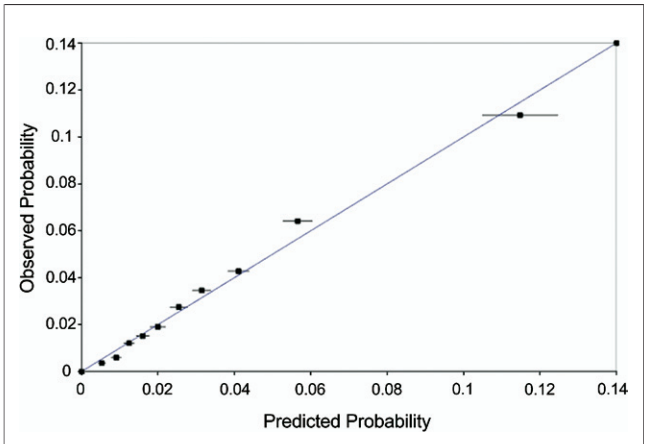

Figure 4 **Predicted Versus Actual In-Hospital Mortality**

The reliability plot for the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) registry nomogram with 95% confidence intervals is shown.

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Table 6 Comparison With Other Prediction Models

Reference	Data Source	n	Time Period	Mortality Rate	Higher Mortality Risk	Lower Mortality Risk
Brophy et al. (4)	Registry	153	Late 1980s to early 1990s	61% in 47 months	Prior admission for HF Hyponatremia Intraventricular conduction delay Cumulative intravenous furosemide dose	
Clinical Quality Improvement Network Investigators (6)	Registry	4,606	1992–1993	19% in-hospital	Age Use of magnesium Use of nitrates	ACE inhibitors Warfarin Aspirin Beta-blockers Calcium-channel blockers
EFFECT, Lee et al. (7)	Registry	4,031	1997–2001	8.9% in-hospital/ derivation cohort; 8.2% in-hospital/ validation cohort; 10.4%–10.7% at 30 days; 30.5%–32.9% at 1 yr	Age Increased respiratory rate Hyponatremia Low hemoglobin Increased blood urea nitrogen Cerebrovascular disease Dementia Chronic obstructive pulmonary disease Cirrhosis Cancer	Increased SBP
Aronson et al. (3)	Clinical trial	541	1996–1999	33%, mean follow-up 343 (± 185) days	Blood urea nitrogen Blood urea nitrogen/ SCr ratio Heart rate Ischemic etiology Age Hyponatremia	Increased SBP
OPTIME-CHF, Felker et al. (2)	Clinical trial	949	1997–1999	9.6% 60-day mortality	Age NYHA functional class IV vs. I–III Blood urea nitrogen	Increased SBP Increased serum sodium
ADHERE, Adams et al. (15)	Registry	33,046 (derivation cohort); 32,229 (validation cohort)	2001–2003	4.2% (derivation); 4% (validation) in-hospital mortality	Blood urea nitrogen above 43 SCr ≥2.75	SBP ≥115 mm Hg
OPTIMIZE-HF	Registry	48,612	2003–2004	3.8% in-hospital mortality	Increased SCr Low serum sodium Age Increased heart rate Liver disease Prior CVA/TIA Peripheral vascular disease Caucasian LVSD Chronic obstructive pulmonary disease	Increased SBP Increased serum sodium Increased diastolic blood pressure Hyperlipidemia Smoking within previous year No known HF before admission HF as primary cause of admission

ADHERE = Acute Decompensated Heart Failure National Registry; CVA/TIA = cerebrovascular accidents/transient ischemic attacks; EFFECT = Enhanced Feedback for Effective Cardiac Treatment; NYHA = New York Heart Association; OPTIME-CHF = Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure; other abbreviations as in Tables 1 and 3.

subsequent HF hospitalizations was a strong predictor of further increased mortality (23). The current study extends these findings and demonstrates that first hospitalization for HF is associated with lower in-hospital mortality, independent of other prognostic variables. African-American patients hospitalized with HF were found to be at lower risk for in-hospital mortality, confirming prior observations (24,25). Although this might reflect the younger age of African-American patients, these findings persisted after multivariable adjustment. Residual confounding by measured and unmeasured variables should be considered in accounting for these observations. However, differences in the pathophysiology of HF and/or response to treatment in African Americans also remain a potential explanation.

Of particular interest in this OPTIMIZE-HF analysis is the finding that treatment with an angiotensin-converting enzyme inhibitor or beta-blocker at the time of hospital admission predicted improved in-hospital survival. Although the mortality benefit of these therapies has been proven in numerous randomized, clinical HF trials, therapies continue to be underused in eligible patients, depriving them of potential benefits. This finding in OPTIMIZE-HF complements an analysis of the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery

Catheterization Effectiveness) dataset, showing in a smaller clinical trial population that beta-blocker use before and during HF hospitalization was associated with improved post-discharge outcomes (26). Efforts should continue to focus on ensuring that all eligible patients are treated with these important therapies.

Easily accessible assessments such as SCr, blood pressure, age, heart rate, sodium, LVSD, and cause of admission can be entered into a print or internet access version of the nomogram to accurately predict in-hospital mortality risk. The unique contribution of this OPTIMIZE-HF analysis is the development of a scoring system and nomogram that simultaneously integrates these parameters—known in virtually all HF patients at the time of admission—and accurately predicts individual patient risk for in-hospital mortality. Applied clinically, such an assessment could readily identify high-risk patients who might require intensive monitoring, early referral to advanced HF management teams with left ventricular assist device/transplant capability, or if appropriate referral to hospice care. Alerting physicians to the existence of this risk is a strategy with the potential to help them target interventions to reduce short-term mortality in this population. Having performed well in both HF clinical trial populations and real-world registry datasets, this model might be particularly useful in HF clinical trial design and subsequent development of improved in-hospital HF treatments and treatment strategies. An essential next step is to study whether prospective application of the risk prediction score will favorably impact patient care and clinical outcomes.

Study limitations. These findings should be considered in the context of several limitations. This model reports in-hospital mortality only and was not validated for post discharge outcomes. Other factors might be of prognostic value for postdischarge mortality or rehospitalization. The OPTIMIZE-HF registry was not a prospective, randomized trial. Unmeasured variables might have been present that could have influenced the findings. The mortality risk might have been influenced by other factors that were not measured, documented, included in the database, or considered as candidate variables. The model can only be applied to patients in whom the model variables have been assessed. Furthermore, these data do not define cause-and-effect relationships. Rather, they identify associations between patient variables and in-hospital mortality. Due to the large number of patients included in OPTIMIZE-HF, some observations might be statistically significant but not necessarily clinically relevant.

Conclusions

Despite numerous advances in the treatment of chronic HF, the OPTIMIZE-HF registry provides further evidence showing that patients still face a high risk of mortality when hospitalized for worsening HF. These results suggest that the in-hospital mortality risk for hospitalized HF patients can be reliably identified with demographic data, vital signs, and laboratory data obtained on hospital admission. Admission SBP, serum creatinine, and patient age are strong independent predictors of in-hospital mortality. The OPTIMIZE-HF risk tool provides clinicians with a well-validated bedside tool for in-hospital mortality risk stratification. Application of the risk-prediction score might help identify patients at high risk for in-hospital mortality who might benefit from aggressive monitoring and intervention. There is a need for further efforts to define and stratify mortality risk for patients hospitalized for HF.

Author Disclosures

Dr. Abraham reported that he has received a research grant from Amgen, Biotronik, CHF Solutions, GlaxoSmithKline, Heart Failure Society of America, Medtronic, Myogen, National Institutes of Health (NIH), Orqis Medical, Otsuka Maryland Research Institute, Paracor, and Scios. He is/has been a consultant/on the Speakers' Bureau for Amgen, AstraZeneca, Boehringer-Ingelheim, CHF Solutions, GlaxoSmithKline, Guidant, Medtronic, Merck, Pfizer, ResMed, Respironics, Scios, and St. Jude Medical. He is on the advisory board of CardioKine, CardioKinetix Inc., CHF Solutions, Department of Veterans Affairs Cooperative Studies Program, Inovise, NIH, and Savacor. He has received honoraria from AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Guidant, Medtronic, Merck, Pfizer, ResMed, Respironics, Scios, and St. Jude Medical. Dr. Fonarow reported that he has received research grants from Amgen, Boston Scientific/Guidant, GlaxoSmithKline, Medtronic, Pfizer, and NIH. He is/has been on the Speakers' Bureau or has received honoraria in the past 5 years from Amgen, AstraZeneca, Biosite, Bristol-Myers Squibb, Boston Scientific/Guidant, GlaxoSmithKline, Medtronic, Merck, NitroMed, Novartis, Pfizer, Sanofi-Aventis, Schering-Plough, Scios, St. Jude Medical, and Wyeth. He is or has been a consultant for Biosite, Bristol-Myers Squibb, Boston Scientific/Guidant, GlaxoSmithKline, Medtronic, Merck, NitroMed, Pfizer, Sanofi-Aventis, Schering-Plough, Scios, and Wyeth. Dr. Albert reported that she is a consultant for GlaxoSmithKline and Medtronic. She is also on the Speakers' Bureau for GlaxoSmithKline, Medtronic, NitroMed, and Scios and is employed by the Cleveland Clinic Foundation. Wendy Gattis Stough, PharmD, reported that she has received research grants from Actelion, GlaxoSmithKline, Medtronic, Otsuka, and Pfizer. She is a consultant or on the Speakers' Bureau for Abbott, AstraZeneca, GlaxoSmithKline, Medtronic, Novacardia, Otsuka, Protein Design Labs, RenaMed, Sigma Tau, and Scios. She has received honoraria from Abbott, AstraZeneca, GlaxoSmithKline, Medtronic, and Pfizer. Dr. Gheorghiade reported that he has received research grants from NIH, Otsuka, Sigma Tau, Merck, and Scios. He is/has been a consultant for Debbio Pharm, Errekappa Terapeutici, GlaxoSmithKline, Protein Design Labs, and Medtronic. He has received honoraria from

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