A Multivariate Model for Predicting Mortality in Patients with Heart Failure and Systolic Dysfunction

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BACKGROUND: Heart failure is a leading cause of morbidity and mortality, but there are no reliable models based on readily available clinical variables to predict outcomes in patients taking angiotensin-converting enzyme (ACE) inhibitors.

METHODS: A multivariate statistical model to predict mortality was developed in a random sample (n = 4277 patients [67%]) of the 6422 patients enrolled in the Digitalis Investigation Group trial who had a depressed ejection fraction (≤45%), were in sinus rhythm, and were taking ACE inhibitors. The model was then validated in the remaining 2145 patients.

RESULTS: Total mortality in the derivation sample was 11.2% (n = 480) at 12 months and 29.9% (n = 1277) at 36 months. Lower ejection fraction, worse renal function, cardiomegaly, worse functional class, signs or symptoms of heart failure, lower blood pressure, and lower body mass index were associated with reduced 12-month survival. This model provided good predictions of mortality in the verification sample. The same variables, along with age and the baseline use of nitrates, were also predictive of 36-month mortality.

CONCLUSION: Routine clinical variables can be used to predict short- and long-term mortality in patients with heart failure and systolic dysfunction who are treated with ACE inhibitors. **Am J Med. 2004;116:300–304.** ©2004 by Excerpta Medica Inc.

Heart failure is a leading cause of morbidity and mortality, and its incidence and prevalence are increasing (1–3). Angiotensin-converting enzyme (ACE) inhibitors improve outcomes in these patients (4) and are recommended as first-line treatment (5). However, the clinical correlates of unfavorable outcomes among patients with heart failure who are treated with ACE inhibitors have not been well defined. The development of risk models to predict outcomes and select treatments has been recognized as a research priority (6).

The Digitalis Group study (7,8) was the largest heart failure trial, and data collected in the study can be used to identify both short- and long-term determinants of heart failure mortality and morbidity. Almost all patients in this trial—which included substantial numbers of women and the elderly—were treated with ACE inhibitors. From this database, we built predictive models for short- and long-term mortality for patients with heart failure and depressed systolic function.

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METHODS

Study Sample

The trial recruited 7788 patients from February 1991 through August 1993 in over 300 North American centers. The design and principal outcomes of this trial, which compared digoxin with placebo in patients with heart failure and normal sinus rhythm, have been published (7,8). The diagnosis of heart failure was based on current or past symptoms and signs, or radiological evidence of pulmonary congestion. Patients were excluded from the trial if they had a serum creatinine level >3.0 mg/dL, age <21 years, unstable coronary syndromes, cor pulmonale, complex congenital heart diseases, or recognizable noncardiac causes of heart failure. This analysis considers only the 6800 patients with sinus rhythm and left ventricular ejection fractions ≤0.45%, of whom 6422 were being treated with ACE inhibitors.

Baseline data were limited to historical, physical examination (recorded by experienced physicians), and routine laboratory results. The ejection fraction was measured using angiographic, radionuclide, or echocardiographic techniques as decided by individual investigators. To facilitate the interpretation of the final results, some continuous variables, including age, have been categorized. Signs and symptoms of heart failure (including rales, elevated jugular venous pressure, peripheral edema, dyspnea at rest, exertional dyspnea, limitation of activity, S_3 gallop, and radiologic evidence of pulmonary congestion) were collated into a single categorical variable (levels 0/1, 2/3, 4/5, 6 or greater).

Patients had regular visits at 4-month intervals. The mean duration of follow-up was 37 months (range, 28 to 58 months). Mortality was determined by chart review or

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family interviews. Vital status was unknown for only 1.4% of patients; even for these patients, information was available until the time of censoring.

Model Selection and Validation

Our objective was to determine the clinical correlates of total mortality at 12 and 36 months. Univariate analysis was performed on a total of 28 baseline variables, and treatment allocation (digoxin vs. placebo). The following 18 variables were then included in multivariate models: sex, race, age group, angina, diabetes, etiology, cardiothoracic ratio, duration of heart failure, New York Heart Association (NYHA) functional class, left ventricular ejection fraction, systolic and diastolic blood pressure, body mass index, serum creatinine level, nitrate use, heart rate, treatment assignment, and a composite variable of clinical signs and symptoms. Ten prespecified interaction terms involving age, sex, diabetes, etiology, renal function, and digoxin treatment (age * etiology, age * treatment, sex * etiology, sex * creatinine, sex * treatment, diabetes * etiology, diabetes * creatinine, diabetes * treatment, treatment * etiology, treatment * creatinine) were also entered into the models. Because stepwise approaches often have difficulty distinguishing between competing models, ignore the uncertainty involved in multivariate model selection, and may overfit models, we used a Bayesian approach that averaged over the set of best models according to posterior model probability. This was performed with the Bayesian Information Criterion (9) using S-Plus (Insightful Corporation, Seattle, Washington). This technique was applied to a random two-third selection of the cohort (derivation sample). This model selection process has optimal properties for predicting events in future patients with similar characteristics. Nevertheless, we validated the model in the remaining one third of the cohort. For each patient in this validation set, we calculated the probability of survival using Cox proportional hazards models (SAS Institute, Cary, North Carolina) with the variables identified from the derivation set. We ranked the predicted values into deciles of mortality, and then compared the observed and predicted mortality for each decile.

RESULTS

Patients in the derivation and validation samples had similar characteristics (Table 1). The mean (± SD) age in the derivation sample was 63.3 ± 11.0 years. Over half were known to have heart failure for at least 12 months. Virtually all had signs and symptoms of heart failure at randomization, and only a minority was in NYHA functional class I. The mean ejection fraction was 28% ± 9%, and the mean creatinine level was 1.3 ± 0.4 mg/dL.

Multivariate Correlations with Outcomes

Total mortality in the derivation sample was 11.2% (n = 480) at 12 months and 29.9% (n = 1277) at 36 months. Increasing age, worse functional class, and more signs or symptoms of heart failure were independently associated with increased 36-month mortality (Table 2), as were lower body mass index and systolic blood pressure. Lower ejection fraction, worse renal function, cardiomegaly, and use of nitrates were also associated with greater long-term mortality. Patients with diabetes and an ischemic etiology for their heart failure (n = 914) were also at increased risk. In general, the same variables were predictive of short-term mortality, except for age and nitrate use; diastolic blood pressure replaced systolic blood pressure. As had been reported, digoxin treatment was not associated with short- or long-term mortality.

Model Validation

Models based on these variables were able to predict observed survival across different risk strata in the validation sample (Figures 1 and 2). For example, the lowest risk decile had a predicted 12-month mortality of 4.0% (vs. an observed mortality of 3.8%), which increased to 11.8% (vs. an observed mortality of 10.7%) at 36 months. In general, the models performed less well for the highest decile, although even here the results were reasonable (e.g., an observed mortality of 30.5% vs. a predicted mortality of 35.1% at 12 months). An example is provided in the Appendix.

DISCUSSION

More than 50 demographic, clinical, biochemical, hemodynamic, electrophysiologic, and echocardiographic factors have been correlated with outcomes in heart failure patients; neurohormonal markers have perhaps the strongest association (10). However, most patients are diagnosed, treated, and followed in general medical practices and do not always have access to these markers. Therefore, we concentrated on predictors that are readily available, and demonstrated that they can be used to predict short- and long-term mortality across a wide spectrum of disease severity. The variables have good face validity and have generally been shown to be associated with adverse outcomes in other studies.

Our model confirms the prognostic value of age (11), impaired left ventricular function (12), cardiomegaly (12), and renal insufficiency (13), which have been identified as predictors of adverse outcome in smaller studies that often antedated the systematic use of ACE inhibitors. Although there is a very weak correlation between cardiothoracic ratio and ejection fraction in this sample (14), we found that both cardiac size and function were independent predictors of mortality.

Signs and symptoms of heart failure were common at

Table 1. Baseline Characteristics of the Patients in the Derivation and Validation Samples, and among Patients in the Derivation Sample Who Died during 36-Month Follow-up

Characteristic	Derivation Sample (n = 4277)	Validation Sample (n = 2145)	Died during 36-Month Follow-up (n = 1277)
	Number (%) or Mean ± SD		
Male sex	3319 (77.6)	1670 (77.9)	1016 (79.6)*
Race			
White	3637 (85.0)	1845 (86.0)	1086 (85.1)
Black	521 (12.2)	232 (10.8)	160 (12.5)
Other	119 (2.8)	68 (3.2)	31 (2.4)
Age (years)			
<50†	510 (11.9)	225 (10.5)	103 (8.1)*
50 to 59	898 (21.0)	443 (20.7)	198 (15.5)
60 to 69	1563 (36.5)	801 (37.3)	478 (37.4)
≥70	1306 (30.5)	676 (31.5)	498 (39.0)
Angina	1126 (26.3)	562 (26.2)	365 (28.6)*
Diabetes	1214 (28.4)	621 (29.0)	438 (34.3)*
Hypertension	1954 (45.7)	968 (45.1)	589 (46.1)
Ischemic etiology	2990 (70.1)	1526 (71.3)	902 (70.9)
Nitrate use	1815 (42.4)	903 (42.1)	636 (49.8)*
NYHA class			
I†	582 (13.6)	272 (12.7)	117 (9.2)*
II	2271 (53.2)	1195 (55.8)	584 (45.8)
III/IV	1420 (33.2)	676 (31.5)	575 (45.0)
Duration of heart failure (months)			
<3	530 (12.4)	247 (11.6)	160 (12.6)*
3 to 12	1454 (34.1)	701 (32.7)	392 (30.8)
13 to 24	665 (15.6)	358 (16.7)	188 (14.8)
>24	1619 (37.9)	835 (39.0)	533 (41.8)
Digoxin treatment	2145 (50.2)	1052 (49.0)	651 (51.0)
Physical examination			
Body mass index (kg/m^2)			
≤23.6	1089 (25.5)	534 (24.9)	400 (31.3)*
23.7 to 26.4	1069 (25.0)	513 (23.9)	314 (24.6)
26.5 to 29.7	1066 (24.9)	533 (24.9)	296 (23.2)
>29.7†	1052 (24.6)	565 (26.3)	267 (20.9)
Systolic blood pressure (mm Hg)			
≤110	1255 (29.4)	609 (28.4)	445 (34.8)*
111 to 121	851 (19.9)	416 (19.4)	264 (20.7)
122 to 139	1011 (23.6)	515 (24.0)	271 (21.2)
>139†	1159 (27.1)	604 (28.2)	297 (23.3)
Diastolic blood pressure (mm Hg)			
≤69	1048 (24.5)	522 (24.4)	374 (29.3)*
70 to 74	1098 (25.7)	549 (25.6)	340 (26.6)
75 to 80	1194 (27.9)	607 (28.3)	330 (25.8)
>80†	935 (21.9)	465 (21.7)	233 (18.3)
No. of signs or symptoms of heart failure‡			
0/1†	136 (3.2)	67 (3.1)	25 (2.0)*
2/3	656 (15.4)	351 (16.4)	137 (10.8)
4/5	1062 (24.9)	534 (24.9)	278 (21.8)
>5	2413 (55.5)	1191 (55.6)	833 (65.4)
Cardiothoracic ratio >0.50	2633 (61.6)	1329 (62.0)	898 (70.3)*
Ejection fraction (%)	28 ± 9	28 ± 8	26 ± 9*
Serum creatinine (mg/dL)	1.3 ± 0.4	1.3 ± 0.4	1.4 ± 0.4*
Heart rate (beats per minute)	79 ± 13	79 ± 13	80 ± 13*

* $P < 0.05$ by comparison with those who lived.

† Represents the baseline reference group for the multivariate analysis presented in Table 2.

‡ Rales, elevated jugular venous pressure, peripheral edema, dyspnea at rest or on exertion, limitation of activity, S_3 gallop, and radiologic evidence of pulmonary congestion.

NYHA = New York Heart Association.

Table 2. Independent Predictors of Short- and Long-term Mortality

Variable*	Mortality at 12 Months	Mortality at 36 Months
	Hazard Ratio (95% Confidence Interval)	
Age	–	1.20 (1.13–1.28)
Ejection fraction (per 10% decrease)†	1.34 (1.22–1.48)	1.34 (1.22–1.48)
NYHA class	1.44 (1.24–1.68)	1.29 (1.18–1.41)
Cardiothoracic ratio >50%	1.60 (1.29–1.97)	1.34 (1.19–1.52)
Clinical signs or symptoms	1.21 (1.06–1.38)	1.14 (1.06–1.24)
Serum creatinine (per mg/dL increase)‡	1.85 (1.49–2.28)	1.73 (1.51–2.02)
Body mass index	1.18 (1.08–1.28)	1.09 (1.04–1.15)
Diastolic blood pressure	1.17 (1.08–1.28)	–
Systolic blood pressure	–	1.11 (1.06–1.16)
Nitrates	–	1.18 (1.06–1.32)
Diabetes* ischemic etiology	1.46 (1.19–1.79)	1.43 (1.26–1.63)

* See Table 1 for the reference groups; hazard ratios are per one-group increase for age, NYHA class, signs or symptoms, and per one-group decrease for body mass index and blood pressure.
† Applicable for baseline ejection fractions between 3% and 45%.
‡ Applicable for baseline creatinine values between 0.3 and 3.0 mg/dL.
NYHA = New York Heart Association.

baseline; when combined into a single score, they were strongly associated with mortality. For example, six or more signs or symptoms increased mortality by 50% at 36 months compared with patients who had one or no sign or symptom. These findings are in general agreement with a recent analysis (15), which found that an elevated jugular venous pressure and third heart sound were associated with repeat hospitalizations, but had a borderline significant association with total mortality.

Other investigators have found that an ischemic etiology for heart failure is associated with decreased survival (16), but this has not been a consistent finding (17). We found a strong interaction between etiology and diabetes: an ischemic etiology was associated with reduced survival among patients with diabetes, whereas etiology was not associated with mortality in patients without diabetes. This confirms previous findings (18). Finally, nitrate use was a predictor of long-term, but not short-term, mortality, perhaps because it is a proxy for more severe heart failure that requires two vasodilators or because it indicates more severe angina.

Our predictive models have several strengths. They are based on a large, relatively unselected, and contemporary cohort of patients being treated with ACE inhibitors, including a substantial proportion of women. The large number of deaths permitted us to estimate the effects of several clinical variables simultaneously. One potential limitation of this study is that all of the subjects were participating in a clinical trial and it is unknown how representative they are of those in routine clinical practice. However, it seems unlikely that there would be substantial bias in patient selection in a trial of almost 7000 patients from 300 clinical sites. Our results may not apply to patients who are not in normal sinus rhythm, or who have severe renal insufficiency. In addition, we did not have neurohormonal, echocardiographic, and hemodynamic data. Our goal, however, was to develop a model that is clinically relevant by including variables that are available to all physicians who care for heart failure patients. Furthermore, the incremental value of these more sophisticated measurements—beyond what can be estimated from clinical variables—has not been confirmed.

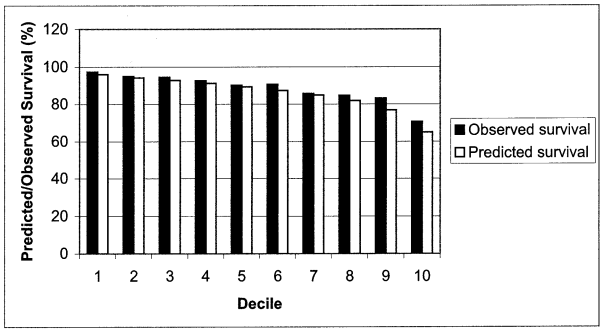

Figure 1. Observed and predicted survival at 12 months. $P = 0.14$ in a goodness-of-fit test.

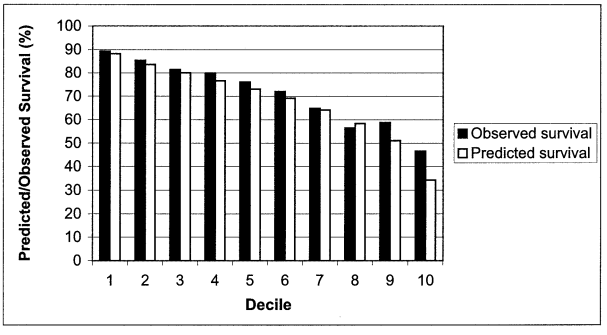

Figure 2. Observed and predicted survival at 36 months. $P = 0.01$ in a goodness-of-fit test.

Prognosis in heart failure is a function of both patient and physician characteristics (19), but we did not have detailed information about the physicians who participated in this trial. We also did not have information on the use of beta-blocker or spironolactone therapy.

In conclusion, we have shown that it is possible to risk stratify patients with heart failure using easily available clinical measurements. High-risk patients may benefit from more intensive multidisciplinary follow-up (20). Predictive models may also facilitate the interpretation of studies of quality of care. The identification of new prognostic variables should evaluate their incremental predictive value beyond that supplied by clinical models. This model should also be evaluated among patients being treated with beta-blockers, which have become an essential part of treatment (21) since this study was completed.

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APPENDIX

The following example shows how to estimate 36-month mortality. Consider a 74-year-old nondiabetic patient, with an ischemic cardiomyopathy, ejection fraction (EF) of 25%, New York Heart Association (NYHA) class III, a creatinine (CR) level of 1.5 mg/dL, a cardiothoracic (CT) ratio >0.5, and a clinical (CLIN) score of 4 (rales, increased jugular venous pressure, rest and exertional dyspnea). The patient is not taking nitrates, and is in the reference group for body mass index and blood pressure. This results in a risk sum as follows:

$$\beta_{AGE}{}^{*}\text{AGE} = \ln(RR_{AGE}){}^{*}\text{age group} = 0.182{}^{*}3 = 0.55$$

$$\beta_{EF}{}^{*}\text{EF} = \ln(RR_{EF}){}^{*}\text{EF} = 0.30{}^{*}(45 - 25)/10 = 0.60$$

$$\beta_{NYHA}{}^{*}\text{NYHA} = \ln(RR_{NHYA}){}^{*}\text{NYHA} = 0.255{}^{*}2 = 0.51$$

$$\beta_{CT}{}^{*}\text{CT} = \ln(RR_{CT}){}^{*}\text{CT} = 0.293{}^{*}1 = 0.29$$

$$\beta_{cong}{}^{*}\text{CLIN} = \ln(RR_{CLIN}){}^{*}\text{CLIN} = 0.131{}^{*}2 = 0.26$$

$$\beta_{Cr}{}^{*}\text{Cr} = \ln(RR_{CR}){}^{*}\text{Cr} = 0.552{}^{*}(1.5) = 0.83$$

Patient sum = 3.04

The average 36-month average survival, S_o (t), is 70.1% and the mean sum is 3.10. Then the patient's predicted 36-month survival is $0.701^{\exp(3.04-3.10)} = 0.701^{0.94} = 0.72$ or 72%.

Survival at 12 months can be estimated based on the overall average 12-month survival of 88.8% and mean sum of 3.42.