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Memory dysfunction, psychomotor slowing, and decreased executive function predict mortality in patients with heart failure and low ejection fraction

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Abstract

Background—The purpose of this study was to evaluate whether dysfunction of *specific cognitive abilities* is a predictor of impending mortality in adults with systolic heart failure (HF).

Methods—166 stable outpatients with HF completed cognitive function evaluation in language, working memory, memory, visuospatial ability, psychomotor speed, and executive function using a neuropsychological test battery. Demographic and clinical variables, comorbidity, depressive symptoms, and health-related quality of life were also measured. Patients were followed for 12 months to determine all-cause mortality.

Results—There were 145 survivors and 21 deaths. In logistic regression analyses, significant predictors of mortality were lower left ventricular ejection fraction (LVEF) and poorer global cognitive scores as determined by the Mini-Mental State Examination (MMSE), working memory, memory, psychomotor speed, and executive function. Memory loss was the most predictive cognitive function variable (overall $\chi^2 = 17.97$, $df = 2$, $p < .001$; Nagelkerke $R^2 = .20$). Gender was a significant covariate in two models, with men more likely to die. Age, comorbidity, depressive symptoms, and health-related quality of life were not significant predictors. In further analyses, significant predictors

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of mortality were lower systolic blood pressure and poorer global cognitive function, working memory, memory, psychomotor speed, and executive function, with memory being the most predictive.

Conclusions—As hypothesized, lower LVEF and memory dysfunction predicted mortality. Poorer global cognitive score as determined by the MMSE, working memory, psychomotor speed, and executive function were also significant predictors. LVEF or systolic blood pressure had similar predictive values. Interventions are urgently needed to prevent and manage memory loss in HF.

Keywords

heart failure; mortality; memory dysfunction; cognitive impairment

Chronic heart failure (HF) is a disabling condition that affects more than 5.6 million people in the United States and is increasing in prevalence worldwide.^{1,2} Mortality rates for patients with HF are high, with 12-month mortality approaching 20%.¹ In 2005, HF was noted on 292,214 death certificates in the United States and was listed as the underlying cause of death on 58,933 of those certificates. Predictors of impending death among 48,612 patients (mean age = 73.2 years) hospitalized for HF were age, heart rate, systolic blood pressure, serum sodium, creatinine, and the presence or absence of left ventricular systolic dysfunction.³ Predictors of early mortality after hospital discharge (60 to 90 days) among 4,402 patients (mean age = 73.1 years) were age, creatinine, comorbid conditions of reactive airway disease or liver disease, lower systolic blood pressure, lower serum sodium, lower admission weight, and depression.⁴ In a community-based sample of 2,445 patients (mean age = 76 years) followed after an acute HF episode, patients at increased risk of dying were age 85 years and older, had a history of chronic obstructive pulmonary disease or HF, and had an elevated serum urea nitrogen level during hospitalization.⁵ In the Seattle Heart Failure Model, 14 variables predicted mortality among five samples of HF patients, including left ventricular ejection fraction (LVEF) and New York Heart Association (NYHA) class.⁶ Serial measures of health status were linearly associated with all-cause mortality in HF (n = 1,358),⁷ but the association between health status and cardiovascular events is inconsistent across studies.⁸

Although measured infrequently by clinicians, cognitive dysfunction has been identified as another predictor of mortality among patients with HF.^{9–11} Understanding the associations between the *dysfunction of specific cognitive abilities* and mortality in HF patients is important because cognitive dysfunction is common in HF. More than 82 studies have been conducted that provide evidence that cognitive dysfunction occurs in HF.^{12–14} Twenty-five to 50% of patients with HF have cognitive dysfunction and in one study 80% had dysfunction. The dysfunction is most often in the domains of *language*, working memory, memory, psychomotor speed, and executive function.^{12–16} Cognitive dysfunction is associated with increased HF severity and in some studies, with longer HF duration, older age, and increased comorbidity.^{12,13,16,17}

The cognitive dysfunction that occurs in HF – particularly decreased attention, memory loss, psychomotor slowing, and diminished executive function – compromises patients' ability to comply with complex medical regimens and dietary sodium restrictions and to make self-care decisions. Noncompliance with medications and diet therapy is frequently documented among HF patients.^{18,19} Likewise, difficulties that patients have in monitoring symptoms of fluid volume excess are reported.²⁰ This inability to comply with therapy, make decisions, and perform HF self-care because of cognitive dysfunction may contribute to mortality.

In a pivotal study using data from 968 elderly hospitalized patients obtained from a large multisite database (mean age 78 years; SD ± 9), the patients with cognitive impairment at baseline had significantly higher inpatient mortality as well as out-of-hospital mortality 12

months later. After adjusting for confounders, patients with cognitive impairment had almost a fivefold increase in mortality (relative risk = 4.9; 95% confidence interval 2.9 to 8.3).⁹ Further analysis of these data (n = 13,635 patients, 1,583 with HF) indicated that systolic blood pressure of less than 130 mm Hg was associated with the cognitive impairment but only among the patients with HF (odds ratio = 0.78, 95% confidence interval 0.71 to 0.86).²¹ In another study, investigators evaluated 1,092 elderly hospitalized patients (mean age 79.5 years); 165 of the patients had HF.¹⁰ The 6-month mortality was 11.8% for the total sample, 5.7% for patients without HF or cognitive impairment, 19% for patients with HF but no cognitive impairment, 31% for patients without HF but with cognitive impairment, and 35.6% for patients with both HF and cognitive impairment (p < .0001). Heart failure patients with cognitive impairment had a significantly increased risk of death compared to HF patients without impairment.

Cognitive impairment predicted 5-year all-cause mortality among 200 elderly patients with HF enrolled in a disease management intervention study.¹¹ Patients were randomized to a specialized HF management program or usual care. Using the Mini-Mental Status Examination (MMSE) to assess cognition, 13.5% of the 200 patients were identified as having cognitive impairment at baseline. Five years later, the patients with baseline cognitive impairment (mean age 80.7 years) had an increased risk of death compared to patients without cognitive impairment (mean age 74.8 years) (96.3% versus 68.2%; relative risk 2.19, 95% confidence interval 1.41 to 3.39; p < .01) regardless of whether they received the specialized intervention program or usual care.

The above studies were important in highlighting the role of cognitive impairment in mortality among HF patients, but they had limitations. Two of the studies included only hospitalized patients,^{9,10} one used a retrospective design,⁹ two were conducted at solitary sites,^{10,11} and all three studies focused on elderly patients and used a single mental status screening questionnaire to assess cognitive dysfunction. Thus, little is known about the associations between the dysfunction of specific cognitive abilities (language, working memory, memory, visuospatial ability, psychomotor speed, and executive function) and mortality in general outpatients with HF.

Knowledge about the dysfunction of *specific cognitive abilities* that contributes to mortality in HF is needed to guide intervention design. For example, if decreased memory is associated with mortality, memory-enhancing interventions would be indicated in addition to compensatory interventions (e.g., educating family caregivers). Alternatively, if diminished executive function is associated with mortality, interventions targeted at assisting patients with self-care decision making and problem solving would be indicated (e.g., contacting their health care providers for early changes in their condition).²² No studies were found that examined the dysfunction of *specific cognitive abilities* as predictors of mortality in a general sample of outpatients with HF using a valid, reliable neuropsychological test battery. Therefore, the purpose of this study was to evaluate whether the dysfunction of *specific cognitive abilities*, measured at baseline, is an early indicator of impending mortality among 166 patients with chronic HF. We hypothesized that among patients with HF, LVEF and dysfunction in language, working memory, memory, visuospatial ability, psychomotor speed, and executive function predict 12-month all-cause mortality. We use the term cognitive dysfunction in this paper rather than cognitive impairment to indicate decreases in cognitive function but not a pre-specified cutoff value that would indicate impairment.

Methods

Procedures

A prospective study design was used. The data were collected as part of a larger study conducted to evaluate cognitive dysfunction among 414 participants (249 HF patients, 63 healthy

participants, and 102 medical participants).²³ Data were collected from September 2004 through April 2009. The HF patients were enrolled from five *outpatient* clinic sites in the Midwest. Eligible patients were invited to participate in the study by clinic staff members. The names and contact information of interested patients were provided to members of the research team. After obtaining informed consent, the baseline data were collected by trained research assistants during face-to-face interviews. The time to complete the baseline interviews were 90 to 120 minutes. A subset of the last 166 patients of the 249 HF patients enrolled in the larger study were re-contacted by telephone 12 months after the face-to-face interviews to obtain follow-up data about their health. At that time, mortality was determined. The study was approved by the institutional review boards at the sites and all participants completed written informed consent.

Sample

Patients with chronic systolic HF and a left ventricular ejection fraction (LVEF) of 40% or less, documented by echocardiographic, nuclear imaging, or cardiac catheterization *in the previous two years*, were eligible for the study. Patients were excluded if they had *documented* conditions known to cause cognitive deficits (e.g., Parkinson's, stroke, *dementia*) or a terminal diagnosis (e.g., end-stage cancer, referral to hospice).²³

Measures

Mortality—Mortality at 12 months after baseline was the outcome measure. Mortality status was obtained during telephone calls to patients' homes to obtain information about their health in the past 12 months. Occurrence and the dates of death were verified by the patients' family members, health care providers, and searches of public death records.

Cognitive dysfunction—To measure cognitive dysfunction, patients completed a neuropsychological test battery designed to be sensitive to cardiovascular conditions.²⁴ All tests have documented validity and reliability and have been shown to discriminate among persons with normal cognition, mild cognitive impairment, and dementia. Although the tests were used to sample a specific cognitive domain, each test actually samples multiple domains. The Mini-Mental State Examination (MMSE) was administered to assess global cognitive function.²⁵ It is a brief 30-point screening measure; higher scores indicate better global cognitive function.²⁵ The Wechsler Test of Adult Reading was administered to estimate premorbid intellect (mean = 100; standard deviation = 15).²⁶ For this test, participants are asked to pronounce a list of words that are phonologically irregular; higher scores are better.

The Boston Naming Test, administered to assess the language domain, requires participants to name the line drawings of common items.²⁷ Higher scores indicate greater ability (raw score = 0 to 60). The Wechsler Adult Intelligence Scale, 3rd edition (WAIS-3) Digit Span Subtest was administered to assess working memory.²⁸ Participants are asked to remember series of numbers that are presented verbally. The raw forward and backward spans were analyzed separately and the total score was transformed into a scaled score (possible forward score 0 to 16; possible backward score 0 to 14; possible scaled score mean = 10, standard deviation = 3 as derived from the WAIS-3). The Hopkins Verbal Learning Test was administered to assess verbal learning and memory.²⁹ Participants are asked to learn an orally presented list of twelve words over three trials, with recall after each list presentation. After a 20-minute delay, they are asked to recall as many of the 12 words as they can. The possible total recall score range is 0 to 36 and the possible delayed recall score range is 0 to 12; higher scores are better. The Figure Copy and Figure Memory Tests were administered to assess visuospatial ability and memory.³⁰ Participants are shown five figures of increasing complexity and are asked to draw each figure. After a 20-minute delay, they are asked to draw the figures again. The variables

analyzed were total (possible score range 0 to 11) and recall (possible score range 0 to 14) with higher scores indicating better performance.

The Digit Symbol Subtest from the WAIS-3 and the Trail Making Test Part A were administered to assess psychomotor speed.^{28,31} In the Digit Symbol Subtest, participants are required to match numbers with symbols using a key that provides the unique pairing of the numbers with symbols. The measure of analysis was the scaled score derived from the WAIS-3 standardization sample (mean = 10, standard deviation = 3). The Trail Making Test Part A requires participants to draw a line that connects numbered circles arrayed on a page as fast as possible. The measure of analysis was the number of seconds to complete the task, with higher scores (longer times) reflecting slowing psychomotor speed.

The Trail Making Test Part B and the Controlled Oral Word Association were administered to assess executive function.^{31,32} For the Trail Making Test Part B, participants are asked to connect numbered and lettered circles sequentially as fast as possible in alternate alpha-numeric order (i.e., number-letter-number-letter). The measure of analysis was the number of seconds to complete the task; higher scores indicate worse performance. For the Controlled Oral Word Association, participants are given a letter of the alphabet and asked to name as many words as possible that begin with that letter. The measure of analysis was the number of words produced after 90 seconds for the letters C, F, and L; higher scores are better.

Demographic, clinical and psychological variables—Demographic and clinical measures were obtained to describe the sample. Additionally, they were compared between the patients who were alive at 12 months with those who died. The LVEF was obtained from the patients' records as part of the inclusion criteria. The New York Heart Association (NYHA) class,³³ HF duration, and blood pressure were assessed during the baseline interviews. The Duke Activity Status Index, a valid reliable measure, was used to measure perceived functional capacity.^{34,35} In this sample, the reliability of the Duke Activity Status Index was Cronbach's alpha 0.82. The Charlson Comorbidity Index,³⁶ was used to measure multiple chronic conditions common in HF. The Index³⁶ is a 21-item list of conditions with “yes” and “no” response scales; a summary score is obtained. The predictive validity of the Index has been reported.^{37,38}

Two psychological variables that were evaluated in the parent study were compared for between patients who were alive at 12 months with those who died for consideration as covariates. Depressive symptoms are common in HF³⁹ and were measured using the Patient Health Questionnaire-8 (PHQ-8).^{40,41} The PHQ-8 is an 8-item questionnaire with 4-point response scales. Higher scores indicate more depressive symptoms. Validity and reliability have been reported;^{41,42} in the current sample the Cronbach's alpha was 0.78. Health-related quality of life was measured using the Minnesota Living with Heart Failure Questionnaire.^{43,44} This 21-item questionnaire with 6-point response scales was developed to measure HF-specific quality of life. Validity and reliability have been reported. In this sample, the Cronbach's alpha was 0.92.

Statistical Analyses

Descriptive statistics were computed for all study variables. Univariate analyses were conducted to compare differences in the variables between the patients who were alive at 12 months with those who died. Student t-tests were used for continuous variables and χ^2 tests were used for categorical variables. Pearson's correlation coefficients, tolerance, and variance inflation factors were computed to assess collinearity among the predictor variables.^{45–47} Correlations of 0.80 or higher between variables, tolerance of 0.1 or lower, and variance inflation factors of 10 or higher were considered indicative of collinearity.

Logistic regression analysis was used to determine predictors of mortality.⁴⁷ A series of regression models was conducted to evaluate *LVEF* and the dysfunction of *specific cognitive abilities* as predictors. Two or three predictor variables were entered simultaneously in the models, based on the sample size of the smaller group of 21 patients who died.⁴⁸ Left ventricular ejection fraction was entered as the first predictor because of its significance in the univariate analyses and its known effect on HF mortality.^{3,6} Next, the cognitive function variables that were significant at $p < .10$ in the univariate analyses were entered as predictors (single neuropsychological test entered in separate equations). Finally, other variables that were significant in the univariate analyses and were significant predictors of mortality in past studies (systolic and diastolic blood pressure, comorbidity) were entered as predictors.^{3,4,5,21} The odds ratios, the Wald statistic and significance levels, and the confidence intervals were examined to evaluate the individual predictor variables. The overall χ^2 was examined to evaluate the goodness of fit and the Nagelkerke R^2 was examined as an index of the partial correlation between the outcome and the predictor variables. The significance level was set at $p < .05$ for logistic regression analyses.

Results

Table 1 presents the demographic and baseline variables for the total sample of 166 patients and of the patients who were alive and those who died over the 12 months. Twelve months after the baseline interviews, 145 patients (87%) were living and 21 patients (13%) had died. A higher percentage of men died compared to women over the 12 months ($p = .056$). No significant differences were found in age, race, ethnicity, marital status, education, and premorbid intellect between the patients who were alive and those who died.

Compared to patients who were alive at 12 months, those who died had significantly lower mean LVEF ($p = .014$). Other variables related to HF were also significantly different between the groups. Patients who died had lower systolic and diastolic blood pressures ($p = .001$ and $.004$, respectively) and poorer perceived functional capacity (Duke Activity Status Index, $p = .001$). No differences were found in NYHA class between the groups ($p = .16$). The patients who died had a longer duration of HF ($p = .064$) and were more likely to have a biventricular pacemaker ($p = .036$). No differences were found in medications between the groups. The patients who died tended to have more comorbid conditions although the mean score differences were small ($p = .052$). No differences were found in depressive symptoms and health-related quality of life between patients who were alive compared with those who died.

Table 2 presents the comparisons of the baseline neuropsychological test scores of patients who were alive at 12 months with those who died. Patients who died had worse scores on measures of *global cognitive function* (MMSE, $p = .004$), working memory (Digit Span backward, $p = .018$), memory (Hopkins Verbal Learning Test delayed recall, $p = .047$); visuospatial ability and recall (Figure Copy, $p = .086$ and Figure Memory recall, $p < .001$), psychomotor speed (Digit Symbol scaled, $p = .031$; Trail Making Test A, $p = .023$), and executive function (Trail Making Test B, $p = .035$). *Therefore*, these variables were evaluated in the logistic regression models because they were significant at the univariate level at $< .10$.

In assessment of collinearity, only the Digit Span scaled score demonstrated possible collinearity with a tolerance of 0.1 and a variance inflation factor of 9.8; it was not used in the analyses. Table 3 and Figure 1 present the results of the logistic regression analyses. *The LVEF was significant in all of the models.* The MMSE, the Digit Span backward, the Hopkins Verbal Learning Test delayed recall, the Figure Memory recall, the Digit Symbol, and the Trail Making Test Parts A and B were significant predictors, as indicated by the Wald statistic significance level, the odds ratios, and the confidence intervals. The overall χ^2 was significant in these models and the Nagelkerke R^2 ranged from 0.14 to 0.20. The model with Figure Memory recall

was most significant. Systolic blood pressure, diastolic blood pressure, and comorbidity *were entered separately as a third predictor* after the LVEF and the cognitive function variables. Systolic blood pressure was significant in most of the models, but the same cognitive function variables remained significant. Diastolic blood pressure and comorbidity were not significant in most of the models and did not improve the goodness of fit.

To further investigate blood pressure, age, and gender as predictors of mortality, additional series of logistic regression models were conducted a posteriori. In the first series, systolic blood pressure was entered as the first predictor variable and the cognitive function variables were entered (each in a separate equation) as the second predictor variable (Table 4). Results of these models were similar to the results with LVEF as the first predictor variable. The systolic blood pressure was significant in all models and the MMSE, the Digit Span backward, the Hopkins Verbal Learning Test delayed recall, the Figure Memory recall, the Digit Symbol, and the Trail Making Test Parts A and B were significant predictor variables. The overall χ^2 was significant in these models and the Nagelkerke R^2 ranged from 0.14 to 0.21.

In the next series of analyses, diastolic blood pressure was entered as the first predictor variable and the cognitive function variables were entered as the second predictor variable. Diastolic blood pressure was significant in all of the models except the model with the Figure Memory recall where Figure Memory recall was the only significant predictor; this model had the best goodness of fit index (overall $\chi^2 = 15.41$, $p = .000$; Nagelkerke $R^2 = 0.17$). The odds ratios, the overall χ^2 , and the Nagelkerke R^2 values were lower in the models with diastolic blood pressure than the models with LVEF or systolic blood pressure.

Finally, a series of analyses was conducted in which all logistic regression models were re-run with age and gender entered as covariates. Age was not significant in any of the models. Gender was a significant predictor in two of the eight models. In the model with LVEF and Figure Copy, gender was significant ($p = .047$, odds ratio = 3.75). In the model with the LVEF and the Trail Making Test A, gender was also significant ($p = .036$, odds ratio = 4.333). In the models with systolic blood pressure and cognitive function, gender was not a significant covariate.

Discussion

To our knowledge, this is the first study to report that dysfunction in specific cognitive abilities of working memory, memory (verbal learning and visuospatial recall), psychomotor speed, and executive function are predictors of 12-month all-cause mortality in a general sample of outpatients with chronic HF. More severe HF as indicated by lower LVEF and worse scores on the MMSE, the Digit Span backward, the Hopkins Verbal Learning Test (delayed recall), the Figure Memory recall, the Digit Symbol, and the Trail Making Test Parts A and B were significant predictors of mortality. Importantly, the decrements in *cognitive dysfunction* were present at baseline and presaged mortality in this sample. A one-unit increase in the MMSE, the Digit Span backward, the Figure Memory recall, or the Digit Symbol scaled score would be predictive of reducing the odds of death by about a fourth. A one-unit increase in the Hopkins Verbal Learning Test delayed recall would be predictive of reducing the odds of death by about a fifth. The odds ratios were smaller for the Trail Making Test Parts A and B, with a one-unit increase in those tests predictive of reducing the odds of death by 1% and 2%, respectively. Overall, the logistic regression results indicate that about a 25% reduction in the odds of mortality independent of LVEF are clinically important.

The results of the present study are consistent with and extend the work of past investigators who found that global measures of cognitive dysfunction were associated with mortality.^{9–}

¹¹ The MMSE was a significant predictor of mortality in this sample, but it is a global measure

that does not provide direction for intervention. It is not surprising that the MMSE would differ between patients who did and did not die because it is designed to detect patients with the most cognitive dysfunction who require further evaluation. However, the MMSE is not as sensitive as other measures for detecting cognitive dysfunction. For example, in discriminating between 21 patients with mild cognitive impairment and 98 cognitively healthy persons, the MMSE had a specificity of 69% and a sensitivity of 44% compared with the Hopkins Verbal Learning Test that had a specificity of 95% and a sensitivity of 79%.⁴⁹ If the MMSE is the only measure used to evaluate cognitive dysfunction, some patients with memory dysfunction in need of intervention would not be identified.^{16,49} The measures *in the current study* requiring memory in the form of *learning and recall* of recent information were significant predictors of mortality. Memory is a complex process that includes the ability to encode, store, and retrieve information.⁵⁰ Recent evidence suggests that memory is a collection of mental abilities and is dependent on separate memory systems within the brain.^{50,51} These memory systems are the ways that the brain processes information for use at a later time.⁵¹ Memory loss has profound consequences for patients and their family members, limiting patients' abilities to adhere to treatment regimens and to perform instrumental activities of daily living.^{50,51}

The finding that diminished performance on tests of memory independently predicted mortality lends support to cerebral hypoperfusion as the etiology for cognitive dysfunction in HF. It was previously believed that the brain was protected from low cardiac output,⁵² but the evidence has converged to support that structural brain changes occur in HF^{53–58} and that patients have cognitive dysfunction that is consistent, to some degree, with these structural brain changes.^{12–16} The most likely mechanisms underlying the memory dysfunction are cerebral hypoperfusion resulting from decreased cardiac output and altered cerebral autoregulation.^{53–58} In three studies using magnetic resonance imaging, Woo and colleagues^{53–55} compared the brain structures of HF patients and age-matched healthy participants. Compared to the healthy participants, the HF patients had significantly more gray matter loss in the parahippocampal areas⁵³ and significantly reduced mammillary body volumes and fornix cross-sectional areas bilaterally after controlling for age, gender, and intracranial volume.⁵⁴ Furthermore, the HF patients had higher values of T2 relaxation that indicated injured brain areas in the sites that are responsible for episodic memory and working memory, including the hippocampus, the fornix fibers, and the frontal lobes.^{50,51,55} The changes are consistent with cerebral hypoperfusion and cerebral autoregulation abnormalities, but global reductions in brain volumes were not noted so it is unlikely that cerebral hypoperfusion was the only cause of the deficits.⁵⁵ Woo and colleagues found no evidence of emboli as an etiology of cognitive dysfunction,^{53–55} although other investigators reported a 34% prevalence of silent strokes among 168 consecutive patients being evaluated for transplantation.⁵⁹ Further research is needed to determine the specific etiologies of the cognitive dysfunction of HF to prevent this disabling condition.

The mean LVEF and systolic and diastolic blood pressures differed significantly between the patients who were alive at 12 months and those who died. The LVEF is a known predictor of HF mortality and was significantly and independently associated with mortality in this sample, lending validity to the study results. However, systolic blood pressure had similar predictive values compared to models with LVEF. The lower LVEF and lower systolic blood pressure noted in the group of patients who died are indicators of more severe HF that predicted mortality, and in our study *decreased working memory*, *memory loss*, *psychomotor slowing*, and *executive function* are other indicators of more severe HF.^{9,60} Memory loss is likely associated with end-organ damage that occurs as part of the HF syndrome. Previously, investigators found a relationship between LVEF and cognitive dysfunction in HF patients.^{61–63}

We found limited support for comorbidity as a predictor of mortality. The mean score differences in comorbidity were small, and it was not significant in the logistic regression models. Others found specific comorbid conditions of liver disease⁴ and chronic obstructive pulmonary disease⁵ were significant mortality predictors. *In this sample*, men had higher mortality than women. The sample included more men than women and in a separate analysis, the men had significantly poorer memory, slower psychomotor speed, and visuospatial recall ability than women.¹⁶ Gender was a significant covariate in two models with LVEF and cognitive function variables, but the current study was limited in sample size to compare men and women. Further prospective studies are needed with larger samples to fully evaluate differences between men and women in cognitive dysfunction and mortality.

In contrast to past studies,^{3–5,39,64,65} we found no differences in age, depressive symptoms, and health-related quality of life between the patients who were alive and who died at 12 months. Patients in the current study were younger with a mean age of 65.6 years compared to the other samples in which the mean ages were older than 70 years of age. As a covariate, age was not a significant predictor in any of the logistic regression analyses, supporting HF (i.e., LVEF, systolic blood pressure) and cognitive dysfunction as predictors of mortality independent of age. Additionally, compared to patients in past studies, patients in the current sample were recruited as outpatients rather than during hospitalization. In past studies, depressive symptoms were predictors of poor outcomes, including mortality,^{39,64,65} but none measured cognitive dysfunction. Survey measures of depressive symptoms such as the PHQ-8 are valid and reliable, but they may not fully capture the brain or other physiological changes that occur with depressive symptoms and that are associated with mortality. Investigators have found that health-related quality of life and health status are predictors of mortality,⁸ but our results did not support this association. Again, none of these studies measured cognitive dysfunction and as measured in this study, cognitive dysfunction was an objective assessment of performance on neuropsychological tests. The smaller sample size in our study may have limited our ability to detect the associations between the groups on depressive symptoms and health-related quality of life. The PHQ-8 and the Living with Heart Failure Questionnaire had satisfactory validity and reliability and in this sample, a post hoc analysis demonstrated that they were strongly correlated with one another ($r = 0.66$, $p < .000$), lending support to the validity of the measures.

Strengths of the current study are the inclusion of a general sample of HF outpatients recruited from five sites. Not all patients were elderly, as in past studies. A valid, reliable neuropsychological test battery allowed us to determine the dysfunction *in specific cognitive abilities* that were predictors of 12-month mortality in order to identify potential interventions.

The study had a number of limitations. One limitation was that patients with terminal cancer and ventricular assist devices were excluded and patients with the most severe HF were less likely to participate in the parent study. Therefore, the mortality rate may actually be higher than 13%. The study is only applicable to patients with systolic HF with LVEF < 40%. It is unknown if similar results would be found among patients with HF with preserved systolic function. Furthermore, the LVEF was measured as much as two years prior to the neuropsychological testing which is a limitation. However, LVEF was used to document left ventricular systolic impairment as part of the inclusion criteria and not as a response variable. Comorbidity and HF duration were obtained by self report. The sample size of 21 deaths among the 166 patients limited the number of predictors that could be examined in the analyses. More fully-adjusted models based on larger sample sizes might yield different results. We did not study whether memory dysfunction predicted hospitalization and readmission rates in HF patients, but it is reasonable to speculate that memory dysfunction contributes to increased hospitalizations. Future studies are warranted to determine whether dysfunction *in specific cognitive abilities* in HF predicts hospitalization. Finally, even though the neuropsychological

tests were specified to measure one domain, they actually measure multiple cognitive domains and cognitive functions are inter-connected.

In conclusion, lower LVEF, poorer global cognitive function as determined by the MMSE, poorer working memory, poorer recall memory, *psychomotor slowing, and executive function* were predictors of mortality at 12 months in this sample of HF patients. Lower systolic blood pressure was also a significant predictor of mortality. Evidence is increasingly strong that cognitive dysfunction in general and memory loss in particular are indicators of the end-organ damage that occurs with the syndrome of HF. There is an urgent need for interventions to prevent and delay the memory loss of HF.

There are many clinical implications of memory dysfunction and loss in HF. Patients with memory loss may not be able to remember providers' recommendations and thus have difficulty complying with complex medical regimens. Providers may not be aware of this memory loss. There is a danger of labeling patients as noncompliant when in fact, memory loss is present. Noncompliance with medications is as high as 40% in some populations and is an independent predictor of hospital readmission.¹⁹ Patients need to be routinely assessed for memory loss and those who are perceived as noncompliant should be the first group to undergo evaluation in order to diagnose potential memory loss and formulate plans of care to compensate for it. Patients with new onset or moderate to severe memory dysfunction need to be referred for further evaluation and treatment. Referral to appropriate providers will be especially important as new therapies become available to treat memory dysfunction.⁵¹ Involving family members in patients' care and in decision making may be essential to maintaining positive health outcomes. Multidisciplinary teams of providers with HF expertise who are aware of early signs of cognitive decline are needed to meet the challenges of caring for these vulnerable patients.

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References

1. Lloyd-Jones D, Adams R, Carnethon M, DeSimone G, Ferguson TB, Flegal K, et al. Heart disease and stroke statistics - 2009 update: a report from the AHA Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009;119:e21–e181. [PubMed: 19075105]
2. Sanderson JE, Tse T. Heart failure: a global disease requiring a global response. *Heart* 2003;89:585–586. [PubMed: 12748201]
3. Abraham WT, Fonarow GC, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. Predictors of in-hospital mortality in patients hospitalized for heart failure. *J Am Coll Cardiol* 2008;52(5):347–356. [PubMed: 18652942]
4. O'Connor CM, Abraham WT, Albert NM, Clare R, Stough WG, Gheorghiade M, et al. Predictors of mortality after discharge in patients hospitalized with heart failure: an analysis from the Optimized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J* 2008;156(4):662–673. [PubMed: 18926148]

5. Goldberg RJ, Ciampa J, Lessard D, Meyer TE, Spencer FA. Long-term survival after heart failure: a contemporary population-based perspective. *Arch Intern Med* 2007;167:490–496. [PubMed: 17353497]
6. Levy WC, Mozaffarian D, Linker DT, Sutradher SC, Anker SD, Cropp AB, et al. The Seattle Heart Failure Model: prediction in survival of heart failure. *Circulation* 2006;113:1424–1433. [PubMed: 16534009]
7. Kosiborod M, Soto GE, Jones PG, Krumholz HM, Weintraub WS, Deedwania P, et al. Identifying heart failure patients at high risk for near-term cardiovascular events with serial health status assessments. *Circulation* 2007;115:1975–1981. [PubMed: 17420346]
8. Mommersteeg PMC, Denollet J, Spertus JA, Pedersen SS. Health status as a risk factor in cardiovascular disease: a systematic review of current evidence. *Am Heart J* 2009;157(2):208–218. [PubMed: 19185627]
9. Zuccala G, Pedone C, Cesari M, Onder G, Pahor M, Marzetti E, et al. The effects of cognitive impairment on mortality among hospitalized patients with heart failure. *Am J Med* 2003;115:97–103. [PubMed: 12893394]
10. Rozzini R, Sabatini T. Cognitive impairment and mortality in elderly patients with heart failure. *Am J Med* 2004;116:137–138. [PubMed: 14715330]
11. McLennan SN, Pearson SA, Cameron J, Stewart S. Prognostic importance of chronic heart failure patients: Does specialist management make a difference? *Eur J Heart Fail* 2006;8:494–501. [PubMed: 16504580]
12. Bennett SJ, Sauve MJ. Cognitive deficits in patients with heart failure: a review of the literature. *J Cardiovasc Nurs* 2003;18:219–242. [PubMed: 12837012]
13. Pressler SJ. Cognitive functioning and chronic heart failure: a review of the literature (2002 - July 2007). *J Cardiovasc Nurs* 2008;23:239–249. [PubMed: 18437066]
14. Vogels RL, Scheltens P, Schroeder-Tanka JM, Weinstein HC. Cognitive impairment in heart failure: a systematic review of the literature. *Eur J Heart Fail* 2007;9:440–449. [PubMed: 17174152]
15. Sauve MJ, Lewis WR, Blankenbiller M, Rickabaugh B, Pressler SJ. Cognitive impairments in chronic heart failure: a case controlled study. *J Card Fail* 2009;15:1–10. [PubMed: 19181287]
16. Pressler SJ, Subramanian U, Perkins S, Kareken D, Gradus-Pizlo I, Sauve MJ, et al. Cognitive deficits in chronic heart failure. *Nurs Res* 2010;59:127–139. [PubMed: 20216015]
17. Pulicino PM, Wadley YG, McClure LY, Safford MM, Lazar RM, Klapholz M, et al. Factors contributing to global cognitive impairment in heart failure: results from a population-based cohort. *J Card Fail* 2008;14:290–295. [PubMed: 18474341]
18. Bennett SJ, Huster GA, Baker SL, Milgrom LB, Kirchgassner A, Birt J, et al. Characterization of precipitants of hospitalization for heart failure decompensation. *Am J Crit Care* 1998;7:168–174. [PubMed: 9579241]
19. Murray MD, Young J, Hoke S, Tu W, Weiner M, Morrow D, et al. Pharmacist intervention to improve medication adherence in heart failure: a randomized trial. *Ann Intern Med* 2007;146:714–725. [PubMed: 17502632]
20. Jurgens CY, Hoke L, Byrnes J, Riegel B. Why do elders delay responding to heart failure symptoms? *Nurs Res* 2009;58:274–282. [PubMed: 19609179]
21. Zuccala G, Onder G, Pedone C, Carosella L, Pahor M, Bernabei R, et al. Hypotension and cognitive impairment: selective association in patients with heart failure. *Neurol* 2001;59:1986–1992.
22. Dickson VV, Tkacs N, Riegel B. Cognitive influences on self-care decision making in persons with heart failure. *Am Heart J* 2007;154:424–431. [PubMed: 17719284]
23. Bennett SJ, Sauve MJ, Shaw RM. A conceptual model of cognitive deficits in chronic heart failure. *J Nurs Scholarship* 2005;37:222–228.
24. Hachinski V, Iadecola C, Petersen RC, Breteler MM, Nyenhuis DL, Black SE, et al. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards. *Stroke* 2006;37:2220–2241. [PubMed: 16917086]
25. Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–198. [PubMed: 1202204]
26. The Psychological Corporation. Wechsler^R Test of Adult Reading Manual. The Psychological Corporation; San Antonio: 2001.

27. Kaplan, EF.; Goodglass, H.; Weintraub, S. The Boston Naming Test. 2nd ed.. PRO ED Inc.; Austin, TX: 2001.
28. Wechsler, D. Administration and Scoring Manual. 3rd ed.. The Psychological Corporation; USA: 1997. Wechsler Adult Intelligence Scale.
29. Brandt, J.; Benedict, RHB. Hopkins Verbal Learning Test - Revised. Psychological Assessment Resources; Lutz, FL: 2001.
30. Welsh KA, Butters N, Mohs RC, Beekly D, Edland S, Fillenbaum G, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part V. A normative study of the neuropsychological battery. *Neurology* 1994;44:609–614. [PubMed: 8164812]
31. Reitan, RM. Trail Making Test. Reitan Neuropsychological Laboratory; Tucson, AZ: 1992.
32. Benton, AL.; Hamsher, K. Multilingual Aphasia Exam Manual. University of Iowa; Iowa City, IA: 1978. deS
33. New York Heart Association Criteria Committee. Disease of the heart and blood vessels: nomenclature and criteria for diagnosis. 6th ed.. Little, Brown & Co.; Boston: 1964.
34. Hlatky MA, Boineau RE, Higginbotham MB, Lee KL, Mark DB, Califf RM, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). *Am J Cardiol* 1989;64:651–654. [PubMed: 2782256]
35. Carter R, Holiday DB, Grothues C, Nwasuruba C, Stocks J, Tiep B. Criterion validity of the Duke Activity Status Index for assessing functional capacity in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehab* 2002;22:298–308.
36. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–383. [PubMed: 3558716]
37. Chaudhry S, Jin L, Meltzer D. Use of a self-report-generated Charlson Comorbidity Index for predicting mortality. *Med Care* 2005;43:607–615. [PubMed: 15908856]
38. Perkins AJ, Kroenke K, Unutzer J, Katon W, Williams JW Jr, Hope C, et al. Common comorbidity scales were similar in their ability to predict health care costs and mortality. *J Clin Epidemiol* 2004;57:1040–1048. [PubMed: 15528055]
39. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure: a metaanalytic review of prevalence, intervention effects, and association with clinical outcomes. *J Am Coll Cardiol* 2006;48:1527–1537. [PubMed: 17045884]
40. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16(6):606–613. [PubMed: 11556941]
41. Kroenke K, Spitzer RL. The PHQ-9: a new depression diagnostic and severity measure. *Psychiatr Ann* 2002;32:1–7.
42. Spitzer RL, Williams JB, Kroenke K, Hornyak R, McMurray J. Validity and utility of the PRIME-MD Patient Health Questionnaire in assessment of 3000 obstetric-gynecologic patients: the PRIME-MD Patient Health Questionnaire Obstetrics-Gynecology Study. *Am J Obstet Gyn* 2000;183:759–769.
43. Rector TS, Francis GS, Cohn JN. Patients' self-assessment of their congestive heart failure. Part 1: patient perceived dysfunction and its poor correlation with maximal exercise tests. *Heart Failure* 1987;3:192–196.
44. Rector TS, Kubo SH, Cohn JN. Patients' self-assessment of their congestive heart failure, Part 2: content, reliability and validity of a new measure, the Minnesota Living with Heart Failure Questionnaire. *Heart Failure* 1987;3:198–209.
45. Tabachnick, BG.; Fidell, LS. Using multivariate statistics. 5th ed.. Pearson; Boston: 2007.
46. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Statistics in Medicine* 1996;15:361–387. [PubMed: 8668867]
47. Hosmer, DW.; Lemeshow, S. Applied logistic regression. 2nd ed.. Wiley; NY: 2000.
48. Harrell FE, Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modelling strategies for improved prognostic prediction. *Statistics in Medicine* 1984;3:143–152. [PubMed: 6463451]

49. DeJager CA, Schrijnemaekers AMC, Honey TEM, Budge MM. Detection of MCI in the clinic: evaluation of the specificity and sensitivity of a computerised test battery, the Hopkins Verbal Learning test and the MMSE. *Age Ageing* 2009;38:455–460. [PubMed: 19454402]
50. Budson AE, Price BH. Memory dysfunction. *N Engl J Med* 2005;352:692–699. [PubMed: 15716563]
51. Budson AE. Understanding memory dysfunction. *The Neurologist* 2009;15:71–79. [PubMed: 19276784]
52. Leier CV. Regional blood flow in human congestive heart failure. *Am Heart J* 1992;124(3):726–738. [PubMed: 1514501]
53. Woo MA, Macey PM, Fonarow GC, Hamilton MA, Harper RM. Regional brain gray matter loss in heart failure. *J Appl Physiol* 2003;95:677–684. [PubMed: 12716866]
54. Kumar R, Woo MA, Birrer BVX, Macey PM, Fonarow GC, Hamilton MA, et al. Mammillary bodies and fornix fibers are injured in heart failure. *Neurobiol Dis* 2009;33:236–242. [PubMed: 19022386]
55. Woo MA, Kumar R, Macey PM, Fonarow GC, Harper RM. Brain injury in autonomic, emotional, and cognitive regulatory areas in patients with heart failure. *J Card Fail* 2009;15(3):214–223. [PubMed: 19327623]
56. Serber SL, Kumar R, Woo MA, Macey PM, Fonarow GC, Harper RM. Cognitive test performance and brain pathology. *Nurs Res* 2008;57(2):75–83. [PubMed: 18347478]
57. Vogels RLC, Oosterman JM, van Harten B, Gouw AA, Schroeder-Tanka JM, Scheltens P, van der Flier WM, Weinstein HC. Neuroimaging and correlates of cognitive function among patients with heart failure. *Dement Geriatr Cogn Disord* 2007;24:418–423. [PubMed: 17938570]
58. Vogels RLC, Oosterman JM, Laman DM, Gouw AA, Schroeder-Tanka JM, Scheltens P, van der Flier WM, Weinstein HC. Transcranial Doppler blood flow assessment in patients with mild heart failure: correlates with neuroimaging and cognitive performance. *Congest Heart Fail* 2008;14:61–65.
59. Siachos T, Vanbakel A, Feldman D, Uber W, Simpson KN, Pereira NL. Silent strokes in patients with heart failure. *J Card Fail* 2005;11(7):485–489. [PubMed: 16198241]
60. Raphael CE, Whinnett ZI, Davies JE, Fontana M, Ferenczi EA, Manisty CH, et al. Quantifying the paradoxical effect of higher systolic blood pressure on mortality in chronic heart failure. *Heart* 2009;95:56–62. [PubMed: 18653573]
61. Nussbaum PD, Allender J, Copeland J. Verbal Learning in cardiac transplant candidates: a preliminary report. *Int J Rehabil Health* 1995;1:5–12.
62. Zuccala, G.; Cattel, C.; Manes-Gravina, E.; DiNiro, MG.; Cocchi, A.; Bornabei, R. Left ventricular dysfunction: a clue to cognitive impairment in older patients with heart failure.
63. Almeida OP, Tamai S. Congestive heart failure and cognitive function amongst older adults. *Arq Neuropsiquiatr* 2001;59(2B):324–329. [PubMed: 11460173]
64. Jiang W, Kuchibhatla M, Clary GL, Cuffe M, Christopher J, Alexander R, et al. Relationships between depressive symptoms and long-term mortality in patients with heart failure. *Am Heart J* 2007;154:102–108. [PubMed: 17584561]
65. Sherwood A, Blumenthal JA, Trivedi R, Johnson KS, O'Connor CM, Adams KF, et al. Relationship of depression to death or hospitalization in patients with heart failure. *Arch Int Med* 2007;167:367–373. [PubMed: 17325298]

Figure 1.

Means and significance levels for neuropsychological test scores that were significant in logistic regression analyses.

MMSE, Mini-Mental Status Examination; HVL, Hopkins Total Learning Test

Lower scores worse for MMSE, Digit Span backward, HVL Delayed recall, Figure Memory recall, Digit Symbol Scaled; higher scores worse for Trail Making Test Parts A and B

Table 1

Sample Characteristics of Total Group and Patients Who Were Alive and Who Died at 12 Months (n = 166)

Characteristic	Total (n = 166)	Alive (n = 145)	Died (n = 21)	p-value
Age, mean $\pm$ SD	65.6 $\pm$ 13.8	65.2 $\pm$ 13.4	68.0 $\pm$ 16.5	.391
Sex, n (%)				.056
Men	112 (67.5)	94 (65)	18 (86)	
Women	54 (32.5)	51 (35)	3 (14)	
Race, n (%)				.615
African-American	45 (27)	41 (28)	4 (19)	
Asian	1 (< 1)	1 (< 1)	0 (0)	
White	120 (72)	103 (71)	17 (81)	
Ethnicity, n (%)				---
Hispanic	0			
Non-hispanic	165 (99)	144 (99)	21 (100)	
Missing	1 (< 1)	1 (< 1)	0 (0)	
Marital status, n (%)				.634
Married	107 (65)	95 (66)	12 (57)	
Not married	59 (35)	50 (34)	9 (43)	
Education, yrs, (mean $\pm$ SD)	13.0 $\pm$ 2.6	13.1 $\pm$ 2.7	12.1 $\pm$ 2.2	.122
Premorbid intellect, (mean $\pm$ SD) ^d	95.7 $\pm$ 17.0	96.0 $\pm$ 17.0	93.1 $\pm$ 17.2	.471
LVEF, mean $\pm$ SD	27.0 $\pm$ 10.1	27.7 $\pm$ 10.1	22.0 $\pm$ 8.2	.014
Systolic blood pressure	115 $\pm$ 18	116 $\pm$ 19	106 $\pm$ 11	.001
Diastolic blood pressure	68 $\pm$ 12	68 $\pm$ 12	62 $\pm$ 8	.004
Duke Activity Status Index	15.4 $\pm$ 11.9	16.2 $\pm$ 12.3	9.7 $\pm$ 7.0	.001
NYHA class, n (%)				.160
I	27 (16)	27 (19)	0 (0)	
II	62 (37)	54 (37)	8 (38)	
III	59 (36)	49 (34)	10 (48)	
IV	18 (11)	15 (10)	3 (14)	
Duration of HF, yrs	8.1 $\pm$ 8.2	7.4 $\pm$ 7.1	13.0 $\pm$ 12.4	.064
BVP, n (%)				.036
No BVP	119 (72)	108 (74)	11 (52)	
Yes BVP	47 (28)	37 (26)	10 (48)	
ICD, n (%)				.145
No ICD	80 (48)	73 (50)	7 (33)	
ICD	86 (52)	72 (50)	14 (67)	
Medications, n (%)				
ACE inhibitors	102 (61)	91 (63)	11 (52)	.361
ARBs	41 (25)	37 (26)	4 (19)	.521
Beta-blockers	142 (86)	126 (87)	16 (76)	.192
Diuretics	151 (91)	130 (90)	21 (100)	.122
Digitalis	56 (34)	48 (33)	8 (38)	.651
Comorbidity (Charlson)	3.0 $\pm$ 1.7	2.9 $\pm$ 1.7	3.7 $\pm$ 2.0	.052

Characteristic	Total (n = 166)	Alive (n = 145)	Died (n = 21)	p-value
Depressive symptoms (PHQ-8)	6.1 ± 5.0	6.0 ± 5.0	6.5 ± 4.8	.648
Living with HF Questionnaire	41.2 ± 22.6	40.8 ± 23.0	44.3 ± 19.3	.502

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; BVP, biventricular pacemaker; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; PHQ-8, Patient Health Questionnaire-8; SD, standard deviation.

^aWechsler Test of Adult Reading, standard score; nationally standardized sample (mean = 100, SD ± 15)

Table 2

Comparisons of Means and Standard Deviations of Neuropsychological Tests (raw and/or standardized) between Patients Who Were Alive and Who Died at 12 Months (n = 166)

Variable	Total (n = 166)	Mean $\pm$ SD ^a	Alive (n = 145)	Mean $\pm$ SD	Died (n = 21)	Mean $\pm$ SD	t-test	P-value
Mini-Mental State Examination		27.7 $\pm$ 2.2		27.9 $\pm$ 2.2		26.4 $\pm$ 2.2	2.9	.004
Language (Boston Naming Test)		52.3 $\pm$ 7.9		52.6 $\pm$ 7.0		49.6 $\pm$ 12.4	1.1	.289
Working memory								
Digit Span forward		9.6 $\pm$ 2.4		9.6 $\pm$ 2.3		9.4 $\pm$ 3.0	.5	.651
Digit Span backward		5.8 $\pm$ 2.0		6.0 $\pm$ 2.0		4.9 $\pm$ 2.1	2.4	.018
Scaled		9.9 $\pm$ 2.9		10.0 $\pm$ 2.8		9.3 $\pm$ 3.4	1.0	.316
Memory (Hopkins Verbal Learning Test)								
Total recall		19.6 $\pm$ 5.7		19.9 $\pm$ 5.5		17.7 $\pm$ 6.9	1.6	.105
Delayed recall		6.7 $\pm$ 2.9		6.9 $\pm$ 2.8		5.1 $\pm$ 3.7	2.1	.047
Visuospatial ability (Figure Copy and Figure Memory recall)								
Figure Copy		8.6 $\pm$ 1.6		8.7 $\pm$ 1.6		8.0 $\pm$ 1.7	1.7	.086
Figure Memory recall		7.2 $\pm$ 2.7		7.5 $\pm$ 2.5		5.2 $\pm$ 2.9	3.7	<.001
Psychomotor speed								
Digit Symbol Scaled		8.7 $\pm$ 2.8		8.9 $\pm$ 2.8		7.5 $\pm$ 2.0	2.2	.031
Trail Making Test A (time in seconds)		51.8 $\pm$ 25.5		50.0 $\pm$ 24.9		63.9 $\pm$ 27.0	-2.3	.023
Executive function								
Trail Making Test B (time in seconds)		133.2 $\pm$ 68.3		128.9 $\pm$ 65.7		164.1 $\pm$ 80.1	-2.1	.035
Controlled Oral Word Association		30.8 $\pm$ 11.0		31.3 $\pm$ 10.8		27.2 $\pm$ 12.2	1.6	.107

^aSD = Standard deviation

Logistic Regression Analysis for Left Ventricular Ejection Fraction (LVEF) and Neuropsychological Tests as Predictors of 12-Month All-Cause Mortality in Heart Failure (N = 166)

Table 3

Models	Predictor Variables	Beta (Standard Error)	Odds Ratio	95% Confidence Interval for Odds Ratio	p-values
1	LVEF	-.09 (.03)	.92	.87-.97	.004
	MMSE	-.28 (.10)	.76	.63-.91	.004
2	LVEF	-.06 (.03)	.94	.89-.99	.020
	Digit Span backward	-.34 (.15)	.72	.53-.96	.023
3	LVEF	-.07 (.03)	.94	.89-.99	.020
	Hopkins Verbal Learning				
	Test delayed recall	-.19 (.08)	.83	.71-.97	.018
4	LVEF	-.07 (.03)	.93	.88-.99	.015
	Figure Copy	-.20 (.13)	.82	.64-1.07	.140
5	LVEF	-.07 (.03)	.93	.88-.99	.024
	Figure Memory recall	-.29 (.09)	.75	.63-.90	.002
6	LVEF	-.07 (.03)	.93	.88-.99	.012
	Digit Symbol Scaled	-.19 (.09)	.82	.69-.99	.037
7	LVEF	-.07 (.03)	.93	.88-.99	.016
	Trail Making Test A	.02 (.008)	1.02	1.002-1.034	.030
8	LVEF	-.07 (.03)	.93	.88-.99	.016
	Trail Making Test B	.007 (.003)	1.01	1.001-1.013	.034

Model 1: $\chi^2 = 16.15$, $df = 2$, $p < .001$, Nagelkerke $R^2 = .18$

Model 2: $\chi^2 = 12.67$, $df = 2$, $p = .002$, Nagelkerke $R^2 = .14$

Model 3: $\chi^2 = 12.38$, $df = 2$, $p = .002$, Nagelkerke $R^2 = .14$

Model 4: $\chi^2 = 9.47$, $df = 2$, $p = .009$, Nagelkerke $R^2 = .11$

Model 5: $\chi^2 = 17.97$, $df = 2$, $p < .001$, Nagelkerke $R^2 = .20$

Model 6: $\chi^2 = 12.33$, $df = 2$, $p = .002$, Nagelkerke $R^2 = .14$

Model 7: $\chi^2 = 10.87$, $df = 2$, $p = .004$, Nagelkerke $R^2 = .13$

Model 8: $\chi^2 = 10.53$, $df = 2$, $p = .005$, Nagelkerke $R^2 = .13$

Logistic Regression Analysis for Systolic Blood Pressure (SBP) and Neuropsychological Tests as Predictors of 12-Month All-Cause Mortality in Heart Failure (N = 166)

Table 4

Models	Predictor Variables	Beta (Standard Error)	Odds Ratio	95% Confidence Interval for Odds Ratio	p-values
1	SBP	-.05 (.02)	.95	.92-.99	.010
	MMSE	-.25 (.09)	.78	.65-.93	.006
2	SBP	-.05 (.02)	.95	.91-.99	.007
	Digit Span backward	-.39 (.15)	.68	.51-.91	.008
3	SBP	-.05 (.02)	.95	.92-.99	.010
	Hopkins Verbal Learning				
	Test delayed recall	-.21 (.08)	.81	.69-.95	.008
4	SBP	-.04 (.02)	.96	.92-.99	.014
	Figure Copy	-.22 (.13)	.80	.62-1.04	.093
5	SBP	-.05 (.02)	.95	.92-.99	.016
	Figure Memory recall	-.31 (.09)	.74	.61-.89	.001
6	SBP	-.05 (.02)	.95	.92-.99	.011
	Digit Symbol Scaled	-.21 (.10)	.81	.67-.98	.027
7	SBP	-.05 (.02)	.96	.92-.99	.012
	Trail Making Test A	.02 (.008)	1.02	1.002-1.035	.025
8	SBP	-.05 (.02)	.95	.92-.99	.011
	Trail Making Test B	.008 (.003)	1.01	1.002-1.015	.016

Model 1: $\chi^2 = 14.97$, $df = 2$, $p = .001$, Nagelkerke $R^2 = .16$

Model 2: $\chi^2 = 15.85$, $df = 2$, $p < .001$, Nagelkerke $R^2 = .17$

Model 3: $\chi^2 = 14.78$, $df = 2$, $p = .001$, Nagelkerke $R^2 = .16$

Model 4: $\chi^2 = 10.33$, $df = 2$, $p = .006$, Nagelkerke $R^2 = .11$

Model 5: $\chi^2 = 19.77$, $df = 2$, $p < .001$, Nagelkerke $R^2 = .21$

Model 6: $\chi^2 = 13.00$, $df = 2$, $p = .002$, Nagelkerke $R^2 = .14$

Model 7: $\chi^2 = 12.27$, $df = 2$, $p = .002$, Nagelkerke $R^2 = .14$

Model 8: $\chi^2 = 12.29$, $df = 2$, $p = .002$, Nagelkerke $R^2 = .15$