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Usefulness of Cognitive Dysfunction in Heart Failure to Predict Cardiovascular Risk at 180 days

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Abstract

Cognitive dysfunction is common among heart failure (HF) patients. Despite the high prevalence and the adverse associations of cognitive dysfunction in HF, the prognostic implications remain poorly understood. We sought to determine the influence of cognitive dysfunction, identified using the Montreal Cognitive Assessment (MoCA), on 180-day cardiovascular events. We analyzed data on 246 participants in an observational cohort study of adults with HF. The interview-format MoCA was administered to all participants. Time to first cardiovascular event was assessed as a cumulative end point during the 180 days after enrollment. Cox proportional hazards modeling were used for analysis of time to first event. The MoCA score was < 26 for 91 (37%) patients. Patients with a MoCA score <26 were more likely to have a cardiovascular event at 180 days. MoCA score < 26 remained an independent predictor of cardiovascular event risk at 180 days when adjusted for the Seattle Heart Failure Model Score and the Charlson Comorbidity Index (Hazard Ratio 1.7, 95% Confidence Interval 1.1-2.6, $p = 0.03$). In conclusion, in HF patients, cognitive dysfunction identified with a MoCA score of <26 is associated with increased risk of cardiovascular events at 180 days.

Keywords

heart failure; cardiomyopathy; MoCA; cognitive impairment

Introduction

More than 650,000 patients are diagnosed with heart failure (HF) each year in the United States. Despite advances in medical therapy and device technology over the decades, about 50% of patients with HF will die within 5 years of their diagnosis.^{1,2} As many as half of the

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5 million patients living with HF in the US experience cognitive dysfunction.^{3,4} When identified in HF patients, cognitive dysfunction is associated with increased risk of hospitalization, progressive physical disability and higher mortality.⁵⁻⁷ Despite the high prevalence and the adverse associations of cognitive dysfunction in HF, the prognostic implications remains poorly understood. We sought to determine the influence of cognitive dysfunction, identified using the Montreal Cognitive Assessment (MoCA), on 180-day cardiovascular events and to identify subsets of MoCA items that are associated with cardiovascular risk.

Methods

We analyzed data on 246 participants in an observational cohort study of symptoms in adults with HF. All patients were recruited between 2010 and 2013 through a single HF outpatient clinic in the Pacific Northwest. Participants were approached for study participation immediately after a HF clinic visit. Participants were 21 years of age or older with the ability to read and understand English at a 5th grade level and were able to provide informed consent. All patients had symptomatic (New York Heart Association [NYHA] functional class II-IV) HF and were either on optimal HF therapy or were undergoing optimization of medical therapy by a treating HF cardiologist. Patients were ineligible for inclusion in the study if they had a diagnosis of cognitive dysfunction in the medical record, had a major uncorrected visual impairment, or were unable to complete the study requirements.

Written informed consent and Health Insurance Portability and Accountability Act authorization were obtained from all participants by study staff not directly involved in patient care. The study was reviewed and approved by the institutional review board at Oregon Health & Science University. There was a 3% refusal rate for study participation and a 94% completion rate.

Sociodemographic characteristics were assessed by questionnaire. A HF cardiologist determined each participant's NYHA functional class immediately prior to enrollment. Clinical and treatment characteristics were collected during an in-depth EMR review. Comorbidities were assessed with the Charlson Comorbidity Index. A list of 17 comorbid diseases were evaluated and weighted, with possible scores ranging from 0 to 30. Higher Charlson Comorbidity Index scores indicate higher risk of mortality.⁸ Seattle Heart Failure Scores were calculated for each participant using available clinical data. The Seattle Heart Failure Model is a commonly used HF risk prediction tool that uses routinely available clinical information to estimate 1 and 5-year survival.⁹ Depression was measured with the 9-item Patient Health Questionnaire (PHQ9). The PHQ9 has an 88% sensitivity and specificity for major depression using a cutoff score of greater than or equal to 10.¹⁰

Cognitive function was assessed using the MoCA. The MoCA is a 10-minute cognitive tool designed for use by clinicians to detect cognitive dysfunction. The MoCA has a sensitivity of 90% and a specificity of 87% to detect mild cognitive dysfunction, with a cutoff score of 26 in the general population.¹¹ The MoCA has also been adjusted to improve diagnostic accuracy for persons with chronic cardiovascular disease. A cutoff score of 24 was

demonstrated to be 100% sensitive to detect mild cognitive dysfunction in a sample for adults with chronic cardiovascular disease.¹² The MoCA has also been validated in older patients living with HF.¹³ The MoCA assesses 6 cognitive domains: visuospatial ability, executive function, language, short-term memory, orientation and attention, working memory and concentration. The cognitive domains defined in this study and the MoCA tasks comprising each domain are shown in Table 1.

Time to first all cause cardiovascular event (mortality, hospitalization, emergency room visit) was assessed as a cumulative end point during the 180 days after enrollment. Clinical events and associated dates were extracted from the EMR and/or assessed by contacting participants by telephone. A second reviewer independently validated all clinical events and 100 percent consensus was reached that the events were attributable to cardiovascular causes.

Means and standard deviations and proportions were used to describe the sample. Cox proportional hazards modeling were used for analysis of time to first event. Hazard ratios with 95% confident intervals were calculated to quantify the influence of the overall MoCA score and individual MoCA domains on 180-day event risk. The proportional hazards assumption was justified based on Schoenfeld residuals. Model fit was assessed using the overall model X^2 and by calculating Harrell's C statistic. The influence of the overall MoCA score and individual MoCA domains on 180-day event free survival was adjusted for the Seattle Heart Failure Score and the Charlson Comorbidity Index. Multiple other factors including body mass index (BMI), moderate or severe depression and education were considered in Cox modeling but did not improve the model fit or remain independently associated with cardiovascular events when the Seattle Heart Failure Score and Charlson Comorbidity Index were included. All analyses were performed with Stata IC 13.0 (Stata Corp, College Station, Texas).

Results

The baseline characteristics of the study population are described in Table 2. The mean MoCA score was 25.9 $\pm$ 2.6. Additional information regarding MoCA scores including scores for the individual MoCA domains are shown in Table 3. With over 35,000 follow-up days (mean follow-up days 145.9 $\pm$ 60.8), the cardiovascular event risk was 45.6%. At 180 days, 163 patients were alive without cardiovascular events and 6 patients were lost to follow-up. There were 4 deaths at 180 days, 14 emergency room visits for cardiovascular causes and 59 cardiovascular hospitalizations. Patients with a MoCA score <26 were more likely to have a cardiovascular event at 180 days (Figure 1). MoCA score <26 remained an independent predictor of cardiovascular event risk at 180 days when adjusted for the Seattle Heart Failure Score and the Charlson Comorbidity Index (Hazard Ratio [HR] 1.7, 95% confidence interval [CI] 1.1 to 2.6, $p = 0.03$, Harrell's C = 0.65).

Of the 6 MoCA domains, the executive domain was most strongly associated with cardiovascular risk at 180 days. The executive domain score was nearly as predictive as total MoCA score for 180 cardiovascular events. Missing only 1 point out of 4 possible on the MoCA executive domain was associated with increased 180-day cardiovascular event risk

(Figure 2). The MoCA executive domain score remained independently associated with 180-day cardiovascular events after adjustment for Seattle Heart Failure Score and the Charlson comorbidity index (HR 1.6, 95% CI 1.02 to 2.6, $p = 0.04$, Harrell's $C = 0.66$).

Discussion

Cognitive dysfunction is increasingly recognized as an important determinant of morbidity in patients with HF. Understanding cognitive dysfunction in the HF population is challenging in part because HF is a heterogeneous clinical syndrome. Identifying uniform groups of patients with HF and controlling for differences between HF patients is difficult. In addition, the risk of developing of cognitive dysfunction in HF is likely multifactorial.¹⁴ Hypoperfusion is postulated to contribute to cognitive dysfunction in patients with HF.¹⁴⁻¹⁷ Age,¹⁸ prior cardiopulmonary bypass,¹⁹ cardiovascular risk factors,²⁰ vascular disease and stroke,¹⁴ chronic kidney disease and anemia,²¹ decreased physical activity,²² obesity,²³ depression,²⁴ and genetic risk factors such as apolipoprotein E4,²⁵ may also contribute to cognitive dysfunction in HF. Furthermore, there is no consensus in the literature regarding the definition of, or methodology used to identify, cognitive dysfunction in HF. The cumbersome methodology used in many research studies cannot readily be applied in HF clinical practice.^{26,27}

When it is identified, the implications of cognitive dysfunction are significant. We have previously shown the presence of even mild cognitive dysfunction in HF patients was associated with poor self-care maintenance (the ability of patients to adhere to medications, diet and follow-up appointments) and management (the ability of patients to evaluate and respond to HF symptoms when they occur).²⁸ Inability to engage in self-care is well known risk factor for hospital admission among patients with HF.²⁹

The presence of cognitive dysfunction in patients with HF has been associated with increased risk of morbidity and mortality. Pulignano and colleagues prospectively followed 190 stable outpatients age 70 years and older with at least one prior admission for HF requiring intravenous diuretics, inotropes or vasodilator therapies. Cognitive function was measured with age and education corrected Folstein Mini Mental State examination (MMSE). In a multivariate analysis, moderate or severe cognitive impairment identified as a MMSE score < 24 was associated with increased risk of hospitalization for worsening HF and the combination of all-cause mortality and HF hospitalizations.²¹ Zuccala and collaborators identified 1,113 patients with a mean age of 78 years admitted to the hospital for HF. Cognitive dysfunction, assessed using the Hodkinson Abbreviated Mental Test, was associated with increased in-hospital and one-year mortality.⁷

In this study, we have shown that cognitive dysfunction is prevalent in a younger population of patients with HF, largely due to nonischemic cardiomyopathy, with a 5 year predicted survival of 32% using the Seattle Heart Failure Score and relatively few co-morbid diseases. In this population, the presence of mild cognitive dysfunction, identified with a MoCA score of < 26 , is predictive of cardiovascular risk events even over a short follow-up duration of 180 days. Pertinent for the clinician with limited time, a subset of the MoCA focused on

evaluation of the executive domain, can be used to identify patients with mild and often subclinical cognitive dysfunction at increased risk for future events.

Though there are inherent limitations to an observational study, we had a low refusal rate and a high study completion rate. Our study population was comprised of patients referred to a tertiary care advanced HF clinic, which may limit generalization to other patient populations. We chose the MoCA as our screening instrument for cognitive dysfunction due to its ease of use and validation in populations with cardiovascular disease. Using multiple measures of cognitive dysfunction could have improved our ability to detect cognitive dysfunction. We did not measure cognitive function over time and therefore cannot comment on how changes in cognition over the study period may impact cardiovascular risk.

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Figure 1. Unadjusted Cox proportional hazard curve for 180 day cardiovascular event free survival for HF patients by Montreal cognitive assessment (MoCA) score. HF patients with a MoCA score < 26 were more likely to have a cardiovascular event at 180 days. HR = Hazard ratio, CI = Confidence interval

Figure 2.

Unadjusted Cox proportional hazard curve for 180 day cardiovascular event free survival by executive domain score. HF patients with an executive domain score ≤ 3 were more likely to have a cardiovascular event at 180 days. HR = Hazard ratio, CI = Confidence interval

Table 1

Cognitive domains assessed in the Montreal Cognitive Assessment

Cognitive Domain (Total points)	MoCA Tasks Included (Individual points assigned)
Visuospatial ability (4 points)	Copy Cube (1 point) Draw Clock (3 points)
Executive function (4 points)	Trail making (1 point) Phonetic fluency (1 point) Verbal abstraction (2 points)
Short-term memory (5 points)	Delayed recall at 5 minutes (5 points)
Language (5 points)	Naming animals (3 points) Sentences repeated (2 points) Phonetic fluency (1 point)
Orientation (6 points)	Date (1 point) Month (1 point) Year (1 point) Day (1 point) Place (1 point) City (1 point)
Attention, working memory and concentration (6 points)	Tapping (1 point) Serial subtraction (3 points) Forward/backward numbers (2 points)

Table 2

Characteristics of the study population

Patient Demographics		
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Female		92 (37.8%)
Male		153 (62.2%)
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White/Caucasian		196 (88.4%)
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Ischemic cardiomyopathy		81 (32.9%)
Non-ischemic cardiomyopathy		165 (67.1%)
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NYHA Class II		98 (39.8%)
NYHA Class III		135 (54.9%)
NYHA Class IV		13 (5.3%)
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Ejection fraction < 40%		196 (80.3%)
Ejection fraction ≥ 40%		48 (19.7%)
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Medication Use	Diuretic	210 (85.4%)
	ACE Inhibitor or ARB	202 (82.1%)
	Beta blocker	220 (89.4%)
	Aldosterone Antagonist	114 (46.3%)
	Statin	140 (56.9%)
	Digoxin	59 (24.0%)
	Antiplatelet or anticoagulation	197 (80.1%)
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Married or Partnered		145 (62.8%)
Single, divorced, widowed, separated		86 (37.2%)
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High school or less education		74 (32.0%)
Some college or higher education		157 (68.0%)
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Moderate or severe depression		59 (25.8%)
Charlson	1	90 (36.6%)
Comorbidity	2	72 (29.3%)
Index	3	53 (21.5%)
	4	19 (7.7%)
	≥ 5	12 (4.9%)
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Age (years)		56.6 ± 13.1
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Body Mass Index (kg/m ²)		31.4 ± 7.7
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Seattle Heart Failure Survival Model predicted 1-year survival (%)		75.1 ± 0.2
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Seattle Heart Failure Survival Model predicted 5- year survival (%)		32.1 ± 0.2
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ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker

Table 3

Distribution of Montreal Cognitive Assessment scores

MoCA standard cutoff	< 26	91 (37.0%)
	>= 26	155 (63.0%)
MoCA cardiovascular cutoff	< 24	38 (15.4%)
	>=24	208 (84.6%)
Visuospatial domain (4 points)	4	153 (62.2%)
	< 4	93 (37.8%)
Executive domain (4 points)	4	124 (50.4%)
	< 4	122 (49.6%)
Short-term memory domain (5 points)	>=3	162 (65.9%)
	<3	84 (34.1%)
Language domain (5 points)	5	168 (68.3%)
	< 5	78 (31.7%)
Orientation domain (6 points)	6	232 (94.3%)
	<6	14 (5.7%)
Attention, working memory and concentration domain (6 points)	6	151 (61.4%)
	<6	78 (38.6%)