Mild Cognitive Impairment Predicts Death and Readmission within 30 days of Discharge for Heart Failure

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Short title: Cognitive impairment and HF readmission

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Abstract

Background: Cognitive impairment is highly prevalent in heart failure (HF), but their contribution to short-term readmission is undefined. This study investigated the role of cognition in predicting 30-day readmission or death in HF.

Methods: This study followed 565 patients from an Australia-wide HF longitudinal study. Cognitive function (MoCA score) together with standard clinical and non-clinical factors, mental health and 2D echocardiograms were collected before hospital discharge. The study outcomes were death and readmission within 30 days of discharge. Logistic regression, Harrell's C-statistic, integrated discrimination improvement (IDI) and net reclassification index were used for analysis.

Results: Among 565 patients, 255 (45%) had at least mild cognitive impairment (MoCA≤22). Death (n=43, 8%) and readmission (n=122, 21%) within 30 days of discharge were more likely to occur among patients with mild cognitive impairment (OR=2.00, p=0.001). Continuous MoCA score was also negatively associated with 30-day readmission or death (OR=0.91, p<0.001) independently of other risk factors. Adding MoCA score to an existing prediction model of 30-day readmission significantly improved discrimination (C-statistic=0.715 vs. 0.617, IDI estimate 0.077, p<0.001). From prediction models developed from our study, adding MoCA score (C-statistic=0.83) provided incremental value to that of standard clinical and non-clinical factors (C-statistic=0.76) and echocardiogram parameters (C-statistic=0.81) in predicting 30-day readmission or death. Reclassification analysis suggests that addition of MoCA score improved classification for a net of 12% of patients with 30-day readmission or death and of 6% of patients without (p=0.002).

Conclusions: Mild cognitive impairment predicts short-term outcomes in HF, independent of clinical and non-clinical factors.

Key words: mortality, rehospitalisation, heart failure, cognitive function, depression

Heart failure (HF) is the leading cause of hospitalization and rehospitalization in older adults,[1, 2] and short-term risks of readmission after a hospitalization with HF remain very high.[3, 4] These events are costly and usually considered preventable,[2] and HF has emerged as a priority condition in the current era of quality improvement and payment reform.[5] Although readmissions shortly after discharge are linked to quality of care,[6] there are other individual patient factors – including the ability for self-care – that may contribute to early readmissions following an index admission of HF.

Cognitive impairment is very common among HF patients, and may involve different domains including learning memory, attention and working memory, executive functions and psychomotor speed. Cognitive function influences a patient's ability for self-care, which is a key to health maintenance and adherence to treatment. Perhaps as a consequence, cognitive impairment is associated with higher risk of cardiovascular events in HF patients.[7] HF patients with moderate to severe dementia have greater risks of readmission or death post-discharge.[8] It is however unknown whether the risk is also elevated with mild cognitive impairment which may be prevalent in up to three quarters of the HF population.[9, 10]

In this study, we assessed patients' cognitive function using the Montreal Cognitive Assessment (MoCA) that was designed to test for mild cognitive impairment. The MoCA has been widely validated and is recommended to be used in HF.[11] Because many cognitively impaired patients may develop depression and/or anxiety disorder - which may confound the relationship between cognitive function and HF - we also assessed and investigated the patients using validated mental health questionnaires. We hypothesized that patients with mild cognitive impairment have higher risk of short-term adverse outcomes in HF regardless of other clinical and non-clinical factors, and sought to determine if cognitive function may provide incremental value to prediction of readmission or death within 30 days of discharge in HF.

Methods

Study population. In this prospective study, we followed 565 HF patients from the Multicentre Australian Risk Algorithm To predict Heart failure readmissiON (MARATHON) study, an Australia-wide longitudinal study of HF. Recruitment was carried out between January 2014 and June 2015 in

most Australian States (Tasmania, Victoria, New South Wales, Queensland and South Australia). Patients were identified by the confirmed primary diagnosis of decompensated HF by their treating doctors. Exclusion criteria were: age<18 years, inability to provide written consent, moderate or worse primary mitral or aortic valve disease, concomitant unstable angina or acute myocardial infarction, cardiac device malfunction, endocarditis, patients with LV assist device, potentially reversible LV dysfunction including post-partum, alcoholic cardiomyopathy and hyperthyroidism, and concomitant terminal non-cardiac illnesses that could influence 12-month prognosis. Baseline data from eligible patients who provided written consent were collected before hospital discharge. This study was approved by the Tasmanian Health and Medical Human Research Ethics Committee.

Primary outcome. The primary outcome of this study was all-cause readmission or death within 30 days of discharge. Follow-up phone calls were performed at 30 days of discharge. Dates of readmissions or death were obtained from medical records.

Cognitive function and mental health data. Patients' cognitive function was assessed before discharge by trained personnel using the MoCA. The MoCA examines different domains of cognition including visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall and orientation. It takes approximately 20 minutes to finish the test. The MoCA was designed to detect mild cognitive impairment with excellent sensitivity (90%) and specificity (87%).[12] MoCA cut-points of 23 and 17 were used to define mild cognitive impairment and dementia as previously suggested.[13] Patients who did not finish college/grade 12 had one point added to their MoCA score as instructed in the protocol. Depression was assessed using the Patient Health Questionnaire (PHQ-9), with cut-points of 5, 10 and 15 used to define mild, moderate and moderately severe/severe depression respectively. Anxiety was assessed using the Generalized Anxiety Disorder scale (GAD-7), with cut-points of 5, 10 and 15 used to define mild, moderate and severe anxiety respectively.

Clinical data. Clinical data including past medical history, medications, physical measurements and blood tests were collected before discharge. Standard physical measurements included body weight, blood pressure, heart rate, respiratory rate, and electrocardiography. Two-dimensional echocardiographic parameters included left ventricular (LV) ejection fraction, LV volume indices, left atrial volume index, right atrial pressure, pulmonary arterial systolic pressure and E/e' (as a surrogate

of LV filling pressure), using standard techniques and procedures following the American Society of Echocardiography guidelines.[14] Biochemical measurements included troponin I, C-reactive protein, albumin, blood urea nitrogen, sodium, creatinine, hematocrit, hemoglobin, cholesterol, and B-type natriuretic peptide. HF functional class was defined using the New York Heart Association (NYHA) Class.[15] The Charlson comorbidity index was calculated as previously described.[16] Patients were considered to have a history of life-threatening arrhythmia if they had at least an episode of ventricular tachycardia or fibrillation shortly prior to or during their admission with HF.

Non-clinical data. Non-clinical data included age, sex, language background, marital status, living alone, education, residential address, medical insurance, and any home health care services provided. Socioeconomic status based on residential postcode was derived using the Australian Bureau of Statistics Index of Relative Socioeconomic Disadvantage.[17] The remoteness index - based on residential address - reflects how far away a geographical area is from service towns of different sizes based on road distance.

Statistical analyses. Categorical variables are reported as the number of patients with percentages, and continuous variables are reported as median with interquartile range. Logistic regression was used to estimate the relationship between cognition, mental health and other predictors with the study primary outcome. Prediction models of 30-day HF readmission or death were developed as previously described.[4] To make sure there was no over fitting in our prediction models, we observed changes in standard errors when adding new variables to the models. These changes were small (<10%), implying limited variance in our models and over fitting was not an issue. Another previously published prediction model by Eapen *et al* using linked data from the Get With The Guidelines-Heart Failure (GWTG-HF) registry and Medicare database was applied to our study population by using the regression coefficients described in the original paper.[3] The incremental values of MoCA continuous score in prediction of 30-day readmission or death were determined by adding these predictors to the aforementioned prediction models, using integrated discrimination improvement index and net reclassification index. Comparisons between the areas under the receiver operating characteristic curves were performed using the Hanley and McNeil method.[18] STATA 12.0 (Statacorp, College Station, Texas, USA) was used for analyses.

Results

Baseline characteristics. Table 1 shows the socio-demographic, cognitive function and mental health status of patients at baseline. The group was typical of HF, with a median age of 74 years, approximately one third of the patients living alone, and a similar proportion living outside of major metropolitan areas. Approximately three quarters of the patients were classified as having mild cognitive impairment. A similar proportion of the patients were also classified as having at least mild depression or anxiety.

Table 2 shows the clinical characteristics at baseline. Most patients (75%) were classified as NYHA class II/III. Approximately two-thirds of the patients had hypertension and dyslipidemia; other common comorbidities included atrial fibrillation, cardiomyopathy and diabetes.

Outcomes and associations with cognitive function and mental health. Of the 565 HF patients included in this study, 43 (8%) patients died and 122 (21%) were readmitted within 30 days of discharge. These outcomes were negatively associated with MoCA score as shown in Table 3. Most of the individual components of the MoCA score were more strongly associated with 30-day readmission than with 30-day death. When stratifying all the patients by their cognitive function, those with mild cognitive impairment or dementia were more likely to die or be readmitted within 30 days of discharge (Table 3). The positive association of PHQ-9 and GAD-7 scores with the outcomes are shown in Supplementary Table 1. Patients with depression or anxiety had significantly greater odds of death or readmission within 30 days of discharge.

Table 4 demonstrates the negative associations of MoCA score with the outcomes that were independent of both GAD-7 and PHQ-9 scores. The associations of having mild cognitive impairment with 30-day readmission or death also remained unchanged after adjusting for depression (odds ratio OR=2.03 [95% CI: 1.30, 3.15]) or anxiety (OR=2.08 [95% CI: 1.33, 3.24]). These findings were consistent for the composite outcome and separate outcomes of readmission or death within 30 days.

Incremental value of cognitive function. Figure 1 illustrates the discriminatory power of the existing GWTG-HF predictive model in predicting 30-day death or readmission in our study population, with and without the addition of MoCA score. Integrated discrimination improvement analysis (estimate

0.077 p<0.001) showed a significant improvement in discrimination. Table 5 shows the prediction models of 30-day death or readmission developed from our study population using standard clinical and non-clinical predictors (Clinical Model), with an addition of echocardiogram parameters (Physiological Model), and with an addition of MoCA score (Cognitive Model). These findings show significant improvement in discrimination of prediction models after respectively adding echo parameters and MoCA score. This is further illustrated in Figure 2. Table 6 shows the net reclassification among HF patients who died or were readmitted within 30 days of discharge and those who did not. These findings suggest that addition of MoCA score improved classification for a net of 12% of patients with the short-term adverse events and of 6% of patients without an event (p=0.002).

Discussion

The short-term risks of death or readmission after a hospitalization with HF remain very high. Our study demonstrates that HF patients with mild cognitive impairment have a higher risk of being readmitted or dying within 30 days of discharge, independent of mental health and other risk factors. Inclusion of MoCA score – a comprehensive test of cognitive function – significantly increased the discrimination of prediction model of 30-day readmission or death in HF, and improved the reclassification of patients into correct categories of risk.

Cognitive function and HF. Cognitive impairment in HF may involve different domains, which may result from a reduction in cerebral blood flow associated with HF.[19] Cognitive impairment compromises the patient's ability for self-care, which is a key to health maintenance and adherence to treatment, and may lead to higher risk of readmission or death. This is supported by our findings where patients with cognitive impairment were more likely to be readmitted due to exacerbation of HF (67%) than those without cognitive impairment (41%). This study also shows that mild cognitive impairment may increase the risk of readmission or death within 30 days of discharge among HF patients, independent of depression or anxiety and other clinical and non-clinical predictors. This finding is novel and may have a huge clinical implication because approximately half of the HF patients included in our study were classified as at least mildly cognitively impaired (MoCA score

≤22). This high prevalence of cognitive damage in HF is consistent with that found in other studies,[9, 10] and is much higher than the prevalence of cognitive impairment (approximately 20-25%) found in the general older population.[20, 21]

A recent study by Patel *et al* has shown that HF patients with moderate to severe cognitive impairment have greater risks of readmission or death post-discharge.[8] Although the screening tool used in this study (the Mini-Cog) is brief and easy to use, it is a test for moderate to severe dementia and therefore detects mild cognitive impairment with only modest accuracy.[22] Thus, while our and other studies consistently identified at least half of HF patients with at least mild cognitive impairment by using the MoCA,[9, 10] Patel *et al* identified 23% of HF patients with moderate to severe dementia.[8] Assuming that the HF patients in each study were comparable, these findings imply that if the Mini-Cog is used to assess cognitive function in HF for the purpose of identifying patients with higher risks of short-term readmission or death, a substantial proportion of the patients will be misclassified. Furthermore, by using MoCA, we were able to demonstrate and quantify the effect of small differences in cognitive function in predicting risk of short-term adverse outcome in HF. This cannot be done with screening tools that only provide binary results such as the Mini-Cog.

Depression, anxiety and HF. A relationship has been documented between depression and adverse outcomes in HF patients in previous studies,[23] although the association of depression or anxiety with short-term HF readmission is unclear. As a secondary analysis, we demonstrated the independent associations of depression and anxiety with 30-day readmission or death in HF. Although the mechanism underlying the association between depression and rehospitalisation or death is unknown, this relationship may be attributable in part to lack of social and family support. For example, our study showed a trend for patients with moderately-severe or severe depression to be more likely to live alone than patients without depression (relative risk 1.52, p=0.057). In addition, differences in help-seeking behaviour,[24] health behaviour and treatment adherence[25] may play a role in driving different outcomes between patients with and without depression. Some data also suggest several biological mechanisms shared by depression and HF such as sympathetic activation and increased inflammation.[26, 27]

Possible interventions to reduce risk. Improvement of cardiac function with heart transplantation,[28] medications,[29, 30] and exercise training[31] may improve cognition in HF patients. However, such improvements of cardiac function are uncommon. However, even if cognitive impairment is irreversible, recognition of this problem may allow specific interventions to support and assist these individuals. Provision of greater social/family support and medical attention to enhance adherence to treatment plan and medications may reduce short-term readmission and mortality risk among these high risk patients. Moreover, it seems likely that patients with mild, rather than moderate to severe, cognitive impairment are more likely to benefit from these interventions and support, and are the most feasible targets for reducing short-term adverse outcomes in HF. In any event, treating physicians should be aware of the greater risk of repeat hospitalizations and death among these patients and ensure that appropriate care and treatment are provided. Future studies are clearly needed to confirm the benefits as well as to estimate the cost-effectiveness of these interventions.

Strengths and limitations. This study included a range of patients from an Australia-wide study of HF, which favors the generalizability of our findings. The prospective nature of this study allowed us to collect a wide range of potential predictors and avoid the known limitations of administrative codes as in retrospective studies. The inclusion of an extensive range of clinical and non-clinical variables enabled us to demonstrate the independent relationship of cognitive function with the outcomes, and reduce the likelihood of residual confounding. Although our findings that patients with mild cognitive impairment were more likely to be readmitted due to exacerbation of HF than those without cognitive impairment suggest causation, further studies are needed to confirm the causal pathway between poor cognitive function and short-term outcomes in HF. We did not assess cognitive function at follow-up and were not able to determine if any changes in cognitive function from baseline to follow-up may contribute to the adverse outcomes in HF. Future intervention studies are therefore needed to address this question. Finally, being included in this prospective study of HF might have resulted in better management and care for the patients during the study period.

Conclusions. Mild cognitive impairment increases the risk of 30-day readmission or death among HF patients. Inclusion of MoCA score significantly increased the discrimination of prediction model of

30-day readmission or death in HF, and improved the reclassification of patients into correct categories of risk. Our findings suggest that any assessment of HF patients in this context should include cognitive function testing. Given the high mortality risk and economic burden associated with repeated hospitalizations, a greater level of care should be provided to patients with cognitive impairment.

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Figure legends

Figure 1. Comparing area under the curve of the Get With The Guidelines-Heart Failure (GWTG-HF) predictive model with and without the addition of MoCA score

Figure 2. Incremental values of echocardiographic measures and MoCA in predicting 30-day readmission or death.