Physical Health Status Measures Predict All-Cause Mortality in Patients With Heart Failure

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Background—Physical health status measures have been shown to predict death in heart failure (HF); however, few studies found significant associations after adjustment for confounders, and most were not representative of all HF patients.

Methods and Results—HF patients from southeastern MN were prospectively enrolled between 10/2007 and 12/2010, completed a 12-item Short Form Health Survey (SF-12) and a 6-minute walk, and were followed through 2011 for death from any cause. Scores ≤25 on the SF-12 physical component indicated low self-reported physical functioning, and the first question of the SF-12 measured self-rated general health. Low functional exercise capacity was defined as ≤300 m walked during a 6-minute walk. Over a mean follow-up of 2.3 years, 86 deaths occurred among the 352 participants. A 1.6-fold (95% confidence interval, 1.0–2.7) and 1.8-fold (95% confidence interval, 1.1–2.9) increased risk of death was observed among patients with low self-reported physical functioning and low functional exercise capacity, respectively. Poor self-rated general health corresponded to a 2.7-fold (95% confidence interval, 1.5–4.9) increased risk of death compared with good to excellent general health. All measures equally discriminated between who would die and who would survive (C-statistics: 0.729, 0.750, and 0.740 for self-reported physical functioning, self-rated general health, and functional exercise capacity, respectively).

Conclusions—Three physical health status measures, captured by the SF-12 and a 6-minute walk, equally predict death among community HF patients. Therefore, the first question of the SF-12, which is the least burdensome to administer, may be sufficient to identify HF patients at greatest risk of death. (Circ Heart Fail. 2013;6:669-675.)

Key Words: health status ■ heart failure ■ mortality ■ physical functioning ■ survival

Approximately 5.7 million US adults are living with heart failure (HF), and the median survival among HF patients is only 5 years.1 Physical health status measures have been shown to predict survival among HF patients in several previous studies, although limitations involving the selection of patients and appropriate adjustment for confounding factors limit the ability to draw robust inference. For example, the 6-minute walk, which is an objective measure of physical health used widely in clinical practice, has been shown to predict mortality in HF patients.2,3 However, these studies were restricted to patients with left ventricular systolic dysfunction, and were thus not representative of the case mix of patients presenting with HF in the community.4 Furthermore, only 1 reported significant associations after adjustment for confounders.5

In addition, self-reported measures of physical health have also been shown to predict mortality in some studies of HF patients, although the results are heterogeneous and not all report significant associations.5 A few cohort studies reported significant associations of physical health status measures with mortality even after multivariable confounder adjustment.6–8 However, many others reporting significant associations were restricted to patients with either severe9 or mild to moderate HF,10 patients hospitalized for HF-related reasons,11 or were among patients enrolled in clinical trials.12,13 Furthermore, in many others, a significant association of physical health status with death was only apparent in univariate models, and no association was present after adjustment for important clinical predictors of mortality.14–17

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Because many studies examining associations of physical health status with survival were performed among subgroups of patients who are not representative of the general HF population and because of the lack of consistent association between physical health status measures and death after adjustment for important confounding variables, further work is warranted to address the utility of physical health status measures
in predicting death among HF patients in the community. Thus, the goal of our study was to assess, within community HF patients from southeastern MN (including incident and prevalent HF, inpatients and outpatients, as well as those with both preserved and reduced ejection fraction), the association of various measures of physical health with all-cause mortality.

Methods

Study Setting
This study was conducted in southeastern MN. This area of MN is relatively isolated from other urban centers, and only a few providers, including Mayo Clinic, Olmsted Medical Center, and a few other practices, deliver most health care to local residents. The Rochester Epidemiology Project, a record-linkage system, allows the indexing of medical records among residents in southeastern MN, thus enabling the retrieval of all healthcare-related events occurring in this geographic area.28,29 This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

Identification of the Study Cohort
HF diagnoses from October 2007 through December 2010 were identified among residents of Olmsted, Dodge, and Fillmore Counties, MN, using natural language processing of electronic medical records.20,21 Prompt ascertainment of HF diagnoses was possible as documentation from a clinical visit is transcribed and available in the medical records within 24 hours of the encounter. HF diagnoses were validated by trained nurse abstractors by reviewing the medical records to verify that the Framingham criteria were met.22 Both incident and prevalent HF patients identified during either an inpatient or outpatient visit and who met the Framingham criteria were eligible for participation. Patients were then contacted to obtain consent for study participation, and a follow-up visit was scheduled within 2 months to obtain a blood sample, an echocardiogram (if one was not available clinically within the past 6 months), a 6-minute walk test, and to administer questionnaires related to physical and emotional well-being, social support, and HF symptom burden.

Physical Health Status Classification
Cohort participants completed a 12-item Short Form Health Survey (SF-12) and a 6-minute walk as part of the follow-up visit. Self-reported physical functioning was assessed using the physical component of the SF-12, and those scoring ≤25 were categorized as having low self-reported physical functioning, whereas scores >25 indicated moderate to high physical functioning. In addition, the first question of the SF-12 was used as a measure of self-rated general health. Responses to the first question, “In general would you say your health is,” were categorized as poor, fair, and good to excellent general health. Finally, distance walked during a 6-minute walk defined functional exercise capacity as low (≤300 m) and moderate to high (≥300 m). We excluded from the analysis those who refused to do the 6-minute walk, but those who could not perform the 6-minute walk because of their HF were included in the low category of functional exercise capacity.

Clinical Data Collection
Current (within the past 6 months) cigarette smoking status, marital status, and educational status were obtained from medical records. Body mass index was calculated as weight (in kg) divided by height (in meters) squared. Information on comorbid conditions was abstracted from medical records and a score was calculated using the Charlson comorbidity index.23 A history of hypertension was defined as 2 or more ambulatory blood pressure readings ≥140 mm Hg systolic or ≥90 mm Hg diastolic, or a physician diagnosis of hypertension. Prevalent diabetes mellitus was defined according to the American Diabetes Association criteria.24 A clinical diagnosis documented in the medical records identified those with hyperlipidemia, depression, chronic obstructive pulmonary disease, or a previous myocardial infarction. Treatments for HF, including use of statins, β blockers, and angiotensin converting enzyme inhibitors or angiotensin II receptor blockers were manually abstracted from the medical records.

The closest serum sodium, serum creatinine, and hemoglobin values within 1 year of the HF date were obtained. Glomerular filtration rate was estimated using the Modification of Diet in Renal Disease Study equation.25 Anemia was defined by WHO criteria,26 as hemoglobin <13 mg/dL in men and <12 mg/dL in women. Resting left ventricular ejection fraction (LVEF, %) was determined using values collected from any echocardiogram performed within 6 months before to 2 months after study enrollment.

Ascertainment of All-Cause Mortality
Participants were followed through December 31, 2011 for deaths from any cause. Deaths were obtained from inpatient and outpatient medical records and death certificates obtained on a quarterly basis from the state of MN. In addition, the Mayo Clinic registration office records the obituaries and notices of death in the local newspapers.

Statistical Analysis
Statistical analyses were performed using SAS statistical software, version 9.2 (SAS Institute Inc, Cary, NC) and Splus statistical software, version 8 (TIBCO Software, Inc, Palo Alto, CA). Differences in baseline participant characteristics between low and moderate to high self-reported physical functioning were compared using 2-sample t tests for normally distributed continuous variables, Wilcoxon rank-sum tests for non-normal continuous variables, and χ² tests or Fisher exact tests for categorical variables. Person-years of follow-up were calculated from HF date until death, last follow-up visit, or December 31, 2011, whichever came first.

Kaplan–Meier survival plots were constructed to illustrate the association of physical health status measures with all-cause mortality, and differences in survival curves by physical health status level were tested using the log-rank test. The crude rates of death were computed using Poisson regression. Cox proportional hazards regression was used to estimate associations of physical health status with all-cause mortality. Variable selection for the Cox models was implemented by including a set of variables determined as important confounders a priori (age, sex, ejection fraction, incident versus prevalent HF) with the addition of other potential confounders after backward stepwise elimination using a P<0.10 cutpoint for significance. The fully adjusted Cox model included adjustment for age, sex, Charlson comorbidity index (log transformed), LVEF (<50% versus ≥50%), incident versus prevalent HF, and depression. In addition, a sensitivity analysis was performed further adjusting for anemia, estimated glomerular filtration rate, and medications (statins, β blockers, and angiotensin converting enzyme inhibitors/angiotensin II receptor blockers). The proportional hazards assumption was tested using scaled Schoenfeld residuals and found to be valid.

The concordance (C-statistic), a measure of discrimination, was calculated for the fully adjusted Cox regression models for each physical health status measure, and 95% confidence intervals (CIs) for the C-statistics were estimated using approximate jackknife methods.27 To compare the discrimination of a model with 1 physical health status measure to a model with a different physical health status measure, we created 1000 bootstrap samples, sampling individuals with replacement, and estimated a 95% CI for the difference in concordance between the 2 models. Finally, C-statistics for a fully adjusted Cox model including both self-reported physical functioning and functional exercise capacity and a second model including both self-rated general health and functional exercise capacity were calculated to determine whether a combination of physical health status measures better predicts death compared with an individual measure of physical health.

Results
A total of 902 HF patients were approached to participate in our study, and 519 (58%) consented. Of the 519 HF patients who consented to our study between October 2007 and
December 2010, 91 did not complete the questionnaire, 62 refused to do the 6-minute walk, and 14 had missing variables for the covariates in our fully adjusted model. Thus, 352 cohort participants (mean age, 72.7 years; 59.4% men) remained for analysis. Fifty (14%) patients had low self-reported physical functioning and 302 (86%) had moderate to high self-reported physical functioning. In addition, 45 (13%) reported poor, 107 (30%) reported fair, and 200 (57%) reported good to excellent general health, based on responses to the first question of the SF-12. Finally, 155 (44%) had low and 197 (56%) had moderate to high functional exercise capacity.

HF patients reporting low physical functioning were more likely to be women, had a higher Charlson comorbidity index, were more likely to have depression, and had slightly higher LVEF compared with those with moderate to high self-reported physical functioning (Table 1). Thirty-four (68.0%) of those with low self-reported physical functioning had prevalent HF and 16 (32.0%) had incident HF. In those with moderate to high self-reported physical functioning, 165 (54.6%) had prevalent HF and 137 (45.4%) had incident HF.

Over a mean follow-up of 2.3 years (maximum of 4.2 years), 86 deaths occurred. Low levels of self-reported physical functioning and functional exercise capacity and poor self-rated general health were associated with worse survival compared to prevalent HF and 137 (45.4%) had incident HF. In those with moderate to high self-reported physical functioning, 165 (54.6%) had prevalent HF and 137 (45.4%) had incident HF.

Table 1. Baseline Participant Characteristics by Self-Reported Physical Functioning

<table>
<thead>
<tr>
<th>Value</th>
<th>Overall (n=352)</th>
<th>Low (n=50)</th>
<th>Moderate to High (n=302)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at heart failure onset, y</td>
<td>76 (65–83)</td>
<td>76 (66–84)</td>
<td>76 (64–83)</td>
<td>0.52</td>
</tr>
<tr>
<td>Male</td>
<td>209 (59.4)</td>
<td>23 (46.0)</td>
<td>186 (61.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.9 (26.2–34.8)</td>
<td>31.1 (27.8–36.4)</td>
<td>29.7 (26.0–34.5)</td>
<td>0.12</td>
</tr>
<tr>
<td>Current smoking status</td>
<td>28 (8.0)</td>
<td>3 (6.0)</td>
<td>25 (8.3)</td>
<td>0.78</td>
</tr>
<tr>
<td>Married</td>
<td>215 (61.1)</td>
<td>27 (54.0)</td>
<td>188 (62.3)</td>
<td>0.27</td>
</tr>
<tr>
<td>&gt;High-school education</td>
<td>164 (48.0)</td>
<td>18 (37.5)</td>
<td>146 (50.0)</td>
<td>0.18</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>3 (2–5)</td>
<td>5 (3–7)</td>
<td>3 (2–5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate, mL/min per 1.73 m²</td>
<td>57.8 (22.7)</td>
<td>54.5 (27.2)</td>
<td>58.3 (21.9)</td>
<td>0.30</td>
</tr>
<tr>
<td>Serum sodium, mmol/L</td>
<td>140 (138–142)</td>
<td>140 (138–142.6)</td>
<td>140 (138–142)</td>
<td>0.61</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>285 (81.0)</td>
<td>41 (82.0)</td>
<td>244 (80.8)</td>
<td>0.84</td>
</tr>
<tr>
<td>Hypertension</td>
<td>318 (90.3)</td>
<td>48 (96.0)</td>
<td>270 (89.4)</td>
<td>0.20</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>132 (37.5)</td>
<td>24 (48.0)</td>
<td>108 (35.9)</td>
<td>0.10</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>92 (26.1)</td>
<td>17 (34.0)</td>
<td>75 (24.8)</td>
<td>0.17</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>90 (25.6)</td>
<td>19 (38.0)</td>
<td>71 (23.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Depression</td>
<td>135 (38.4)</td>
<td>26 (52.0)</td>
<td>109 (36.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Ejection fraction &lt;50%</td>
<td>192 (54.5)</td>
<td>23 (46.0)</td>
<td>169 (56.0)</td>
<td>0.19</td>
</tr>
<tr>
<td>Prevalent heart failure</td>
<td>199 (56.5)</td>
<td>34 (68.0)</td>
<td>165 (54.6)</td>
<td>0.08</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>293 (83.2)</td>
<td>43 (86.0)</td>
<td>250 (82.8)</td>
<td>0.57</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors/angiotensin II receptor blockers</td>
<td>240 (68.2)</td>
<td>31 (62.0)</td>
<td>209 (69.2)</td>
<td>0.31</td>
</tr>
<tr>
<td>Statins</td>
<td>206 (58.5)</td>
<td>29 (58.0)</td>
<td>177 (58.6)</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Values are mean (SD) or median (25th, 75th percentile) for continuous variables and n (%) for categorical variables.
In this prospective study of HF patients in the community, 3 physical health status measures predicted all-cause mortality over a mean follow-up of 2.3 years. A 1.6-fold increased risk of death was found for individuals who scored low (≤ 25 points) on the SF-12 physical component and a 1.8-fold increased risk of death was observed among those who walked ≤ 300 m during a 6-minute walk. In addition, compared with those rating their general health as good to excellent, those indicating poor health exhibited a 2.7-fold increased risk of all-cause mortality. Each of these physical health status measures, when added to a model with age, sex, Charlson comorbidity index, LVEF, incident versus prevalent HF, and depression had equally good discrimination for predicting death. Most importantly, a single question asking a patient to rate his or her general health, which can be very easily administered, performed as well as an objective measure often used in clinical practice, the 6-minute walk. However, the combination of 2 physical health status measures in 1 model did not improve the ability to discriminate who would die and who would survive over a single measure of physical health.

Self-Reported Measures of Health and Mortality
Self-rated measures of health have been shown to predict mortality independently of objective physical measures of health, indicating that patients may have knowledge about their health beyond what is objectively measured by their physician. In HF patients, a single question about perceived health included in the 36-item Short Form and SF-12 questionnaires, “In general would you say your health is,” with responses of excellent, very good, good, fair, and poor, has been shown to be predictive of survival. Fair or poor and good self-rated perceived health were associated with 4.2-fold and 2.3-fold increased risks of all-cause mortality and 4.9-fold and 2.4-fold increased risks of cardiovascular mortality, respectively, compared with those reporting excellent or very good health.

In addition, the physical component scores of the SF-12 or 36-item Short Form have also been predictive of death in 3 studies; however, after adjustment for confounders, only 1 of these studies still reported an association of physical functioning with death. In that study of patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) trial, patients scoring below the median on the physical component score of the SF-12 exhibited an 89% increased risk of death, whereas a 42% increased risk of death was observed for each 10-point decrease in the physical component score in multivariable models.

Our results build on the previous findings adding evidence that measures of physical health are independently associated with all-cause mortality in active HF patients from the community. We observed, even after adjustment for important confounding factors such as demographics, comorbidities, LVEF, incident versus prevalent HF, and depression, a 2.7-fold increased risk of death among those reporting poor general health compared with good to excellent general health and a 1.6-fold increased risk of death among individuals scoring ≤25 versus >25 on the physical component of the SF-12. In addition, our study included both inpatients and outpatients, as well as those with both preserved and reduced ejection fraction, and is thus more representative of HF patients in general than most previous studies.

Objective Measures of Health and Mortality
Although self-rated measures of health have been shown to be more predictive of death and may also be more predictive of changes in health-related quality of life compared with objective measures of health, some objective measures of physical health have been shown to predict death in HF patients. Among HF patients with an LVEF <40%, a 30-m increase in walk distance during a 6-minute walk was associated with a 16% reduction in death in univariate models; associations were similar after adjustment for age, New York
Heart Association class, and C-reactive protein, although they became nonsignificant (hazard ratio, 0.85; 95% CI, 0.71–1.02). In the Studies of Left Ventricular Dysfunction (SOLVD) Registry Substudy, a 3.7-fold and 2.8-fold increased risk was found among individuals walking <300 m and between 300 and 375 m, respectively, compared with those walking >450 m during a 6-minute walk test. After adjustment for age, sex, cause of HF, New York Heart Association class, and LVEF, a 50% increased risk of death with a decrement of 120 m walked was reported.2 Within our cohort, those walking >450 m during a 6-minute walk test.2 After adjustment for age, sex, cause of HF, New York Heart Association class, and C-reactive protein, although they became nonsignificant (hazard ratio, 0.85; 95% CI, 0.71–1.02). In the Studies of Left Ventricular Dysfunction (SOLVD) Registry Substudy, a 3.7-fold and 2.8-fold increased risk was found among individuals walking <300 m and between 300 and 375 m, respectively, compared with those walking >450 m during a 6-minute walk test. After adjustment for age, sex, cause of HF, New York Heart Association class, and LVEF, a 50% increased risk of death with a decrement of 120 m walked was reported.2 Within our cohort, a 1.8-fold increased risk of death was found among those who walked ≤300 m compared with those who walked >300 m. In addition, we found the 6-minute walk to be equally predictive of death as self-reported physical functioning and self-rated general health, even after controlling for demographics, comorbidity, LVEF, incident versus prevalent HF, and depression.

Clinical Implications
Our results indicate that measures of physical health, including self-rated measures based on the responses to the SF-12 and an objective measure based on distance walked during a 6-minute walk test, independently predict all-cause mortality equally well in patients with HF. In particular, the independent associations of self-rated measures of health with mortality indicate that patients may have knowledge about their health above and beyond what can be measured by tests, the presence of comorbidities, and physician assessments of patients’ physical state. Thus, the addition of a self-rated measure of health in the management of HF patients may be a useful tool as an indicator of prognosis.

Limitations and Strengths
There are some limitations to consider while interpreting these results. First, the relatively small sample size of our cohort and the small number of deaths that occurred among patients in our cohort affected the precision of our estimates and may have limited our ability to detect differences among the different physical health status measures or between a model with 2 physical health status measures compared with a model with only 1 measure of health status. In addition, these factors may have limited our ability to identify potential effect modifiers of the association between physical health status measures and all-cause mortality and to conduct stratified analyses by potential effect modifiers. Second, our study results may have been impacted by differences in patients willing to enroll in the study compared with those who refused. Third, deaths occurring outside of MN may not have been captured; however, we expect very minimal misclassification of the outcome such that our results would not be affected. Finally, the vast majority of participants in our cohort were white, and although the results may be generalizable to other whites throughout the United States, it is
possible that our results are not well generalizable to individuals of other race groups or ethnicities.

Our study also has several strengths. Our prospective cohort consists of active HF patients from the community (both inpatients and outpatients with either incident or prevalent HF, including those with both preserved and reduced ejection fraction) enrolled after rigorous validation of each HF event. After enrollment, participants completed the SF-12 and underwent a 6-minute walk, thus allowing the comparison of different physical health status measures, individually or in combination, in the prediction of all-cause mortality in community HF patients.

Conclusions

We have shown that 3 different measures of physical health, captured by responses to the SF-12 and distance walked during a 6-minute walk test, independently predict survival among community patients with HF. Each of these 3 measures had good discrimination and predicted death equally well. Moreover, the use of 2 physical health status measures did not improve predictive ability. Thus, any measure of physical health may be useful in the management of HF, but the first question of the SF-12, which is the least burdensome, may be sufficient to identify HF patients at greatest risk of death. Further research, including developing individual risk-prediction models in large cohorts of HF patients, is warranted.

Acknowledgments

We thank Kay A. Traverse, RN for assistance in data collection, Jill M. Killian and Ruoxiang Jiang for assistance with statistical analysis, and Deborah S. Russell for secretarial assistance.

Sources of Funding

This work was supported by grants from the National Institutes of Health (RO1 HL72435) and the National Institute on Aging (RO1 AG034676). Dr Roger is an Established Investigator of the American Heart Association. The funding sources played no role in the design, conduct, or reporting of this study.

Disclosures

None.

References


Physical health status has been shown to predict death in heart failure (HF) patients; however, community data are lacking. The goal of our study was to assess, within community HF patients (including incident and prevalent HF, inpatients and outpatients, as well as those with both preserved and reduced ejection fraction), the association of various measures of physical health with all-cause mortality. Three measures of physical health, including 2 self-rated measures based on the 12-item Short Form Health Survey and an objective measure based on a 6-minute walk test, independently predicted mortality. HF patients who scored ≤25 on the 12-item Short Form Health Survey physical component exhibited a 1.6-fold increased risk of death compared with those with scores >25. Patients who responded poor to the first question of the 12-item Short Form Health Survey, “In general would you say your health is,” had a 2.7-fold higher risk of death compared with those who answered good, very good, or excellent. Those who walked ≤300 m during a 6-minute walk exhibited a 1.8-fold increased risk of mortality compared with those who walked >300 m. In addition, all 3 physical health status measures equally discriminated between who would die and who would survive, and the use of 2 measures together did not improve the predictive ability beyond a single measure. Therefore, any of these measures may be useful in the management of HF. However, the administration of a single question asking a patient to rate their general health is the least burdensome, yet provides valuable information about the patient’s current state of physical health.
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_Circ Heart Fail._ 2013;6:669-675; originally published online April 26, 2013; doi: 10.1161/CIRCHEARTFAILURE.112.000291
_Circulation: Heart Failure_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

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