Long-term Survival in Elderly Patients Hospitalized for Heart Failure

14-Year Follow-up From a Prospective Randomized Trial

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Background: The growing heart failure epidemic imposes a substantial burden on the US health care system. The ability to accurately assess prognosis would allow clinicians to triage patients to appropriate therapy and to plan the intensity of care following hospital discharge.

Methods: A cohort of 282 elderly (mean ± SD age, 79.2 ± 6.1 years) patients with heart failure were followed for up to 14 years after enrollment in a prospective randomized multidisciplinary disease management trial conducted from 1990 through 1994. Kaplan-Meier survival curves were constructed to assess the probability of survival during the follow-up period. A Cox proportional hazards model was developed to identify independent predictors of long-term survival. C statistics were calculated to assess the utility of the model for predicting mortality at 6 months, 1 year, and 5 years.

Results: During the 14-year follow-up period, 269 patients (95%) died and the median survival was 894 days. Cox analysis identified 7 variables that were independent predictors of shorter survival time: older age (hazard ratio [HR], 1.14 per 5 years; 95% confidence interval [CI], 1.03-1.26), serum sodium level less than 135 mEq/L (HR, 1.67; 95% CI, 1.19-2.32), coronary artery disease (HR 1.51; 95% CI, 1.16-1.95), dementia (HR, 2.02; 95% CI, 1.13-3.61), peripheral vascular disease (HR, 1.74; 95% CI, 1.20-2.52), systolic blood pressure (HR, 0.95 per 10 mm Hg; 95% CI, 0.92-0.98), and serum urea nitrogen level (HR, 1.20 per 10 mg/dL [3.57 mmol/L]; 95% CI, 1.12-1.29). C statistics for the model were 0.84, 0.79, and 0.75 at 6 months, 1 year, and 5 years, respectively. A risk score for mortality was developed using the 7 independent predictor variables. One-year mortality rates among patients with 0 to 1 (n=89), 2 to 3 (n=153), and 4 or more (n=37) risk factors were 9.0%, 22.2%, and 73.0%, respectively (P<.001).

Conclusions: Among elderly patients hospitalized with heart failure, median survival is about 2.5 years. However, there is considerable heterogeneity in survival, with 25% of patients dying within 1 year and 25% surviving for more than 5 years. A simple 7-item risk score, based on data readily available at the time of admission, provides a reliable estimate of prognosis.

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Heart Failure (HF) affects 5 million people in the United States, with over 1 million hospital admissions each year.\(^1\) Hospital discharges for HF have increased by 155% during the last 20 years, and HF has become the leading cause of hospitalization in persons older than 65 years.\(^2\) In 2005, the estimated total direct and indirect cost for HF in the United States was $27.9 billion, making HF the largest and most expensive diagnosis-related group.\(^3\) Moreover, people 65 years and older represent the fastest growing segment of the population, and the risk of HF increases progressively with age.\(^4\) Thus, the HF epidemic imposes considerable burden on the US health care system, and the magnitude of this burden is likely to increase as the population ages.

In recent years, an increasing array of options has become available for treating patients with HF. Many of these options, such as implantable defibrillators and biventricular pacemakers, entail invasive procedures and considerable expense. However, the extent to which these costly interventions should be applied to elderly patients with HF is unknown, in part because a clinically useful method for assessing prognosis in these patients remains elusive.

The objectives of this study, therefore, were to determine predictors of long-term survival in a cohort of elderly patients hospitalized with HF who were enrolled in a prospective randomized multidisciplinary intervention trial and to develop a mortality risk score based on readily available clinical parameters to enable clinicians to gauge long-term prognosis early in the hospital course.
A detailed description of the methods and results of the multidisciplinary intervention trial has been reported. Briefly, the study was a prospective randomized clinical trial conducted at Washington University Medical Center, St Louis, Mo, from 1990 through 1994. A total of 282 patients 70 years and older with HF with 1 or more risk factors for early hospital readmission were randomized to either conventional care (n = 140) or to a nurse-directed multidisciplinary intervention designed to reduce the risk of rehospitalization (n = 142).

The intervention consisted of intensive education about HF and its treatment by a cardiovascular research nurse; dietary assessment and instruction by a registered dietician; early discharge planning by social service personnel; an analysis of medications by a geriatric cardiologist; and intensive follow-up after discharge through the hospital’s home health service, supplemented by individualized home visits and telephone contacts with members of the study team. The principal goals of follow-up were to reinforce patient education, ensure compliance with medications and diet, and identify recurrent symptoms amenable to treatment on an outpatient basis. The conventional care group was eligible to receive all standard treatments and services as ordered by the primary care physician or cardiologist. The duration of the intervention was 90 days, and all patients were initially followed for 1 year, after which there was no regularly scheduled follow-up.

In the present study, the primary outcome of interest was time to death from any cause. We used the hospital database and the National Death Index to determine the date of death of all subjects for up to 14 years. Survival days were calculated from the date of hospital admission to the date of death or until September 2004 in survivors. Potential determinants of long-term survival included baseline demographic factors, medical history, clinical characteristics, and laboratory data obtained from hospital records at the time of initial hospital admission. Patients were also screened for cognitive dysfunction using the Short Blessed Test, a widely used 6-item instrument that assesses orientation, memory, and concentration. A detailed list of all medications was recorded at the time of hospital discharge.

### STATISTICAL ANALYSIS

Baseline characteristics of intervention and control group subjects were compared using 2-tailed t tests for normally distributed continuous variables and the Wilcoxon rank sum test for continuous variables with skewed distributions. The χ² statistic was used for discrete variables. Kaplan-Meier survival curves were constructed to assess the probability of survival during the follow-up period. A log-rank test was used to compare survival (in days) in the treatment and control groups.

Patient characteristics univariately associated with survival days were identified using linear regression analysis. Clinically relevant variables were chosen to construct a Cox proportional hazards model using a forward stepwise procedure, with P<.10 set as the entry criterion and P<.05 as the stay criterion. C statistics derived from receiver operating characteristic curves were used to assess the goodness of fit of the model at predicting survival at 6 months, 1 year, and 5 years. The 6-month, 1-year, and 5-year mortality models were internally validated using the bootstrap technique by generating 150 random resampled data sets with replacement and performing stepwise Cox regression analysis on each. The bootstrap-validated 95% confidence interval (CI) was determined and compared with the original model estimates.

### RESULTS

Table 1 gives the baseline patient characteristics in the control and intervention groups, as well as variables that
Long-term survival in 282 patients 70 years and older with heart failure (P=.50).

Figure 1. Long-term survival in 282 patients 70 years and older with heart failure (P=.50).

Table 2. Univariate Predictors of Mortality

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Regression Coefficient</th>
<th>HR (95% CI)</th>
<th>χ²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUN, per 1 mg/dL (0.36 mmol/L)</td>
<td>0.02</td>
<td>1.02 (1.01-1.03)</td>
<td>41.61</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systolic BP, per 1 mm Hg</td>
<td>-0.01</td>
<td>0.99 (0.99-1.00)</td>
<td>18.04</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PVD</td>
<td>-0.76</td>
<td>2.14 (1.49-3.06)</td>
<td>17.87</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Short Blessed score, per 1 point</td>
<td>0.04</td>
<td>1.04 (1.02-1.06)</td>
<td>17.76</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Creatinine, per 1 mg/dL</td>
<td>0.19</td>
<td>1.21 (1.10-1.34)</td>
<td>15.49</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CAD</td>
<td>-0.48</td>
<td>1.61 (1.26-2.06)</td>
<td>14.57</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diastolic BP, per 1 mm Hg</td>
<td>-0.01</td>
<td>0.99 (0.98-1.00)</td>
<td>13.48</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dementia</td>
<td>-0.94</td>
<td>2.56 (1.45-4.51)</td>
<td>11.26</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ejection fraction, per 1%</td>
<td>-0.02</td>
<td>0.98 (0.97-0.99)</td>
<td>10.84</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Albumin, per 1 g/dL</td>
<td>-0.51</td>
<td>0.60 (0.44-0.82)</td>
<td>10.29</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Serum sodium, per 1 mEq/L</td>
<td>-0.05</td>
<td>0.96 (0.92-0.99)</td>
<td>6.81</td>
<td>.009</td>
</tr>
<tr>
<td>NYHA class, per 1 class</td>
<td>0.15</td>
<td>1.16 (1.03-1.31)</td>
<td>6.21</td>
<td>.01</td>
</tr>
<tr>
<td>BMI, per 1 point</td>
<td>-0.03</td>
<td>0.97 (0.95-0.99)</td>
<td>6.05</td>
<td>.01</td>
</tr>
<tr>
<td>Diastolic HF</td>
<td>0.34</td>
<td>1.39 (1.04-1.85)</td>
<td>5.07</td>
<td>.02</td>
</tr>
<tr>
<td>Male</td>
<td>0.31</td>
<td>1.36 (1.06-1.74)</td>
<td>5.85</td>
<td>.02</td>
</tr>
<tr>
<td>Prior HF hospitalization</td>
<td>-0.33</td>
<td>1.39 (1.04-1.85)</td>
<td>5.07</td>
<td>.02</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>-0.24</td>
<td>0.79 (0.62-1.00)</td>
<td>3.81</td>
<td>.05</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>-0.29</td>
<td>0.71 (0.52-1.00)</td>
<td>3.42</td>
<td>.07</td>
</tr>
<tr>
<td>Age, per 1 y</td>
<td>0.02</td>
<td>1.02 (1.00-1.04)</td>
<td>2.93</td>
<td>.09</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; CAD, coronary artery disease; CI, confidence interval; HF, heart failure; HR, hazard ratio; NYHA, New York Heart Association; PVD, peripheral vascular disease; SUN, serum urea nitrogen; TIA, transient ischemic attack.

* Cox regression χ² statistic.

were considered as candidates for inclusion in the prognostic models. During the 14-year follow-up period, 269 patients (95%) died, with an overall median survival of 894 days (interquartile range, 355-1821 days). The 13 patients (4.6%) still alive had a median survival of 4022 days. Median survival times in the control group and treatment group were 790 days (interquartile range, 341-1780 days) and 999 days (interquartile range, 337-1871 days), respectively (P = .50) (Figure 1).

Results of univariate analysis for potential predictors of survival days are given in Table 2. Variables are listed in order of statistical strength as represented by the Cox regression χ² statistic. A total of 18 variables met the inclusion criteria (P<.10) based on univariate analysis and were considered for inclusion in the multivariable model. Candidate variables not readily available at the time of hospital admission, and those with 5 or more missing data points, including left ventricular ejection fraction (LVEF), serum albumin level, and the Short Blessed score, were excluded from the model. The final model included 7 variables that were independent predictors of shorter survival time (Table 3). The C statistics for the all-cause mortality model were 0.84, 0.79, and 0.75 for 6-month, 1-year, and 5-year mortality, respectively. The bootstrap analysis demonstrated a tight distribution of the standard error for the variables compared with the results predicted by the model (Table 4).

A risk score for mortality was developed using these 7 independent predictor variables, dichotomizing continuous variables at clinically meaningful cutoffpoints. Figure 2 illustrates differences in median survival time with each prognostic risk factor. One point was assigned for each of the 7 risk factors, and the sum of the number of risk factors for each patient composed the risk score. Six-month mortality rates for patients with 0 to 1 risk factor, 2 to 3 risk factors, and 4 or more risk factors were 7.9%, 9.8%, and 59.5%, respectively (Table 5). Patients with 4 or more risk factors had HRs for 6-month
mortality of 7.56 and 6.06 compared with those with 0 to 1 risk factor and 2 to 3 risk factors, respectively. **Figure 3** illustrates Kaplan-Meier survival curves for patients with 0 to 1 risk factor, 2 to 3 risk factors, and 4 or more risk factors (P<.001 for each comparison).

### COMMENT

Despite major advances in the treatment of HF, morbidity and mortality remain high. Median survival in our population was about 2.5 years, which is comparable to previously published community-based surveys. 4,8 Importantly, however, individual prognosis in our study was heterogeneous, with 25% of patients dying within 1 year of hospital discharge, 50% surviving 1 to 5 years, and 25% surviving for more than 5 years. An important implication of this observation is that the management of elderly patients hospitalized with HF should be predicated on a reasonable assessment of the patient's short- and intermediate-term prognosis. Our risk score, while requiring validation in future studies, provides a simple tool for gauging prognosis in elderly patients admitted to the hospital with acute decompensated HF.

### PRIOR STUDIES

Although numerous prior studies have shown that multidisciplinary HF disease management programs reduce hospital readmissions, the impact of these interventions on mortality is less clear, in part because most studies have been relatively small and the duration of follow-up has been 12 months or less. 9-11 To our knowledge, our study provides the longest prospective follow-up of a multidisciplinary HF intervention. After a follow-up of approximately 14 years, we were not able to demonstrate a significant survival advantage in the treatment group compared with the control group at any time during the follow-up period. This contrasts with the trial conducted by Stewart and Horowitz, 12 who reported significantly fewer unplanned readmissions or deaths (primary end point) with a home-based intervention during 4.2 years of follow-up. With respect to all-cause mortality, these authors found a strong trend toward prolonged survival (P = .06) and reduced risk of death (P = .06) in the intervention group. This apparent discrepancy could be due to differences in patient populations (our population was older and had more comorbid conditions), differences in the nature of the intervention, or the play of chance (both studies enrolled fewer than 300 subjects).

Our survival model selected 7 readily available factors that identify patients with significantly shorter survival, including older age, hyponatremia, history of coronary artery disease, history of dementia, history of peripheral vascular disease, lower systolic blood pressure, and higher serum urea nitrogen level. None of these prognostic factors are novel, and all are consistent with other reports. Prior studies have also used multivariate logistic regression to derive predictive models for survival, but follow-up in these studies was shorter, ranging from 18 months to 5 years. 13-20 In addition, prior studies have often excluded many patients commonly seen in routine clinical practice (eg, those with dementia, diabetes mellitus, or kidney disease), have lacked data on common medical comorbid conditions (eg, peripheral arterial disease, dementia, stroke, and atrial fibrillation), or have included variables not readily available in patients with HF at the time of hospital admission (eg, LVEF). In contrast, age, systolic blood pressure, serum sodium level, serum urea nitrogen level, and the historical items of coronary artery disease, peripheral vascular disease, and dementia are all easily obtainable by clinicians caring for elderly patients with HF, including those in the emergency department.

Our model for predicting HF mortality is unique in several respects. Unlike other prognostic models, our model predicts mortality during short- (6 months), intermediate- (12 months), and long-term (5 years) follow-up. We also rigorously assessed the prognostic performance of the model using receiver operating characteristic curves, and we internally validated the model using the bootstrap procedure. The predictive ability of our model was moderately strong, with C statistics for all-cause mortality of 0.84, 0.79, and 0.75, at 6 months, 1 year, and 5 years, respectively (where a C statistic of 0.5 indicates no discriminatory power and 1.0 indicates perfect discrimination). 21 Our model performance compared favorably with that of Lee et al 120 (C statistic of 0.77 for 1-year mortality) and Pocock et al 128 (C statistic of 0.75 for 2-year mortality).

### PROGNOSTIC VARIABLES

Although elevated systolic blood pressure is associated with increased risk of cardiovascular events and death in the general population, prior studies in patients with HF have consistently shown that relatively low blood pressure is associated with worse prognosis, most likely reflecting a more advanced state of hemodynamic and neu-

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**Figure 2.** Median survival in days according to predictors of survival. CAD indicates coronary artery disease; Na, serum sodium; PVD, peripheral vascular disease; SBP, systolic blood pressure; SUN, serum urea nitrogen; plus sign, with; minus sign, without. To convert SUN to millimoles per liter, multiply by 0.357.
Dementia is a well-known predictor of mortality in the general population. In our HF population, dementia also independently predicted survival, consistent with previous HF studies that included patients with dementia. Similarly, it is not surprising that prevalent coronary artery disease and peripheral arterial disease were independent predictors of mortality in our population, since both of these conditions are associated with markedly increased risk for coronary and cerebrovascular morbidity and mortality.

Interestingly, elevated serum urea nitrogen level was the strongest independent predictor of mortality in our model. Similarly, Fonarow et al recently found that the best predictor for in-hospital mortality in patients with HF was a high admission serum urea nitrogen level (>43 mg/dL [>15.35 mmol/L]). Likewise, a serum urea nitrogen level higher than 25 mg/dL (8.93 mmol/L) was found to be an independent predictor of defibrillator discharge or death in the second Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) population. A possible explanation for these concordant findings may be that serum urea nitrogen level, a less specific measure of kidney function compared with serum creatinine level, may be a marker for renal hypoperfusion, with enhanced activation of the sympathetic nervous system and renin-angiotensin-aldosterone system in patients with HF.

LIMITATIONS

Our study has several important limitations. As with all prognostic indexes, the validity and generalizability of our survival model need to be confirmed in other settings and patient populations. Our study population consisted entirely of patients enrolled in a clinical trial. These patients were selected because they were elderly (age ≥70 years) and had risk factors for early hospital readmission. The study was conducted at a single university teaching hospital, and the sample size was relatively small. For these reasons, results of this study may not be generalizable to all HF populations.

We did not include certain variables in our model, most notably LVEF, because of incomplete data ascertainment. Although LVEF has been associated with increased mortality in some studies, others have not found it to be an independent predictor in multivariate analysis. Moreover, while LVEF is important for guiding therapy, it is often not available to clinicians in practice, especially those in the emergency department or hospital setting who are providing care to elderly patients with acute decompensated HF. We also did not include medications in our model because medication use was not randomized (introducing the potential problem of confounding by indication), interim follow-up on medication changes was lacking, and the study population was heterogeneous with respect to LVEF.

Stroke and atrial fibrillation have been associated with increased mortality in some but not all prior studies. Neither of these variables was an independent predictor in our analysis, perhaps reflecting the study’s limited power. Alternatively, it is possible that these conditions do not significantly impact long-term survival in elderly patients with HF.

Our trial was conducted prior to the landmark studies documenting the benefits of β-adrenergic blocking drugs and aldosterone antagonists in patients with HF. Although survival rates have improved since the introduction of these drugs, there is little reason to believe that the primary predictors of mortality have changed significantly. Indeed, Koelling et al found that an HF survival score provided similar prognostic information regardless of β-blocker use.

Our data set lacked information on clinical events, including rehospitalizations, beyond 1 year, and we also...
had no information on cause of death. However, over 90% of deaths in patients with HF can be attributed to cardiovascular causes, most commonly progressive HF or arrhythmias. Moreover, the primary objective of our analysis was to develop a simple index for assessing prognosis based on data readily available at the time of hospital admission. In this regard, it is reassuring that despite a follow-up period of up to 14 years, our findings are in agreement with most other short- and intermediate-term studies.

CLINICAL IMPLICATIONS

Our mortality risk score identified 3 groups of patients having low (0-1 risk factor), moderate (2-3 risk factors), or high (≥4 risk factors) risk of mortality. The identification of patients at high risk of death within 6 months may enable clinicians to better advise patients about prognosis, adjust management accordingly, and permit consideration of palliative care in those anticipated to have particularly poor short-term survival. Conversely, patients with a more favorable prognosis may be suitable candidates for more aggressive interventions, such as an implantable defibrillator, although individual patient factors and preferences would still require careful consideration.

Although the 7 prognostic predictors identified in our model are not currently amenable to modification, they still provide clinically important information for stratifying risk in elderly patients with HF at the time of admission to help guide diagnostic and therapeutic decision making, including appropriate selection of invasive and costly interventions. Prognostic indicators can also identify those areas of HF management requiring further investigation. For example, the effect of treating hyponatremia by vasopressin blockade in patients with HF is the subject of ongoing clinical trials. Future trials are also needed to determine if there is an optimal blood pressure range for elderly patients with HF, given the potential conflict between aggressive titration of HF medications and data such as ours, suggesting that excessive reduction of blood pressure may contribute to adverse outcomes.

CONCLUSIONS

The prognosis of elderly patients hospitalized with HF is highly variable. A simple risk score, based on 7 variables readily obtainable at the time of hospital admission, can effectively stratify patients into low-, intermediate-, and high-risk categories for subsequent mortality. This information, in turn, can be used as an aid to guide diagnostic and therapeutic decision-making.

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