# Cognitive Impairment in Older Adults with Heart Failure: Prevalence and Impact on Outcomes

Jessica Chetrit

Division of Experimental Medicine

Faculty of Medicine

McGill University

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**English Abstract**

Background: As heart failure (HF) incidence increases with aging, geriatric conditions must be taken into account in the evaluation of frailty in HF patients. Cognitive impairment (CI) is one of the most common co-occurring conditions among older adults with HF however, the place of cognitive impairment in a definition of frailty has been widely debated. Currently, there is no consensus on which screening tool is most appropriate to assess for cognitive impairment in HF patients and there is a lack of understanding on how cognition impacts adverse health outcomes in this population.

Objectives: The aim of this study was to determine the prevalence of cognitive impairment among community-dwelling older adults with HF and to investigate role cognition plays in predicting adverse health outcomes in HF patients.

Methods: This study is a cross-sectional sub-study of the FRAILTY-HF study, a prospective, multicentre, observational cohort study initiated at four heart failure clinics (Jewish General Hospital, Royal Victoria Hospital, St-Mary's Hospital and Cité-de-la-Santé). Older adults ≥60 years with a clinical diagnosis of HF were enrolled and underwent a comprehensive frailty assessment. Minor neurocognitive disorder (minor NCD) was classified as a Mini-Cog score ≤3/5. A total score of ≤8/12 on the Short Physical Performance Battery (SPPB) was required for a diagnosis of physical frailty. Incident disability was defined as institutionalization or ≥2 new deficits in basic and instrumental activities of daily living (ADL and IADL), as captured by the Older American Resources and Services (OARS) tool, a multidimensional questionnaire that permits assessment of an individuals' functioning. Worsening disability was defined as a positive change in disability score at 3 months from baseline. Linear regression was used to determine if

cognitive impairment is predictive of worsening disability. Multivariable logistic regression modeling was used to determine the impact of cognitive impairment and physical frailty on all-cause mortality or hospitalization, adjusting for covariates.

Results: The final cohort consisted of 222 patients with a mean age of 77.5 ± 8.1 years and was 35% female. The prevalence of minor NCD was 32%, in which individuals with minor NCD exhibited worsening disability at 3 months. Cognitive impairment was not associated with death or readmissions at 3 months however, physical frailty score was highly predictive of death and hospitalization at 3 months.

Conclusion: The Mini-Cog proves to be a useful screening tool in identifying HF patients with minor NCD and an abnormal Mini-Cog score is predictive of worsening disability at 3 months. The Mini-Cog can serve as a brief and effective method for clinicians to screen for the specific cognitive profile seen in HF patients and can help to identify patients at higher risk of adverse health outcomes.

**French Abstract**

Introduction: À mesure que l'incidence de l'insuffisance cardiaque (IC) augmente avec le vieillissement, les conditions gériatriques doivent être prises en compte dans l'évaluation de la fragilité chez les patients atteints d'IC. Le déclin cognitif est l'une des affections concomitantes les plus courantes chez les personnes âgées atteintes d'IC, mais la place de déclin cognitif dans la définition de la fragilité fait l'objet d'un large débat. À l'heure actuelle, il n'y a pas de consensus sur l'outil de dépistage le plus approprié pour évaluer le déclin cognitif chez les patients atteints d'IC, et l'on comprend mal l'impact de la cognition sur les effets négatifs pour la santé de cette population.

Objectifs: La présente étude a pour but de déterminer la prévalence de déclin cognitif chez les personnes âgées souffrant d'IC qui vivent en collectivité et de cerner le rôle de la cognition dans la prédiction des effets négatifs sur la santé des patients atteints d'insuffisance cardiaque.

Méthodes: Cette étude est une sous-étude transversale de l'étude FRAILTY-HF, une étude de cohorte prospective, multicentrique et observationnelle lancée dans quatre cliniques d'insuffisance cardiaque (Hôpital Général Juif, Hôpital Royal Victoria, Hôpital St-Mary's et la Cité-de-la-Santé). Nous avons inscrit des adultes âgés de plus de 60 ans ayant reçu un diagnostic clinique d'IC et les avons soumis à une évaluation exhaustive de la fragilité. Le déclin cognitif s'est vue attribuer une note Mini-Cog $\leq$3/5. Il fallait une note totale de $\leq$8/12 sur la Batterie de Performance Physique Courte (SPPB) pour obtenir un diagnostic de fragilité physique. L'aggravation de l'incapacité a été définie comme institutionnalisation ou $\geq$2 nouveaux déficits dans les activités de base et instrumentales de la vie quotidienne, tel que capturé par l'outil "Older American

Resources and Services″ (OARS), un questionnaire multidimensionnel qui permet d'évaluer le fonctionnement d'un individu. Nous avons utilisé une régression linéaire pour déterminer si la DC est prédictive de l'aggravation de l'incapacité. Une modélisation de régression logistique multivariable a été effectuée pour définir l'impact de déclin cognitif et la fragilité physique sur la mortalité ou l'hospitalisation, toutes causes confondues, en tenant compte des covariables.

Résultats: La cohorte finale était composée de 222 patients âgés en moyenne de 77.5 ± 8.1 ans, dont 35% étaient des femmes. La prévalence de déclin cognitif était de 32%, les personnes atteintes de déclin cognitif présentant une incapacité qui s'aggravait au bout de 3 mois. Le déclin cognitif n'était pas associée aux réadmissions à 3 mois, mais le score de fragilité physique était considérablement prédictif de l'hospitalisation à 3 mois.

Conclusion: La Mini-Cog s'avère un outil de dépistage utile pour identifier les patients ayant un déclin cognitif et une Mini-Cog faible peut prédire l'aggravation de l'incapacité à 3 mois. Les cliniciens peuvent s'en servir comme méthode brève et efficace de dépistage du profil cognitif spécifique observé chez les patients atteints d'insuffisance cardiaque et peut aider à identifier les patients présentant un risque plus élevé d'effets négatifs pour la santé.

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**Contribution of Authors**

Jessica Chetrit, BSc

MSc candidate. Jessica has conducted an extensive literature review and has taken the lead in recruitment for the FRAILTY-HF study which includes enrolling eligible patients and administration of frailty assessments, as well as follow-up questionnaires within 1 year of recruitment. Assisted with data analysis and writing of manuscript. Attended weekly research team meetings and presented findings to the MSc Thesis Committee.

Aayushi Joshi, MSc

Research Assistant. Designed the FRAILTY-HF study which involved writing the protocol, creating assessment forms and submitting documents to the ethics boards. Aayushi was vital to the progression of this study and continued to contribute in patient recruitment and in data analysis.

Jonathan Afilalo, MD, MSc

Thesis supervisor. Dr. Afilalo provided continuous guidance on how to structure my project and which direction to pursue. He regularly provided support and feedback along the way and helped to review the manuscript.

Mathieu Walker, MD

Member of thesis committee. Attended committee meetings and provided feedback on the study findings.

Cyril Launay, MD, PhD

Member of thesis committee.

Member of thesis committee. Attended committee meetings and provided feedback on the study findings.

Koren Mann, PhD

Academic Advisor. Attended committee meetings and provided feedback on the study findings. Helped to navigate administrative processes.

# CHAPTER 1: THESIS INTRODUCTION

The global aging population heralds an increase in age-related illnesses such as frailty and cognitive decline which pose a serious challenge to the healthcare, economic and social systems. As heart failure incidence increases with aging, geriatric conditions must be taken into account in the evaluation of HF patients. Frail older adults experience decline in reserve and function in one or more domains (physical, cognitive, social) and are more vulnerable to poor outcomes such as increased risk of hospitalization, institutionalization and death[1]. Studies show that cognitive impairment (CI) is one of the most common co-occurring conditions among older adults people with HF, with prevalence ranging from 25% to 75%[2]. As such, a better understanding of the relationship between frailty and cognitive impairment will be needed to move forward if we are to effectively manage and prevent these conditions.

The place of cognitive impairment in a definition of frailty has been widely debated. Cognitive impairment is the decline of intellectual functions such as thinking, remembering, reasoning and planning[3]. It is common among older people but the effects range from minor forms of forgetfulness to severe and debilitating major neurocognitive disorder (major NCD). Minor neurocognitive disorder (minor NCD) is a term used to define a state of cognitive decline that is not accompanied by any significant functional disability[3]. It has a high rate of progression to all types of major NCD in which severe cognitive impairment is accompanied by increasing physical decline, eventually leading to full physical dependency.

The growing body of scientific evidence on the association between the physical frailty syndrome and cognitive impairment has led to the emergence of the term “cognitive frailty”. Researchers highlight the importance of assessing both physical and cognitive function in older

adults for the planning of timely interventions and state that the inclusion of cognitive measures in the assessment of frailty can improve the predictive validity of the phenotype regarding adverse health outcomes in this population[4].

The purpose of this thesis was to conduct a literature review on the current understanding of cognitive impairment in HF and to investigate the link between physical frailty and cognition. Additionally, the objective was to perform a prospective cohort study and present the manuscript titled "Cognitive impairment in older adults with heart failure: prevalence and impact on outcomes", which explores the prevalence of minor NCD in HF patients and its impact on adverse health outcomes. Lastly, the thesis conclusion summarizes the main findings of the study, the clinical relevance and future implications related to the field of cognition in HF.

# CHAPTER 2: LITERATURE REVIEW

## Defining heart failure

Heart failure is a complex clinical syndrome in which abnormal heart function impairs the heart's ability to pump enough blood to meet the body's metabolic needs[5]. In addition to its major economic burden, heart disease remains one of the leading causes of deaths worldwide and more than 600 000 Canadians are currently diagnosed with HF[6]. Due to a reduction in cardiac output and inefficient venous return, the weakened heart cannot deliver oxygen and nutrient-rich blood to the body's cells, which is essential for normal functioning. This results in symptoms such as fatigue, shortness of breath (dyspnea), lower extremity edema, coughing and palpitations. Everyday activities such as walking, climbing stairs or carrying grocery bags can become difficult. The New York Heart Association (NYHA) functional classification is commonly used to describe the severity of HF symptoms, classifying patients into 4 groups based on their functional limitations (Table 1)[7]. HF is classified based on ejection fraction (EF) which is the percentage of blood ejected with each heartbeat. Heart failure with reduced ejection fraction (HFrEF) defines HF with an EF of $\leq$40% while HF with preserved ejection fraction (HFpEF) defines HF with an EF of $\geq$50%[8].

| Class | Symptoms |
|---|---|
| I (mild) | No limitation of physical activity. Ordinary physical activity does not cause symptoms (angina, breathlessness, palpitation or fatigue). Extra-ordinary activity may results in symptoms. |
| II (mild) | Slight limitation of physical activity. Patients are comfortable at rest. Ordinary activity may results in symptoms. |
| III (moderate) | Marked limitation of physical activity without symptoms. Although patients are comfortable at rest, less than ordinary activity will lead to symptoms. |
| IV (severe) | Inability to carry out any physical activity without symptoms. Symptoms are present at rest. |

Table 1: NYHA Classification[7]

## Frailty Overview

*Definitions of frailty*

Frailty is defined as an aging-related syndrome, characterized by decreasing physiological reserve and predisposition to increased vulnerability to adverse health outcomes. Most of the available definitions have privileged the physical dimension of the frailty syndrome, mostly relying on signs and symptoms like weight loss, muscle weakness, slow gait speed and sedentary behavior. Fried's model describes a wasting syndrome, with weight loss and negative energy balance as important elements and does not include cognitive function in its definition[9], the Short Physical Performance Battery (SPPB) objectively assesses physical function using three categories: gait speed, balance, and lower body strength[10], whereas Rockwood's model allows poor cognition to be included as one of the possible deficits[11].

Moreover, to date despite the ongoing research into frailty there has been no definitive consensus regarding the definition of frailty. There are currently two major concepts of frailty:

- Deficit-driven frailty: the more clinical deficits accumulated the more likely the patient is to be frail. This was operationalized by Rockwood et al as the Frailty Index (FI)[12].
- Phenotypic frailty: Fried et al operationalized frailty as a biological syndrome where declines in specific physiological systems are assumed to be part of the etiology of frailty[9].

*Frailty in heart failure*

Frailty is particularly important for older adults with HF since these patients experience multisystem dysfunction including high comorbidity burden, hormonal dysregulation, accelerated muscle loss and systemic inflammation[13]. There is significant overlap in the underlying pathological mechanisms of heart failure and frailty. Frailty has been associated with chronic inflammation and increased inflammatory cytokines, such as C-reactive protein, tumor necrosis factor–alpha (TNFα), interleukin-6 (IL-6) and fibrinogen[14,15].

Symptoms of heart failure, such as dyspnea, fatigue, and muscle loss, mirror components that occur with frailty. Patients with HF are therefore being predisposed to a state of heightened vulnerability and functional decline. In fact, the highest rates of frailty have been reported in HF patients[16,17]. Recent guidelines by the American Heart Association (AHA) and the Canadian Cardiovascular Society (CCS) have outlined the need to assess patients with HF for frailty in order to optimize their management[18,19].

## Cognitive impairment in heart failure

*Epidemiology*

Cognitive impairment occurs frequently in patients with heart failure, and the presence of cognitive impairment in persons with HF has been shown to heighten risk for adverse clinical

outcomes, disability, poor quality of life and mortality[20,21]. Most HF patients suffer from minor neurocognitive disorder (minor NCD), which is a measurable deficit with memory or another core cognitive domain. Up to 60% of people with heart failure have been reported to have minor NCD[22]. Patients with minor NCD have cognitive deficits that are more pronounced than those seen in normal aging, but lack other symptoms of major neurocognitive disorder, such as impaired judgment or reasoning. Minor NCD often will not impede a patient's ability to carry out the activities of daily living (ADLs) independently, but patients may have difficulty in performing some instrumental activities of daily living (IADLs), such as remembering medications, scheduling provider appointments. Overall, patients with HF seem to be worse cognitively compared to healthy controls.

Heart failure adversely affects multiple domains of cognition. The most common domains affected by HF are memory and executive function[23]. Deficits in initial learning as well as delayed information recall were reported in the literature and memory was demonstrated to slowly decline in HF patients[24,25]. Most of the studies on the relationship between memory tasks and HF reveal deficits both on immediate and delayed recall, while semantic memory is less compromised[2]. As well, measurements of executive functioning (problem solving, planning and reasoning) were impaired in most of the studies reviewed, and have a strong impact on a patient's everyday life[25]. Furthermore, in a study by Callegari et al, 26% of patients with HF had impairment in one cognitive domain and 30% had impairment in four or more domains[26]. People with HF have more than a four-fold risk for CI compared to people without HF after controlling for other factors such as age, gender, and comorbidities[27].

*Predictors of cognitive impairment in HF*

Different predictors have been associated with CI in patients with HF (Figure 1). Various studies support a correlation between functional status and cognitive decline in HF. Performance in timed walk tests[28] and NYHA functional class[29] have been correlated with CI in HF. Low cardiac output and cardiac index in cardiac patients are associated with minor and major NCD[30,31]. Festa et al associated low ejection fraction with memory impairment, in which recall memory was most impaired[32]. Hypotension and low cardiac output can cause hypoperfusion of the cerebral circulation, which may be detrimental to cognition. In the GIFA study, hypotension was more commonly seen in patients hospitalized with HF with CI when compared to HF without CI (46% vs. 27%)[33]. As well, B-type natriuretic peptide (BNP) levels seem to influence general cognitive decline as well as major NCD. In a cohort study by Kerola et al, BNP was the only variable that significantly predicted cognitive decline and was associated with new diagnosis of major NCD over a five year period[34].

In addition, Alosco et al showed obesity in HF associated with cognitive decline. An interaction between hypoperfusion and obesity was noted for its adverse effects on executive function and attention[35]. In the Heart ABC study, higher BMI was associated with poorer attention span and executive function in male HF subjects[36]. Alosco et al also associated COPD with reduced cognition and poor physical fitness in HF[37]. In their analysis, COPD was significantly associated with deficits in attention and executive function domains.

Furthermore, both anemia and renal failure occur with the progression of HF and may play a role in cognitive decline. In Pulignano et al's prospective study, anemia and renal disease were independently associated with CI in elderly HF subject[38].

Lastly, atrial fibrillation is the most common arrhythmia seen in older adults and is associated with HF[39]. In HF subjects, it is associated with memory impairment, minor NCD and hippocampal atrophy[40]. Reduced cerebral blood flow and increased cerebral white matter ischemic changes may be a mechanism by which atrial fibrillation causes cognitive decline. Left atrial enlargement with HF has been associated with atrial fibrillation, low cardiac output and cerebral white matter ischemic changes[41].

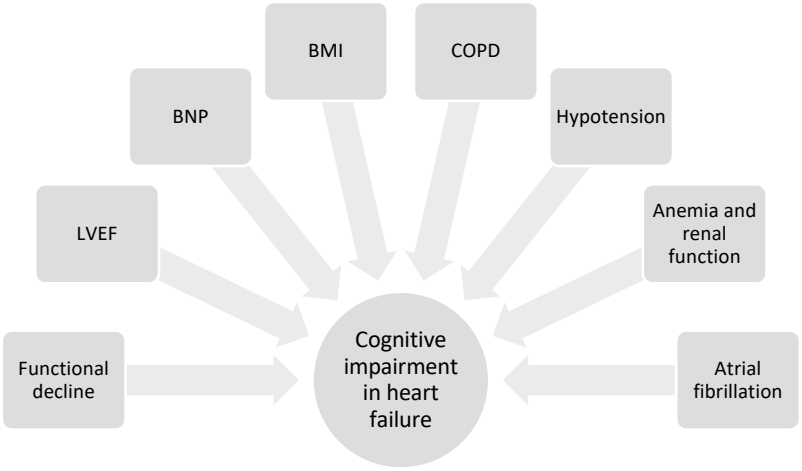


Figure 1: Potential predictors of cognitive impairment in heart failure

## Concept of cognitive frailty

Given that the operational definition of frailty is still uncertain, it is even more difficult to establish a precise definition for cognitive frailty. While physical frailty has been acknowledged to be an important geriatric syndrome, cognitive frailty is still a novel concept. The importance of addressing the construct of cognitive frailty has been recognized. In the past, cognitive frailty has been used to refer to cognitive impairment related to advanced age or cognitive disturbances occurring simultaneously with other comorbidities[42].

The term cognitive frailty was first used in a cohort study of older adults on the performance on a clock-drawing test and its associations with risk factors for Alzheimer's disease[43]. This term was subsequently proposed in a study reviewing pre-dementia syndrome vascular risk factors[44]. Since then, research has shown that both cognitive and physical factors are predictors of mortality[45]. In 2013, a consensus on the definition of cognitive frailty was reached by an international consensus group (the International Academy on Nutrition and Aging and the International Association of Gerontology and Geriatrics)[4]. The panel defined cognitive frailty as "a syndrome in older adults with evidence of both physical frailty and cognitive impairment without a clinical diagnosis of Alzheimer disease or another dementia"[4]. As a consequence, secondary prevention targeting frailty could be an effective way of slowing down cognitive decline. This definition also suggests physical frailty and cognition to be associated. However, the causal links between physical frailty and neurocognitive disorder as common pathophysiological mechanisms remain unclear. Cognitive frailty was suggested to be a fundamental determinant of the individual's vulnerability and resilience to stressors[4]. Nevertheless, in the clinical setting there is still much uncertainty regarding the definition, validity and relevance of cognitive frailty.

**Parallels between physical frailty and cognitive frailty**

Frailty is a multidimensional syndrome. It is important to consider cognition as a mediator in the development and progression of frailty. Neurocognitive disorder has a synergistic effect on physical frailty. Both physical frailty and cognitive frailty can co-exist in an individual. There are shared factors causing both physical frailty and cognitive frailty. Factors leading to physical frailty may cause cognitive frailty, and vice-versa. Both minor and major NCD have been found to be more prevalent in frail individuals compared to those who are pre-frail or robust[47,48]. Both physical

frailty and neurocognitive disorder act in a cycle of decline leading to further physical and cognitive decline and decreased quality of life[48,49]. Age is a common risk factor for the development of both cognitive impairment and frailty. Additionally, mechanisms such as chronic inflammation, nutrition, presence of vascular diseases, depression and endocrinological disorders have been found to be implicated in both frailty and cognitive impairment [50,51,52].

Moreover, cardiovascular disease has been found to be associated with both frailty and cognitive impairment. Cardiovascular disease is independently associated with both baseline and incident frailty at 3 years[53,54]. This might be due to an increased risk of sarcopenia, an age-related decline in skeletal muscle mass and muscle function, which is intrinsically related to the development of frailty. Furthermore, a relationship might exist between sarcopenia and cognitive decline, wherein the prognosis of neurodegenerative diseases are worsened by sarcopenia[55]. Cardiovascular disease is associated with the development of cognitive decline and major NCD as it is an underlying risk factor for stroke and cerebrovascular disease[56].

**Screening instruments used in heart failure**

Cognitive impairment has been identified as an important clinical issue in numerous recently conducted studies, though no consensus has been achieved so far regarding optimal diagnostics and treatment tools in patients suffering from both HF and CI. There is a definite limitation on this issue in the literature as investigators have used several different tools and the assessment of cognition has not been standardised in cardiology practice. HF patients are not routinely screened for CI, and a suitable and standard measurement instrument for assessing CI in HF has not been established. Table 2 summarizes the most commonly used screening methods used in the literature.

*Mini-Mental State Examination (MMSE)*

The MMSE is the most frequently used screening measure in the HF population, but does not appear to be adequate in terms of detecting the type of CI seen in HF. The MMSE was originally developed as a screening tool for major NCD, and has proven to have poor sensitivity in detecting minor NCD[57]. While the MMSE covers a wide range of domains, it does not have the capacity to test executive function, and has been shown to have high sensitivity and specificity in HF only when impairment is severe[58]. Most studies using the MMSE used a score of <24 to indicate CI, however a few studies have used higher cut-off points (<26-28) to identify more patients with impairment[59,60,61]. Furthermore, this could cause patients with normal cognition to be inappropriately labeled as impaired, and does not allow for consistent comparisons across studies using the same screening instrument.

*Montreal Cognitive Assessment (MoCA)*

The MoCA is an instrument that was specifically designed to identify minor NCD and covers eight cognitive domains. The MoCA has been used to test the impact of minor NCD in HF patients. When the MoCA was used to screen for cognitive deficits in an older outpatient HF population, 70% of patients scored <26, the cut-off score indicative of neurocognitive disorder. This high prevalence could be attributed to the increased sensitivity of the MoCA to detect minor NCD in HF patients[62]. Athilingam et al compared the MoCA to the MMSE for their ability to detect minor NCD in HF patients in a community setting. The MoCA identified 54% of participants with minor NCD (using cut-off score <26) compared to only 2.2% identified by the MMSE (using cut-off score <24)[58]. The results provide additional evidence that the MMSE is not sensitive enough to identify subtle neurocognitive disorder in HF. Even though the MoCA is a

more sensitive and comprehensive assessment, it takes the longest time and may contribute to participant burden.

*Clock Drawing Test (CDT)*

The CDT mainly screens for impairments in visuospatial and executive function domains[63]. The patient is asked to draw a circle, and then put the numbers on as if it were a clock face. Then the patient is asked to draw the hands of the clock to represent a specific time. Riegel et al compared the CDT to three other approaches to determine which was the most useful in identifying minor NCD[57]. Patients were considered impaired if they scored <2. The authors reported that the screening instruments varied in effectiveness and noted that the CDT indicated cognitive impairment in 50% of the patients, while the MMSE only identified 2.4% of the cohort as impaired[57]. The CDT was considered the most useful; however the authors warn that it should not be used as a standalone screening measure in HF as it does not detect issues with memory or verbal learning.

*Short Portable Mental Status Questionnaire (SPMSQ)*

This instrument is used to evaluate the prevalence of CI in older adults and include tests of orientation, memory and recall. The patient is asked to state the date, day of the week, place, address, birth date, current and prior presidents, and mother's maiden name, in addition to a serial subtraction task[64]. The SPMSQ has been used in few HF studies as part of different comprehensive geriatric assessments. The scoring and interpretation of cognitive impairment vary across these studies. One study dichotomized scores as zero errors (no impairment) and one or more errors (any impairment)[65]. Two other studies used the instrument to derive an index along with other

instruments, and scoring approaches were not reported[66,67]. The SPMSQ is appealing because of its brevity but its validity has not yet been demonstrated.

Table 2: Comparison of screening instruments used in HF

| Screening tool | Cognitive domain measured | Average time (min) | Number of items | Range of scores | Scoring | Sensitivity/Specificity | Evaluation for HF |
|---|---|---|---|---|---|---|---|
| **Mini Mental Exam (MMSE)**[68,69] | • Attention<br>• Language<br>• Orientation<br>• Short term memory<br>• Visuospatial | 8 | 30 | 0-30 | • <24 indicative of CI<br>• Varies across populations (often adjusted for older adults, as low as 20) | • 87%/82% with cut point 24<br>• 98%/89% with cut point 25 | • Does not include executive function<br>• Does not detect minor NCD<br>• Lengthy screening measure |
| **Montreal Cognitive Assessment (MoCA)**[70] | • Attention<br>• Executive function<br>• Language<br>• Orientation<br>• Memory<br>• Visuospatial | 10 | 30 | 0-30 | • 25-17 minor NCD<br>• ≤16 possible major NCD | 90%/87% | • Longest time to screen |
| **Clock Drawing Test (CDT)**[71,72] | • Attention<br>• Executive function<br>• Semantic Memory<br>• Visuospatial | 2 | 1 | 0-3 | • ≤2 indicates CI<br>• Scoring options vary | 59%/70% | • Does not include short-term memory<br>• Has not been often used in HF patients<br>• Limited success in detecting minor NCD |
| **Short Portable Mental Status Questionnaire (SPMSQ)**[64,73] | • Attention<br>• Orientation<br>• Semantic memory | 3 | 10 | 0-10 | • 0-1 = intact<br>• 2 = borderline impairment<br>• 3 = moderate<br>• ≥4 = severe<br>• 0 = no CI , ≥1 = CI | 74%/91% | • Has not been validated<br>• Does not include short-term memory or executive function<br>• Has not been often used in HF patients |

**Clinical implications of cognitive impairment in HF patients**

In summary, cognitive impairment is a common problem among individuals with HF. A typical frailty assessment is heavily focused on physical parameters without consideration of cognitive dysfunction. Cognitive function should also be assessed routinely in persons with heart failure and incorporating geriatric measures in heart failure management would allow for more treatment strategies aimed at improving physical function, cognitive outcomes, and quality of life.

The neuropsychological batteries used most often in HF are long and impractical for clinic use. When selecting a screening instrument to use in the HF population, clinicians may need to prioritize the importance of a comprehensive tool that considers the cognitive profile specific to HF. As the population ages and the incidence of HF rises, the high morbidity and mortality associated with frailty and cognitive impairment will only increase. Information gained from simple, inexpensive physical performance measures, when used in combination with cognitive screening, may enhance the ability to evaluate change that signal onset of frailty and cognitive impairment and subsequently manage these conditions to improve adverse health outcomes.

## CHAPTER 3: MANUSCRIPT TO BE SUBMITTED

# COGNITIVE IMPAIRMENT IN OLDER ADULTS WITH HEART FAILURE: PREVALENCE AND IMPACT ON OUTCOMES

Jessica Chetrit, BSc (1,2), Aayushi Joshi, MSc (1,2), Caroline Michel MD (3), Richard Sheppard MD (3), Nadia Giannetti MD (4), Abhinav Sharma MD PhD (4), Viviane Nguyen MD MSc (5), Esther Laforest RN MSc (3), Delina Maghakian RN (3), Jonathan Afilalo, MD MSc (1,2,3)

(1) Centre for Clinical Epidemiology, Jewish General Hospital, Montreal, QC, Canada

(2) Division of Experimental Medicine, McGill University, Montreal, QC, Canada

(3) Division of Cardiology, Jewish General Hospital, McGill University, Montreal, QC, Canada

(4) Division of Cardiology, McGill University Health Centre, McGill University, Montreal, QC, Canada

(5) Division of Cardiology, Hôpital Cité-de-la-Santé de Laval, QC, Canada

**Correspondence**

Jonathan Afilalo, MD, MSc, FACC, FRCPC

Associate Professor, McGill University

Director, Geriatric Cardiology Fellowship Program

Co-Chair, ACC Geriatric Cardiology Section Research Working Group

Jewish General Hospital, 3755 Cote Ste Catherine Rd, E-222, Montreal, Quebec, H3T 1E2

Phone: (514) 340-8222 | Fax: (514) 221-3785 | Email: jonathan.afilalo@mcgill.ca

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None.

**ENGLISH ABSTRACT**

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cognitive impairment is predictive of worsening disability. Multivariable logistic regression modeling was used to determine the impact of cognitive impairment and physical frailty on all-cause mortality or hospitalization, adjusting for covariates.

Results: The final cohort consisted of 222 patients with a mean age of 77.5 ± 8.1 years and was 35% female. The prevalence of minor NCD was 32%, in which individuals with minor NCD exhibited worsening disability at 3 months. Cognitive impairment was not associated with death or readmissions at 3 months however, physical frailty score was highly predictive of death and hospitalization at 3 months.

Conclusion: The Mini-Cog proves to be a useful screening tool in identifying HF patients with minor NCD and an abnormal Mini-Cog score is predictive of worsening disability at 3 months. The Mini-Cog can serve as a brief and effective method for clinicians to screen for the specific cognitive profile seen in HF patients and can help to identify patients at higher risk of adverse health outcomes.

## INTRODUCTION

Heart Failure (HF) is a major health problem, affecting 1%-2% of the adult population worldwide with a rising prevalence of 6%-10% in individuals over 65 years old[1]. Older adults with HF often present with complex comorbidities and clinical features that may further complicate the course of the disease[1]. Frailty, defined as a decrease physiologic reserve and resistance to stressors, is a very common condition in older adults with HF. It is recognized that frailty is associated with poorer prognosis in terms of hospitalizations, mortality and quality of life[2]. As HF incidence increases with aging, geriatric conditions must be taken into account in the evaluation of frailty in HF patients. Cognitive impairment is one of the most common co-occurring conditions among older adults with HF, with prevalence ranging from 25% to 75%[3,4]. A systematic review showed diminished performance in memory, executive function and global cognition when comparing HF patients to healthy subjects[5]. The place of cognitive impairment in a definition of frailty has been widely debated. Cognitive impairment is the decline of intellectual functions such as thinking, remembering, reasoning and planning[6]. Most HF patients suffer from minor NCD, which is considered a transitional period between normal ageing and the development of moderate cognitive impairment, with memory and executive function being the most commonly impaired domains[6].

There are important gaps in our understanding of the association between physical frailty and cognition. Intact memory and executive function are necessary to recognise worsening symptoms, adhere to medication regimens and lifestyle modifications, and even minor cognitive deficits may interfere with adherence to self-care practices, disability and quality of life. The recognition of cognitive impairment in HF patients has important implications given the complex requirements for optimal heart failure disease management and can have a meaningful influence

on adverse health outcomes. Furthermore, it is critical to determine which measures can reliably assess cognitive impairment in HF patients. This study aims to determine the prevalence of minor neurocognitive disorder in HF and to investigate the impact of cognitive impairment in predicting adverse health outcomes in HF patients.

## METHODS

### *Study Design*

This study is a cross-sectional sub-study of the Frailty-HF Study, a prospective multicentre, observational cohort study, that was conducted at four HF clinics at the following institutions: Jewish General Hospital (JGH), Royal Victoria Hospital (RVH) and Cité-de-la-Santé and St-Mary's Hospital. Patients were recruited from April 2019 to July 2021. Older adults $\geq$60 years with a clinical diagnosis of HF were enrolled and underwent a comprehensive frailty assessment. Minor NCD was classified as a Mini-Cog score $\leq$3/5. A total score of $\leq$8/12 on the Short Physical Performance Battery (SPPB) was required for a diagnosis of physical frailty. Ethics approval was obtained from the Jewish General Hospital's institutional review board.

### *Participants*

The study sample included: (1) community dwelling outpatients, (2) aged 60 years or older, (3) diagnosed with HF with preserved or reduced ejection fraction for at least the past 3 months, (4) who have agreed to participate and signed an informed consent form.

Our study sample excluded: (1) patients with a recent hospital admission within the past 3 months, (2) acutely decompensated HF status at the time of their visit, (3) received intravenous

diuretics or inotropes within the past 3 months, (4) moribund health status with life expectancy less than 3 month, (5) underwent or scheduled to undergo a major surgical or percutaneous procedure within the past or upcoming 3 months, (6) implantation of a cardiac resynchronization device within the past 3 months, (7) history of heart transplant or currently on the transplant list, (8) major neurocognitive disorder (Alzheimer's or dementia), (9) non English or French speaking.

*Assessment of Cognitive Function*

Cognition was evaluated using the Mini-Cog, which is a composite of a 3-item recall test and a clock-drawing test[7]. We conducted the test by asking patients to repeat three unrelated words, the patient was then asked to complete the clock-drawing test, and finally the patient was asked to recall the three words. The Mini-Cog was scored on a 5-point scale (1 point for each word correctly recalled and 2 points for a correct clock drawing), and a score of ≤3 was considered abnormal and suggestive of minor NCD (Appendix A). The patients were also asked four orientation questions specific to the day of the week, the month, the name of the hospital they were in and the floor they were on (Appendix B).

*Assessment of Physical Frailty*

The Short Physical Performance Battery (SPPB) objectively assess physical function and encompasses slowness, weakness, and balance in its test battery[8]. This is measured by a series of 3 timed physical performance tests (gait speed, chair rises, tandem balance). The total score indicates the patient's degree of disability, where a higher score indicates fewer disabilities (Appendix C). A total score ≤8/12 was required for a diagnosis of physical frailty.

*Outcomes*

The primary outcome was change in disability. The Older American Resources and Services (OARS) tool is a multidimensional functional assessment questionnaire that permits assessment of an individuals' functioning on 5 domains: social, economic, mental health and self-care capacity (Appendix D). Incident disability was defined as institutionalization or ≥2 new deficits in basic and instrumental activities of daily living (ADL and IADL), as captured by the OARS tool. Worsening disability was defined as a positive change in disability score at 3 months from baseline.

Secondary outcomes included the combined endpoints of all-cause mortality and hospitalization within 3 months, determined by medical records or by contact with patients or a family member over the telephone.

*Data Collection*

Analysis of existing data and collection of prospective longitudinal data. Data collection included questionnaires administered by interview, physical performance tests, review of clinically acquired biochemical and imaging tests and chart review conducted by research trainees. Outcomes were assessed at 3 months with a telephone call, where a brief follow up questionnaire was administered to assess whether they experienced a change in health status or physical functioning. Vital status was assessed by electronic medical records or by contact with the patient or family members.

*Statistical Analysis*

Characteristics of the study cohort were reported as percentages for dichotomous variables or as means ± standard deviations for continuous variables. A p-value of <0.05 was considered statistically significant. Linear regression was used to determine if minor NCD is predictive of worsening disability. Multivariable logistic regression modeling was conducted to investigate the impact of minor NCD and physical frailty on secondary outcomes of all-cause mortality and hospitalization, adjusting for covariates. REDCap electronic data capture tools were used to manage study data and statistical analyses were completed using the STATA software package.

**RESULTS**

*Baseline Characteristics*

The final cohort consisted of 222 patients who completed both the cognitive and frailty assessments during the baseline assessment (Figure 1). Overall, the cohort had a mean age of 77.5 ± 8.1 years and was 35% female. The cohort had a mean LVEF of 37.4±15.3, 46% were of ischemic etiology and 37% had HFpEF. Common cardiovascular risk factors were distributed as follows: 72% had hypertension, 61% had dyslipidemia, 42% had coronary artery disease and 58% had atrial fibrillation. The median MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) risk score, which indicates severity of HF and predicts mortality in patients who are admitted to hospital due to HF[9], was 24.6±6.

The median Mini-Cog score among the study population was 3.3±1.5. Overall, the prevalence of minor NCD was 32%. Patients with minor NCD were more likely to be older, were less tolerant to exercise as measured by 6MWT, were more likely to be physically frail as measured

by the SPPB, were more likely to have upper extremity weakness shown by lower grip strength, and had significantly more disability in both ADL and IADL. HF severity also increased in those with abnormal Mini-Cog score, as defined by the MAGGIC risk score. Among the patients with minor NCD, 65% were physically frail whereas among those without cognitive impairment, 44% of patients were physically frail. The baseline characteristics are further detailed in Table 1.

When stratifying the Mini-Cog score by age, patients aged of 70-79 years and 80-89 years had the highest prevalence of cognitive impairment compared to the rest of the cohort (n=24 and n=29, respectively) (Figure 2). Furthermore, after breaking down the cognitive parameters measured, 59% of patients were not able to recall all three words for the word recall task and 31% of patients had an abnormal clock draw (Figure 3A). In terms of orientation questions, most patients were able to answer properly whereas orientation to floor was the most frequently incorrectly answered question, followed by orientation to month (Figure 3B).

*Primary Outcome*

Linear regression was used to determine if minor NCD is associated with worsening disability in HF patients. Notably, patients with abnormal Mini-Cog score were more likely to experience the primary outcome of disability. As shown in Table 2, patients with minor NCD were associated with a higher degree of disability at baseline compared to cognitively intact patients (11±3.7 vs. 12.6±2.2, $p<0.001$). Poor Mini-Cog score was also associated with worsening disability at 3 months (11.1±3.6 vs. 12.3±2.6, $p=0.01$). This analysis revealed an independent association between minor NCD and limitation in both ADL and IADL, where a decrease in 1 point on the OARS was significantly predictive of worsening disability at baseline and at 3 months in those with abnormal Mini-Cog score.

*Secondary Outcomes*

Multivariable logistic regression was used to explore the impact of cognitive impairment and physical frailty on the combined endpoints of all-cause mortality and hospitalizations in HF patients (Table 3). Abnormal Mini-Cog score was not associated with death or hospital readmissions at 3 months (OR=0.891, p=0.428). However, physical frailty (measured by the SPPB) was highly predictive of hospitalization at 3 months (OR=0.842, p=0.012). Age (OR=0.889, p=0.002) and HF severity as measured by the MAGGIC risk score (OR=1.199, p<0.000) were also significant predictors of these short-term outcomes.

**DISCUSSION**

This study aimed to determine the prevalence of cognitive impairment among HF patients and the impact of cognitive dysfunction on adverse health outcomes. The findings indicate minor NCD was present in 32% of patients and that screening for minor NCD using the Mini-Cog identifies HF patients with disabilities, and at increased risk of worsening disability within 3 months. From these results, it may be assumed that cognitive impairment affects the patient's functional capacity and ability to perform everyday activities and therefore limits his/her autonomy. This conclusion was confirmed by the results of several studies in the literature. Among older patients with HF, cognitive dysfunction has been associated with a sixfold increase in the probability of dependence for the activities of daily living and CI has been independently associated with increased functional disability[10]. Formiga et al demonstrated a functional decline in 64% of HF patients and cognitive impairment proved to be a strong risk factor for incident disability in this population[11].

A number of neuropsychological tests for the assessment of cognitive functioning are available, yet most of them are time-consuming and are difficult to administer in everyday clinical practice. The Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), are the most widely used screening tools in the literature. Though the MMSE and the MoCA are useful tests for screening patients with cognitive impairment, they could be insufficient in identifying subtle cognitive deficits, are lengthy to administer, and may not be adequate to identify minor NCD in HF patients[12]. In this study, the Mini-Cog proved to be a simple and brief cognitive screening tool that identifies a significant amount of HF patients with minor NCD. Previous investigators concluded that the Mini-Cog is a valid tool to detect clinically significant cognitive impairment and is useful in addressing the cognitive domains of memory and executive function[14], which are the most commonly impaired domains in HF. If this tool was predictive of our primary outcome, then performing a quick Mini-Cog assessment could help clinicians in the discussion of risk management and in preventing the decline in functionality for this group of patients.

Although we did not find an association between an abnormal Mini-Cog score and our secondary outcomes, establishing that physical frailty is predictive of death and hospital readmissions is valuable in itself. We can conclude that the primary determinant of mortality and hospitalizations in HF patients seems to be physical frailty rather than cognitive dysfunction. Furthermore, the addition of cognitive screening to the assessment of physical frailty may improve the detection of patients who are at a higher risk of adverse health outcomes. This conclusion is consistent with the recent description of "cognitive frailty", in which a person is both physically frail and cognitively impaired in the absence of major NCD (Alzheimer's or dementia)[15]. Consistent with this concept, a study of 6,030 community-dwelling adults aged $\geq$65 found that the

addition of a cognitive assessment to Fried's physical frailty phenotype improved the predictive validity for incident disability and hospitalization[16]. Similarly, Sunita et al found that incorporating a cognitive measure to the assessment of frailty improved the detection of HF patients at high risk of early death and that cognitive impairment strengthened the adverse effect of frailty on overall survival in this population[17]. In a population of older adults hospitalized for HF, cognitive impairment was common (47%) and associated with 6-month mortality or readmission[19]. These findings highlight the importance of further investigating the outcomes of this study to determine the long-term effects of cognitive impairment in HF patients.

There are several limitations to our study. First, the follow-up period was 3 months. This is a short time range in terms of determining clinically relevant adverse outcomes. Second, the cohort consisted of 222 patients, from which 179 patients completed the 3-month follow-up and were included in the short-term analysis. The relatively small cohort for this analysis may limit generalizability of results. Lastly, cognitive status was only measured at baseline. Given that cognition is a dynamic state, it would be important to consider longitudinal changes in cognition over time. It is also important to note that the Mini-Cog has not been validated in the HF population. Future research should incorporate the Mini-Cog in routine cardiology assessments in order to validate this screening tool in HF. The FRAILTY-HF study should continue to build a robust cohort with 1-year follow-up to assess for long-term outcomes. Outcomes should be further investigated to see if cognition continues to change the rate of disability accumulations that we have observed at 3 months and to determine if cognitive impairment is associated with death or hospitalizations over a longer time period.

## CONCLUSION

The Mini-Cog proves to be a useful screening tool in identifying HF patients with minor NCD and abnormal Mini-Cog score is predictive of short-term deficits in disability. The results demonstrate that HF patients with minor NCD had lower scores on the OARS questionnaire, suggesting increased disability in this population and short-term risk of worsening disability. In HF patients, the challenges for clinicians will be not only the treatment of cardiac disease itself but also the identification and the management of associated conditions such as cognitive impairment. The Mini-Cog can serve as a rapid preliminary screening method for clinicians to identify minor cognitive deficits in HF. Even though cognition did not significantly predict mortality or hospital readmissions in HF, we know that physical frailty is an important aspect to intervene on to improve these outcomes. This further emphasizes the need to incorporate a multimodal approach to routine frailty assessments in this population. The knowledge gained from this study will allow us to recommend a reliable cognitive screening tool to identify minor NCD in HF. Future guidelines should consider a cognitive aspect in frailty assessments to improve risk stratification strategies for more vulnerable patients and to prompt a more comprehensive approach to disease-specific management.

### *Clinical Perspective*

Heart failure guidelines recommend screening for cognitive impairment but do not identify how providers should screen or what tool is best to incorporate. As we continue to investigate the characteristics of cognitive impairment specific to HF, there is an opportunity to build on this research. The Mini-Cog is a simple 3-minute screening tool, that can be easily administered by many levels of providers. Although it has not been well studies in HF patients, our findings suggest

that the Mini-Cog can identify minor NCD in a significant number of patients with HF and can be used as a risk assessment tool to identify a subgroup with less favorable outcomes. This sets the stage for future research aimed at interventions to improve those outcomes.

## FIGURE AND TABLES

Figure 1: Flow diagram

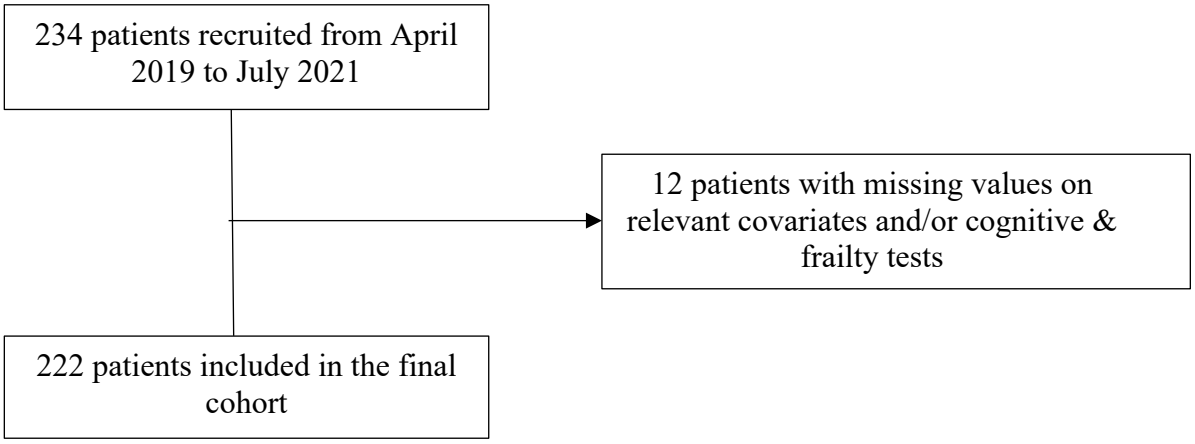
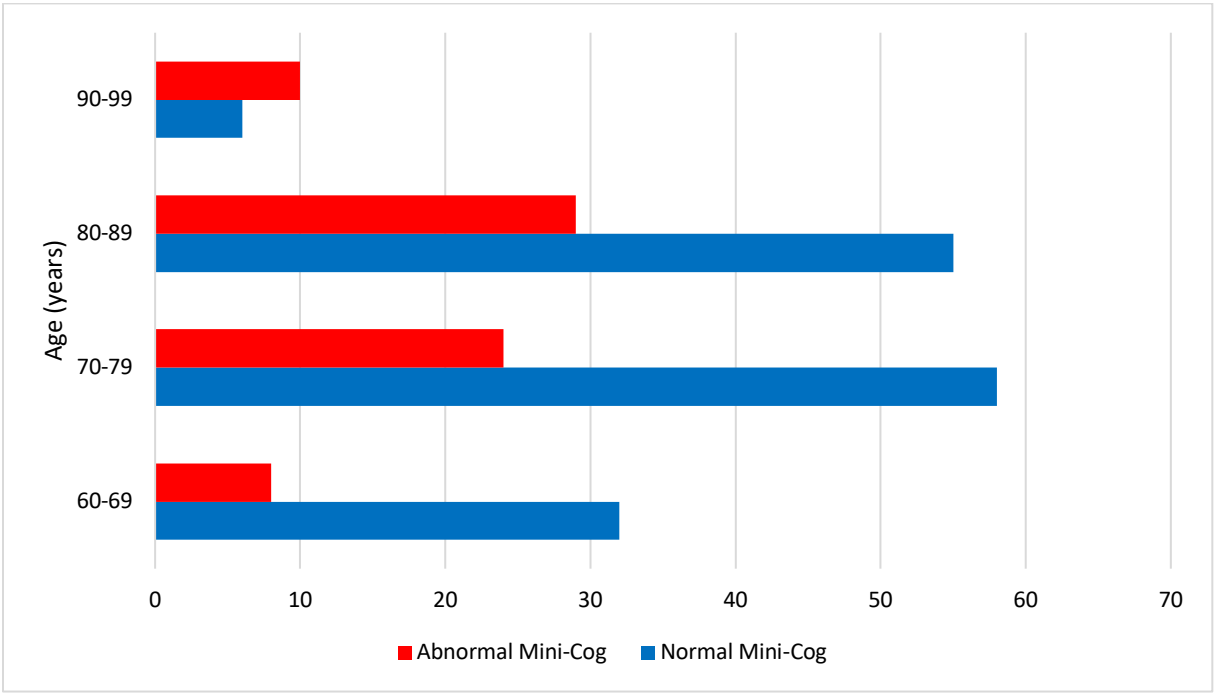


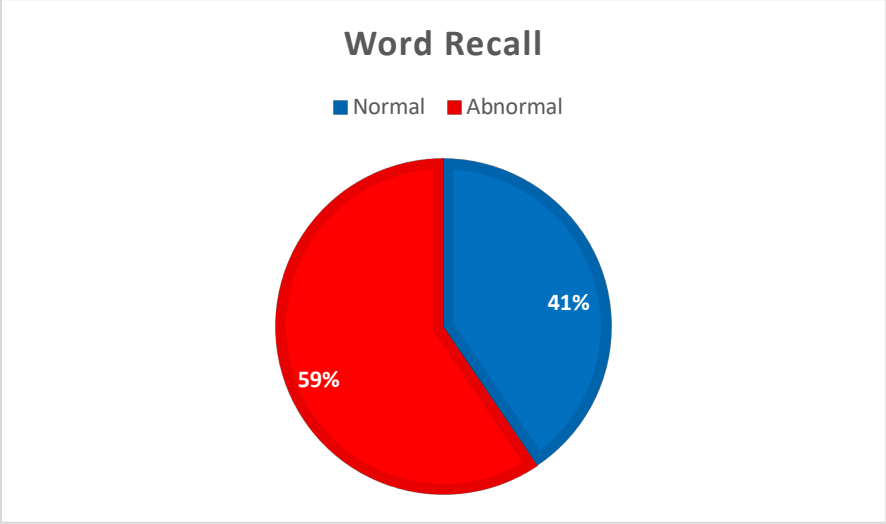

Figure 2: Prevalence of cognitive impairment according to age

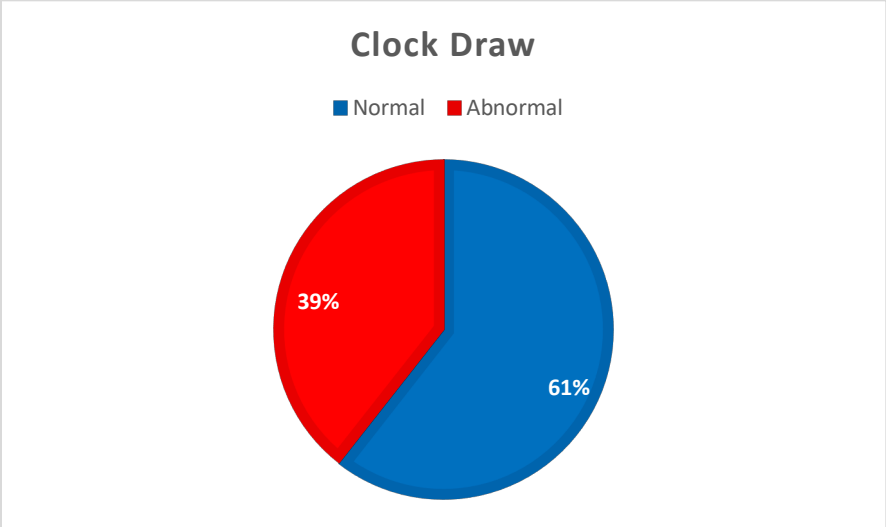



Legend: The blue bars represent the proportion of patients without cognitive impairment, as measured by the Mini-Cog. The red bars represent the proportion of patients with cognitive impairment.

Figure 3: Results of cognitive parameters tested in all subjects

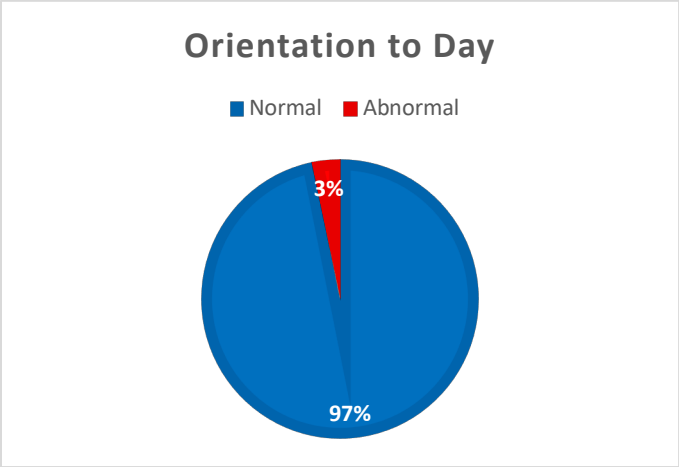
3A. Mini-Cog

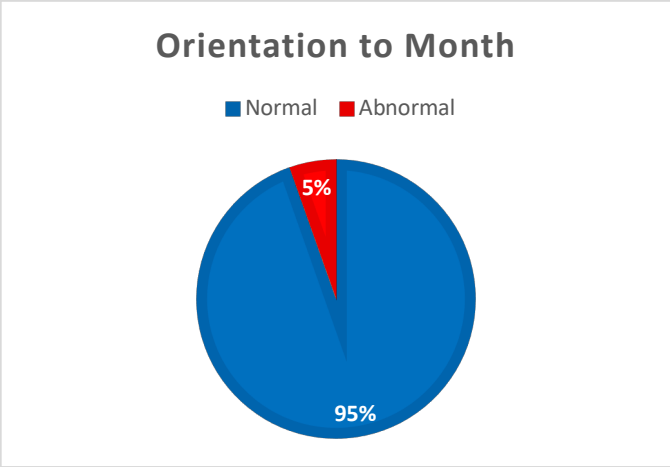


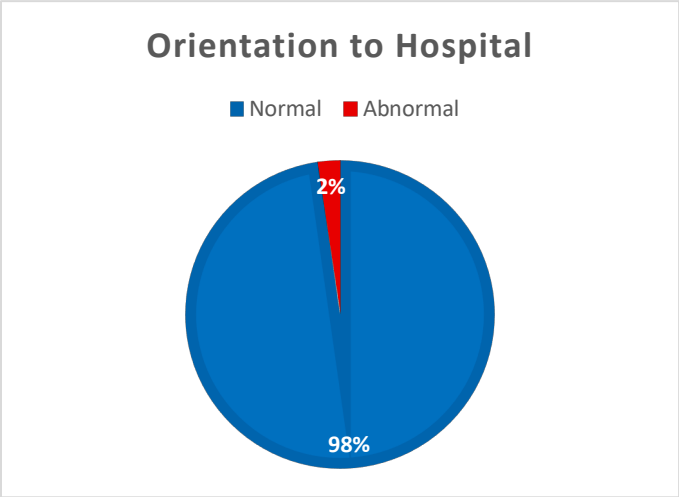



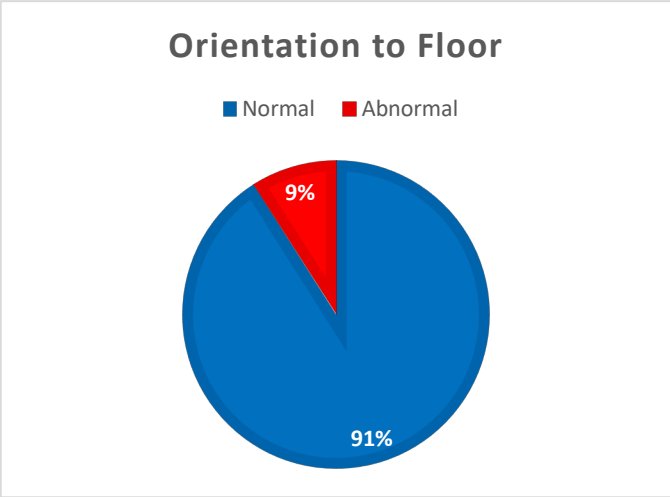

Legend: The blue sections represents the percentage of patients who were able to recall the 3 words correctly and complete the clock draw without error. The red sections represent the percentage of patients who did not complete the word recall and clock draw correctly.

3B. Orientation Questions




Legend: The blue sections represents the percentage of patients who answered each question correctly. The red section represents the percentage of patients who answered each question incorrectly.

Table 1: Baseline characteristics by Mini-Cog score

| | **All patients (n=222)** | **Normal Mini-Cog (n=151)** | **Abnormal Mini-Cog (n=71)** | **P-value** |
|---|---|---|---|---|
| ***Demographics*** | | | | |
| Age (years) | 77.5 ± 8.1 | 76.2 ± 7.8 | 80.1 ± 8.2 | <0.001* |
| Female | 77 (35%) | 51 (34%) | 26 (37%) | 0.68 |
| Height (m) | 1.7 ± 0.1 | 1.7 ± 0.1 | 1.7 ± 0.1 | 0.68 |
| Weight (m) | 78.9 ± 19.4 | 80.2 ± 20 | 76.2 ± 17.9 | 0.16 |
| BMI ($kg/m^2$) | 27.7 ± 6.1 | 28 ± 5.9 | 27 ± 6.6 | 0.27 |
| Obese BMI ≥30 | 66 (30%) | 47 (31%) | 19 (27%) | 0.51 |
| ***Comorbidities*** | | | | |
| LVEF (%) | 37.4 ± 15.3 | 36.9 ± 14.8 | 38.3 ± 16.5 | 0.54 |
| Charlson Comorbidity Index | 5.9 ± 1.7 | 5.9 ± 1.9 | 6 ± 1.3 | 0.79 |
| Coronary artery disease | 93 (42%) | 66 (44%) | 27 (38%) | 0.42 |
| Peripheral artery disease | 12 (5%) | 8 (5%) | 4 (6%) | 0.92 |
| COPD | 28 (13%) | 16 (11%) | 16 (11%) | 0.19 |
| Diabetes | 95 (43%) | 63 (42%) | 32 (45%) | 0.64 |
| Hypertension | 159 (72%) | 107 (71%) | 52 (73%) | 0.71 |
| Dyslipidemia | 136 (61%) | 94 (62%) | 42 (59%) | 0.66 |
| ***HF-related Parameters*** | | | | |
| MAGGIC risk score (/46) | 24.6 ± 6 | 23.8 ± 6.2 | 26.2 ± 5.4 | 0.004* |
| HFpEF | 83 (37%) | 54 (36%) | 29 (41%) | 0.47 |
| Ischemic etiology | 102 (46%) | 77 (51%) | 25 (35%) | 0.03* |
| Atrial fibrillation | 129 (58%) | 85 (56%) | 44 (62%) | 0.42 |
| Long standing diagnosis (≤18 months) | 103 (70%) | 74 (73%) | 29 (63%) | 0.24 |
| Recently hospitalized (≤3 months) | 35 (20%) | 22 (18%) | 13 (24%) | 0.33 |
| ***Frailty/Geriatric Parameters*** | | | | |

| | | | | |
|---|---|---|---|---|
| Fried frailty scale | 1.9 ± 1.3 | 1.7 ± 1.3 | 2.3 ± 1.3 | 0.002* |
| Clinical frailty scale (/9) | 3.6 ± 1.5 | 3.3 ± 1.3 | 4.3 ± 1.5 | <0.001* |
| SPPB score (/12) | 7.7 ± 3.4 | 8.2 ± 3.1 | 6.5 ± 3.6 | <0.001* |
| SPPB score ≥8 | 113 (51%) | 67 (44%) | 46 (65%) | 0.005* |
| Gait speed (m/s) | 0.8 ± 0.4 | 0.9 ± 0.3 | 0.7 ± 0.4 | <0.001* |
| Max grip strength (kg) | 25.6 ± 10.8 | 27.2 ± 11 | 22.3 ± 9.7 | 0.001* |
| Chair rise time (>15s) | 144 (65%) | 89 (59%) | 55 (77%) | 0.007* |
| 6MWT (m) | 268.3 ± 139.1 | 288 ± 140.3 | 220.1 ± 124.8 | 0.003* |
| Essential frailty toolset score (/5) | 1.7 ± 1.3 | 1.3 ± 1.1 | 2.7 ± 1.1 | <0.001* |
| Disability score (/14) | 12.1 ± 2.9 | 12.6 ± 2.2 | 11 ± 3.7 | <0.001* |
| Mini-Cog Score (/5) | 3.3 ± 1.5 | 4.2 ± 0.8 | 1.5 ± 0.7 | <0.001* |

*Significant p-value <0.05

Abbreviations: BMI, Body Mass Index; LVEF, Left Ventricular Ejection Fraction; COPD, Chronic Obstructive Pulmonary Disease; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; HFpEF, Heart Failure with Preserved Ejection Fraction; SPPB, Short Physical Performance Battery; 6MWT, 6 Minute Walk Test.

Table 2: Association between Mini-Cog score and disability at baseline and at 3 months

| | **Baseline** | | **P-value** | **3 months** | | **P-value** |
|---|---|---|---|---|---|---|
| | Normal Mini-Cog | Abnormal Mini-Cog | | Normal Mini-Cog | Abnormal Mini-Cog | |
| **Disability (/14)** | 12.6 ± 2.2 | 11 ± 3.7 | <0.001* | 12.3 ± 2.6 | 11.1 ± 3.6 | 0.01* |
| **ADL (/7)** | 6.5 ± 1.1 | 5.8 ± 2 | 0.002* | 6.4 ± 1.3 | 6 ± 2 | 0.11 |
| **IADL (/7)** | 6.1 ± 1.3 | 5.2 ± 1.9 | <0.001* | 5.9 ± 1.5 | 5.1 ± 1.9 | 0.004* |

*Significant p-value <0.05

Abbreviations: ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living.

Table 3: Multivariable logistic regression for mortality and hospitalization at 3 months

| | OR | P-value | 95% Confidence Interval | |
|---|---|---|---|---|
| **Age** | 0.889 | 0.002* | 0.825 | 0.957 |
| **Female** | 1.282 | 0.588 | 0.523 | 3.143 |
| **MAGGIC score** | 1.199 | 0.000* | 1.096 | 1.313 |
| **SPPB score** | 0.842 | 0.012* | 0.736 | 0.963 |
| **Mini-Cog score** | 0.891 | 0.428 | 0.669 | 1.186 |

*Significant p-value <0.05

Abbreviations: OR, Odds Ratio; SPPB, Short Physical Performance Battery.

**REFERENCES**


1. Executive Summary: Heart Disease and Stroke Statistics—2013 Update. doi:10.1161/CIR.0b013e318282ab8f

2. Bergman H, Ferrucci L, Guralnik J, et al. Frailty: an emerging research and clinical paradigm--issues and controversies. *J Gerontol A Biol Sci Med Sci*. 2007;62(7):731-737. doi:10.1093/gerona/62.7.731

3. Harkness K, Demers C, Heckman GA, McKelvie RS. Screening for Cognitive Deficits Using the Montreal Cognitive Assessment Tool in Outpatients ≥65 Years of Age With Heart Failure. *Am J Cardiol*. 2011;107(8):1203-1207. doi:10.1016/j.amjcard.2010.12.021

4. Davis KK, Mintzer M, Himmelfarb CRD, Hayat MJ, Rotman S, Allen J. Targeted intervention improves knowledge but not self-care or readmissions in heart failure patients with mild cognitive impairment. *Eur J Heart Fail*. 2012;14(9):1041-1049. doi:https://doi.org/10.1093/eurjhf/hfs096

5. Vogels RLC, Scheltens P, Schroeder-Tanka JM, Weinstein HC. Cognitive impairment in heart failure: A systematic review of the literature. *Eur J Heart Fail*. 2007;9(5):440-449. doi:https://doi.org/10.1016/j.ejheart.2006.11.001

6. Leto L, Feola M. Cognitive impairment in heart failure patients. *J Geriatr Cardiol JGC*. 2014;11(4):316-328. doi:10.11909/j.issn.1671-5411.2014.04.007

7. Patel A, Parikh R, Howell E, Hsich E, Landers S, Gorodeski E. Mini-Cog Performance. *Circulation: Heart Failure*. 2015;8:8-16. https://doi.org/10.1161/CIRCHEARTFAILURE.114.001438

8. Guralnik JM, Simonsick EM, Ferrucci L, et al. A Short Physical Performance Battery Assessing Lower Extremity Function: Association With Self-Reported Disability and Prediction of Mortality and Nursing Home Admission. *J Gerontol*. 1994;49(2):M85-M94. doi:10.1093/geronj/49.2.M85

9. Pocock SJ, Ariti CA, McMurray JJV, et al. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. *Eur Heart J*. 2013;34(19):1404-1413. doi:10.1093/eurheartj/ehs337

10. Zuccalà G, Onder G, Pedone C, et al. Cognitive dysfunction as a major determinant of disability in patients with heart failure: results from a multicentre survey. On behalf of the GIFA (SIGG-ONLUS) Investigators. *J Neurol Neurosurg Psychiatry*. 2001;70(1):109-112. doi:10.1136/jnnp.70.1.109

11. Formiga F, Chivite D, Solé A, Manito N, Ramon JM, Pujol R. Functional outcomes of elderly patients after the first hospital admission for decompensated heart failure (HF). A prospective study. *Arch Gerontol Geriatr*. 2006;43(2):175-185. doi:10.1016/j.archger.2005.10.010

12. Hawkins MAW, Gathright EC, Gunstad J, et al. The MoCA and MMSE as Screeners for Cognitive Impairment in a Heart Failure Population: A Study with Comprehensive Neuropsychological Testing. *Heart Lung J Crit Care*. 2014;43(5):462-468. doi:10.1016/j.hrtlng.2014.05.011

13. Pressler SJ, Kim J, Riley P, Ronis DL, Gradus-Pizlo I. Memory dysfunction, psychomotor slowing, and decreased executive function predict mortality in patients with heart failure and low ejection fraction. *J Card Fail*. 2010;16(9):750-760. doi:10.1016/j.cardfail.2010.04.007

14. Borson S, Scanlan JM, Watanabe J, Tu S-P, Lessig M. Simplifying detection of cognitive impairment: comparison of the Mini-Cog and Mini-Mental State Examination in a multiethnic sample. *J Am Geriatr Soc*. 2005;53(5):871-874. doi:10.1111/j.1532-5415.2005.53269.x

15. Kelaiditi E, Cesari M, Canevelli M. Cognitive Frailty: Rational And Definition From An (I.A.N.A./I.A.G.G.) International Consensus Group. *J Nutr*. 2013;17(9):9.

16. Avila-Funes JA, Amieva H, Barberger-Gateau P, et al. Cognitive impairment improves the predictive validity of the phenotype of frailty for adverse health outcomes: the three-city study. *J Am Geriatr Soc*. 2009;57(3):453-461. doi:10.1111/j.1532-5415.2008.02136.x

17. Jha SR, Hannu MK, Gore K, et al. Cognitive impairment improves the predictive validity of physical frailty for mortality in patients with advanced heart failure referred for heart transplantation. *J Heart Lung Transplant Off Publ Int Soc Heart Transplant*. 2016;35(9):1092-1100. doi:10.1016/j.healun.2016.04.008

18. Zuccalà G, Pedone C, Cesari M, et al. The effects of cognitive impairment on mortality among hospitalized patients with heart failure. *Am J Med*. 2003;115(2):97-103. doi:10.1016/s0002-9343(03)00264-x

19. Dodson JA, Truong T-TN, Towle VR, Kerins G, Chaudhry SI. Cognitive impairment in older adults with heart failure: prevalence, documentation, and impact on outcomes. *Am J Med*. 2013;126(2):120-126. doi:10.1016/j.amjmed.2012.05.029

20. Nogueira Á, Álvarez G, Russo F, San-José B, Sánchez-Tomero JA, Barril G. Is SPPB useful as a method for screening functional capacity in patients with advanced chronic kidney disease? *Nefrol Engl Ed*. 2019;39(5):489-496. doi:10.1016/j.nefroe.2019.01.010

## APPENDICES

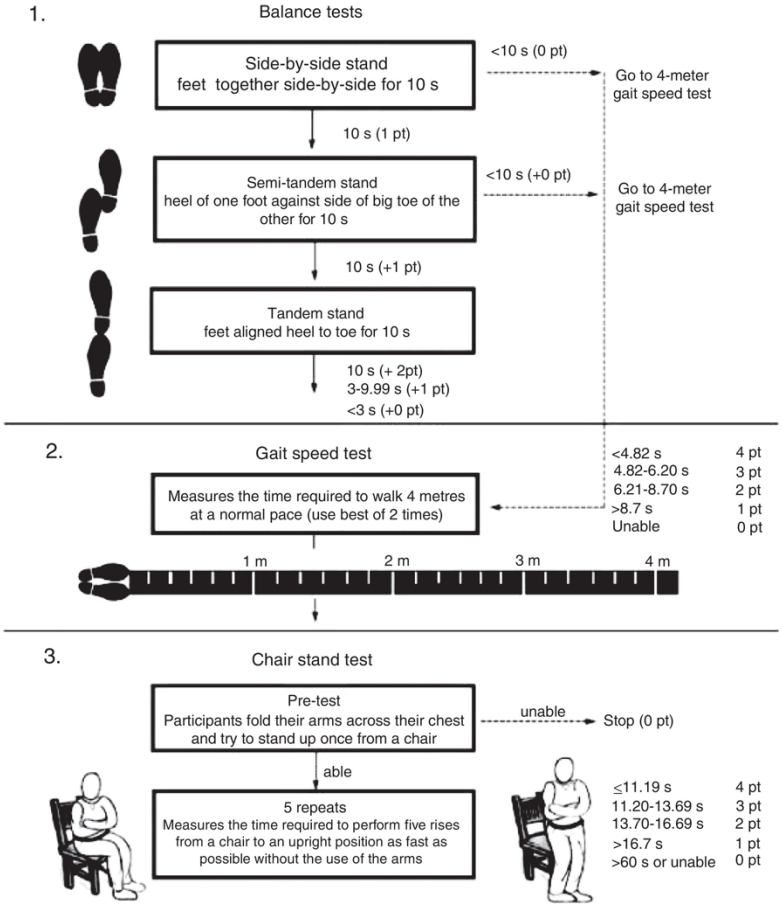
Appendix A: Mini-Cog Scoring[7]

| | |
|---|---|
| Word Recall: 0-3 points | 1 point for each word spontaneously recalled without cueing (3 words total). |
| Clock Draw: 0 or 2 points | Normal clock= 2 points. A normal clock has all numbers placed in the correct sequence and correct position with no missing or duplicate numbers. Hands are pointing to 11 and 2 (11:10). Hand length not scored. Inability or refusal to draw a clock (abnormal) = 0 points |
| Total Score: 0-5 points | Total score= word recall score + clock draw score.<br>A cut point of $\leq$3 on the Mini-Cog is indicative of abnormal cognition. |

Appendix B: Orientation Questions

| | |
|---|---|
| Orientation to day | "What day is it today?" |
| Orientation to month | "What month is it?" |
| Orientation to hospital | "Which hospital are we in?" |
| Orientation to floor | "What floor are we on?" |

## Appendix C: Short Physical Performance Battery[20]




## Appendix D: OARS Multidimensional Functional Assessment Questionnaire

| | | Without help | With some help | Completely unable |
|---|---|---|---|---|
| 10.1 | Can you use the telephone? (without help includes looking up a # and dialing) | 2 | 1 | 0 |
| 10.2 | Can you get to places out of walking distance? (drive car, take bus or taxi) | 2 | 1 | 0 |
| 10.3 | Can you go shopping for groceries or clothes? | 2 | 1 | 0 |
| 10.4 | Can you prepare your own meals? | 2 | 1 | 0 |
| 10.5 | Can you do your housework? | 2 | 1 | 0 |
| 10.6 | Can you take your own medicine? | 2 | 1 | 0 |
| 10.7 | Can you handle your own money? (write checks, pay bills) | 2 | 1 | 0 |
| 10.8 | Can you eat? | 2 | 1 | 0 |
| 10.9 | Can you dress and undress yourself? | 2 | 1 | 0 |
| 10.10 | Can you take care of your own appearance? (comb your hair, shave) | 2 | 1 | 0 |
| 10.11 | Can you walk? | 2 | 1 | 0 |
| 10.12 | Can you get in and out of bed? | 2 | 1 | 0 |
| 10.13 | Can you take a bath or shower? | 2 | 1 | 0 |
| 10.14 | Do you ever have trouble getting to the bathroom on time? | 2 | 1 | 0 |

# CHAPTER 4: THESIS CONCLUSION

Heart failure is a highly prevalent condition associated with significant deficits in associated geriatric domains. To strengthen the care of this highly vulnerable population, there is imminent need to better appreciate their condition beyond their disease symptoms. The literature presents major knowledge gaps in regard to intervening on the effects of major geriatric deficits such as frailty and cognitive impairment. These conditions are highly relevant due to their added risk of adverse health outcomes such as mortality, rehospitalization and worsening functionality.

The literature review on cognitive impairment outlined the current understanding of cognitive impairment in HF patients and explored the relationship between physical frailty and cognition. Although frailty assessments are used in cardiology practice, a cognitive aspect is rarely included in routine assessments. Furthermore, there is no validated tool to assess for cognitive impairment in HF. None of the screening instruments reviewed were designed specifically for HF patients. In fact, most of these screening instruments are not specific to the nature and pattern of the impairment seen in HF, or are not able to detect minor NCD. This study sought to fill this knowledge gap by assessing the prognostic value and feasibility of the Mini-Cog as a tool to screen for minor NCD in HF.

According to the findings from the manuscript, minor NCD is highly prevalent in older adults with HF. The results demonstrate that approximately one third of older adults with HF had cognitive dysfunction. Although minor NCD was not a significant risk factor for mortality or hospital readmission at 3 months, it was a significant risk factor for worsening disability. Furthermore, physical frailty proved to be an important predictor in terms of our secondary

outcomes. According to our results, the Mini-Cog proves to be a promising tool for identifying cognitive deficits in HF.

It is important to discuss the limitations associated with this study. The cohort for this analysis consisted of 222 patients overall, in which 179 participants were included analyses at 3 months. This relatively small sample size and short time range reduces the external validity of the study by decreasing generalizability of the results. However, this study shows a clear trend suggesting that minor NCD indicates worsening disability over 3 months and this may play an important role in HF prognosis. However, it is important to take into account that the FRAILTY-HF study is a multi-centre prospective cohort study that recruits HF patients at academic hospitals and community-based clinics. Despite lower sample size, the nature of the study increases its internal validity by reducing confounding.

Going forward, the endpoints need to be explored further at 1-year to assess long-term outcomes and to determine if cognitive impairment continues to change the rate of disability accumulations that were observed at 3 months, and to determine if cognition plays a significant role in mortality and hospital readmissions. Furthermore, the best method for cognitive screening in HF needs to be further clarified. To our knowledge, the Mini-Cog has rarely been used as a cognitive assessment tool in the HF population. The Mini-Cog is a promising predictor of adverse events, is feasible in a clinical setting and assesses the cognitive domains relevant to patients with HF. Future research should focus on validation and integration of the Mini-Cog into routine cardiology practice.

**References (Chapters 1 and 2)**


1. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the Concepts of Disability, Frailty, and Comorbidity: Implications for Improved Targeting and Care. *J Gerontol Ser A*. 2004;59(3):M255-M263. doi:10.1093/gerona/59.3.M255

2. Vogels RLC, Scheltens P, Schroeder-Tanka JM, Weinstein HC. Cognitive impairment in heart failure: A systematic review of the literature. *Eur J Heart Fail*. 2007;9(5):440-449. doi:https://doi.org/10.1016/j.ejheart.2006.11.001

3. Butts B, Gary R. Coexisting Frailty, Cognitive Impairment, and Heart Failure: Implications for Clinical Care. *J Clin Outcomes Manag JCOM*. 2015;22(1):38-46.

4. Kelaiditi E, Cesari M, Canevelli M. Cognitive Frailty: Rational And Definition From An (I.A.N.A./I.A.G.G.) International Consensus Group. *J Nutr*. 2013;17(9):9.

5. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38(36):2739-2791. doi:10.1093/eurheartj/ehx391

6. Heart Disease and Stroke Statistics—2021 Update | Circulation. Accessed June 16, 2021. https://www.ahajournals.org/doi/10.1161/CIR.0000000000000950

7. Classes of Heart Failure. www.heart.org. Accessed June 16, 2021. https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure

8. Shah KS, Xu H, Matsouaka RA, et al. Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction: 5-Year Outcomes. *J Am Coll Cardiol*. 2017;70(20):2476-2486. doi:10.1016/j.jacc.2017.08.074

9. Fried LP, Tangen CM, Walston J, et al. Frailty in Older Adults: Evidence for a Phenotype. *J Gerontol Ser A*. 2001;56(3):M146-M157. doi:10.1093/gerona/56.3.M146

10. Guralnik JM, Simonsick EM, Ferrucci L, et al. A Short Physical Performance Battery Assessing Lower Extremity Function: Association With Self-Reported Disability and Prediction of Mortality and Nursing Home Admission. *J Gerontol*. 1994;49(2):M85-M94. doi:10.1093/geronj/49.2.M85

11. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ*. 2005;173(5):489-495. doi:10.1503/cmaj.050051

12. Rockwood K, Stadnyk K, MacKnight C, McDowell I, Hébert R, Hogan DB. A brief clinical instrument to classify frailty in elderly people. *Lancet Lond Engl*. 1999;353(9148):205-206. doi:10.1016/S0140-6736(98)04402-X

13. Pandey A, Kitzman D, Reeves G. Frailty Is Intertwined With Heart Failure. *JACC Heart Fail*. 2019;7(12):1001-1011. doi:10.1016/j.jchf.2019.10.005

14. Hubbard RE, Woodhouse KW. Frailty, inflammation and the elderly. *Biogerontology*. 2010;11(5):635-641. doi:10.1007/s10522-010-9292-5

15. The heart on fire: inflammasome and cardiomyopathy - Abbate - 2013 - Experimental Physiology - Wiley Online Library. Accessed July 1, 2021. https://physoc.onlinelibrary.wiley.com/doi/full/10.1113/expphysiol.2012.069021

16. Afilalo J, Alexander KP, Mack MJ, et al. Frailty Assessment in the Cardiovascular Care of Older Adults. *J Am Coll Cardiol*. 2014;63(8):747-762. doi:10.1016/j.jacc.2013.09.070

17. Newman AB, Gottdiener JS, McBurnie MA, et al. Associations of Subclinical Cardiovascular Disease With Frailty. *J Gerontol Ser A*. 2001;56(3):M158-M166. doi:10.1093/gerona/56.3.M158

18. Ezekowitz JA, O'Meara E, McDonald MA, et al. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. *Can J Cardiol*. 2017;33(11):1342-1433. doi:10.1016/j.cjca.2017.08.022

19. Rich MW, Chyun DA, Skolnick AH et al. Knowledge Gaps in Cardiovascular Care of the Older Adult Population. *Circulation*. 2016;133(21):2103-2122. doi:10.1161/CIR.0000000000000380

20. Alosco ML, Spitznagel MB, Cohen R, et al. Cognitive Impairment is Independently Associated with Reduced Instrumental ADLs in Persons with Heart Failure. *J Cardiovasc Nurs*. 2012;27(1):44-50. doi:10.1097/JCN.0b013e318216a6cd

21. Feola M, Mauro F, Rosso GL, et al. Correlation between cognitive impairment and prognostic parameters in patients with congestive heart failure. *Arch Med Res*. 2007;38(2):234-239. doi:10.1016/j.arcmed.2006.10.004

22. Pullicino PM, Wadley VG, McClure LA, et al. Factors contributing to global cognitive impairment in heart failure: results from a population-based cohort. *J Card Fail*. 2008;14(4):290-295. doi:10.1016/j.cardfail.2008.01.003

23. Pressler SJ, Kim J, Riley P, Ronis DL, Gradus-Pizlo I. Memory dysfunction, psychomotor slowing, and decreased executive function predict mortality in patients with heart failure and low ejection fraction. *J Card Fail*. 2010;16(9):750-760. doi:10.1016/j.cardfail.2010.04.007

24. Mapelli D, Bardi L, Mojoli M, et al. Neuropsychological profile in a large group of heart transplant candidates. *PloS One*. 2011;6(12):e28313. doi:10.1371/journal.pone.0028313

25. Vogels RLC, Oosterman JM, van Harten B, et al. Profile of cognitive impairment in chronic heart failure. *J Am Geriatr Soc*. 2007;55(11):1764-1770. doi:10.1111/j.1532-5415.2007.01395.x

26. Callegari S, Majani G, Giardini A, et al. Relationship between cognitive impairment and clinical status in chronic heart failure patients. *Monaldi Arch Chest Dis Arch Monaldi Mal Torace*. 2002;58(1):19-25.

27. Sauvé 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):1-10. doi:10.1016/j.cardfail.2008.08.007

28. Baldasseroni S, Mossello E, Romboli B, et al. Relationship between cognitive function and 6-minute walking test in older outpatients with chronic heart failure. *Aging Clin Exp Res*. 2010;22(4):308-313. doi:10.1007/BF03324936

29. Almeida OP, Beer C, Lautenschlager NT, Arnolda L, Alfonso H, Flicker L. Two-year course of cognitive function and mood in adults with congestive heart failure and coronary artery disease: the Heart-Mind Study. *Int Psychogeriatr*. 2012;24(1):38-47. doi:10.1017/S1041610211001657

30. Jefferson AL, Himali JJ, Au R, et al. Relation of left ventricular ejection fraction to cognitive aging (from the Framingham Heart Study). *Am J Cardiol*. 2011;108(9):1346-1351. doi:10.1016/j.amjcard.2011.06.056

31. Jefferson AL. Cardiac output as a potential risk factor for abnormal brain aging. *J Alzheimers Dis JAD*. 2010;20(3):813-821. doi:10.3233/JAD-2010-100081

32. Festa JR, Jia X, Cheung K, et al. Association of low ejection fraction with impaired verbal memory in older patients with heart failure. *Arch Neurol*. 2011;68(8):1021-1026. doi:10.1001/archneurol.2011.163

33. Zuccalà G, Onder G, Pedone C, et al. Hypotension and cognitive impairment: Selective association in patients with heart failure. *Neurology*. 2001;57(11):1986-1992. doi:10.1212/wnl.57.11.1986

34. Kerola T, Nieminen T, Hartikainen S, Sulkava R, Vuolteenaho O, Kettunen R. B-type natriuretic peptide as a predictor of declining cognitive function and dementia--a cohort study of an elderly general population with a 5-year follow-up. *Ann Med*. 2010;42(3):207-215. doi:10.3109/07853891003652542

35. Alosco ML, Spitznagel MB, Gunstad J. Obesity as a risk factor for poor neurocognitive outcomes in older adults with heart failure. *Heart Fail Rev*. 2014;19(3):403-411. doi:10.1007/s10741-013-9399-2

36. Hawkins MAW, Gunstad J, Dolansky MA, et al. Greater body mass index is associated with poorer cognitive functioning in male heart failure patients. *J Card Fail*. 2014;20(3):199-206. doi:10.1016/j.cardfail.2013.12.014

37. Alosco ML, Spitznagel MB, Josephson R, Hughes J, Gunstad J. COPD is associated with cognitive dysfunction and poor physical fitness in heart failure. *Heart Lung J Crit Care*. 2015;44(1):21-26. doi:10.1016/j.hrtlng.2014.09.002

38. Pulignano G, Del Sindaco D, Di Lenarda A, et al. Chronic renal dysfunction and anaemia are associated with cognitive impairment in older patients with heart failure. *J Cardiovasc Med Hagerstown Md*. 2014;15(6):481-490. doi:10.2459/JCM.0000000000000005

39. Anter E, Jessup M, Callans DJ. Atrial fibrillation and heart failure: treatment considerations for a dual epidemic. *Circulation*. 2009;119(18):2516-2525. doi:10.1161/CIRCULATIONAHA.108.821306

40. Knecht S, Oelschläger C, Duning T, et al. Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. *Eur Heart J*. 2008;29(17):2125-2132. doi:10.1093/eurheartj/ehn341

41. Oh JE, Shin JW, Sohn E-H, et al. Effect of cardiac function on cognition and brain structural changes in dementia. *J Clin Neurol Seoul Korea*. 2012;8(2):123-129. doi:10.3988/jcn.2012.8.2.123

42. Chouliara Z, Kearney N, Stott D, Molassiotis A, Miller M. Perceptions of older people with cancer of information, decision making and treatment: a systematic review of selected literature. *Ann Oncol Off J Eur Soc Med Oncol*. 2004;15(11):1596-1602. doi:10.1093/annonc/mdh423

43. Paganini-Hill A, Clark LJ, Henderson VW, Birge SJ. Clock drawing: analysis in a retirement community. *J Am Geriatr Soc*. 2001;49(7):941-947. doi:10.1046/j.1532-5415.2001.49185.x

44. Panza F, D'Introno A, Colacicco AM, et al. Cognitive frailty: Predementia syndrome and vascular risk factors. *Neurobiol Aging*. 2006;27(7):933-940. doi:10.1016/j.neurobiolaging.2005.05.008

45. Pilotto A, Rengo F, Marchionni N, et al. Comparing the prognostic accuracy for all-cause mortality of frailty instruments: a multicentre 1-year follow-up in hospitalized older patients. *PloS One*. 2012;7(1):e29090. doi:10.1371/journal.pone.0029090

46. Gobbens RJJ, van Assen MALM, Luijkx KG, Wijnen-Sponselee MT, Schols JMGA. Determinants of frailty. *J Am Med Dir Assoc*. 2010;11(5):356-364. doi:10.1016/j.jamda.2009.11.008

47. Auyeung TW, Lee JSW, Kwok T, Woo J. Physical frailty predicts future cognitive decline - a four-year prospective study in 2737 cognitively normal older adults. *J Nutr Health Aging*. 2011;15(8):690-694. doi:10.1007/s12603-011-0110-9

48. Feng L, Zin Nyunt MS, Gao Q, Feng L, Yap KB, Ng T-P. Cognitive Frailty and Adverse Health Outcomes: Findings From the Singapore Longitudinal Ageing Studies (SLAS). *J Am Med Dir Assoc*. 2017;18(3):252-258. doi:10.1016/j.jamda.2016.09.015

49. Robertson DA, Savva GM, Kenny RA. Frailty and cognitive impairment--a review of the evidence and causal mechanisms. *Ageing Res Rev*. 2013;12(4):840-851. doi:10.1016/j.arr.2013.06.004

50. Arts MHL, Collard RM, Comijs HC, et al. Physical Frailty and Cognitive Functioning in Depressed Older Adults: Findings From the NESDO Study. *J Am Med Dir Assoc*. 2016;17(1):36-43. doi:10.1016/j.jamda.2015.07.016

51. Bonnefoy M, Berrut G, Lesourd B, et al. Frailty and nutrition: searching for evidence. *J Nutr Health Aging*. 2015;19(3):250-257. doi:10.1007/s12603-014-0568-3

52. Leng SX, Cappola AR, Andersen RE, et al. Serum levels of insulin-like growth factor-I (IGF-I) and dehydroepiandrosterone sulfate (DHEA-S), and their relationships with serum interleukin-6, in the geriatric syndrome of frailty. *Aging Clin Exp Res*. 2004;16(2):153-157. doi:10.1007/BF03324545

53. Chaves PHM, Semba RD, Leng SX, et al. Impact of anemia and cardiovascular disease on frailty status of community-dwelling older women: the Women's Health and Aging Studies I and II. *J Gerontol A Biol Sci Med Sci*. 2005;60(6):729-735. doi:10.1093/gerona/60.6.729

54. Woods NF, LaCroix AZ, Gray SL, et al. Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. *J Am Geriatr Soc*. 2005;53(8):1321-1330. doi:10.1111/j.1532-5415.2005.53405.x

55. Nourhashémi F, Andrieu S, Gillette-Guyonnet S, et al. Is there a relationship between fat-free soft tissue mass and low cognitive function? Results from a study of 7,105 women. *J Am Geriatr Soc*. 2002;50(11):1796-1801. doi:10.1046/j.1532-5415.2002.50507.x

56. de la Torre JC. The vascular hypothesis of Alzheimer's disease: bench to bedside and beyond. *Neurodegener Dis*. 2010;7(1-3):116-121. doi:10.1159/000285520

57. Riegel B, Bennett JA, Davis A, et al. Cognitive impairment in heart failure: issues of measurement and etiology. *Am J Crit Care Off Publ Am Assoc Crit-Care Nurses*. 2002;11(6):520-528.

58. Athilingam P, King KB, Burgin SW, Ackerman M, Cushman LA, Chen L. Montreal Cognitive Assessment and Mini-Mental Status Examination compared as cognitive screening tools in heart failure. *Heart Lung J Crit Care*. 2011;40(6):521-529. doi:10.1016/j.hrtlng.2010.11.002

59. Debette S, Bauters C, Leys D, Lamblin N, Pasquier F, de Groote P. Prevalence and determinants of cognitive impairment in chronic heart failure patients. *Congest Heart Fail Greenwich Conn*. 2007;13(4):205-208. doi:10.1111/j.1527-5299.2007.06612.x

60. McLennan SN, Pearson SA, Cameron J, Stewart S. Prognostic importance of cognitive impairment in chronic heart failure patients: does specialist management make a difference? *Eur J Heart Fail*. 2006;8(5):494-501. doi:10.1016/j.ejheart.2005.11.013

61. Cameron J, Worrall-Carter L, Riegel B, Lo SK, Stewart S. Testing a model of patient characteristics, psychologic status, and cognitive function as predictors of self-care in persons with chronic heart failure. *Heart Lung J Crit Care*. 2009;38(5):410-418. doi:10.1016/j.hrtlng.2008.11.004

62. Harkness K, Demers C, Heckman GA, McKelvie RS. Screening for cognitive deficits using the Montreal cognitive assessment tool in outpatients ≥65 years of age with heart failure. *Am J Cardiol*. 2011;107(8):1203-1207. doi:10.1016/j.amjcard.2010.12.021

63. Nishiwaki Y, Breeze E, Smeeth L, Bulpitt CJ, Peters R, Fletcher AE. Validity of the Clock-Drawing Test as a screening tool for cognitive impairment in the elderly. *Am J Epidemiol*. 2004;160(8):797-807. doi:10.1093/aje/kwh288

64. Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc*. 1975;23(10):433-441. doi:10.1111/j.1532-5415.1975.tb00927.x

65. Formiga F, Chivite D, Solé A, Manito N, Ramon JM, Pujol R. Functional outcomes of elderly patients after the first hospital admission for decompensated heart failure (HF). A prospective study. *Arch Gerontol Geriatr*. 2006;43(2):175-185. doi:10.1016/j.archger.2005.10.010

66. Altimir S, Lupón J, González B, et al. Sex and age differences in fragility in a heart failure population. *Eur J Heart Fail*. 2005;7(5):798-802. doi:10.1016/j.ejheart.2004.09.015

67. Pilotto A, Addante F, Franceschi M, et al. Multidimensional Prognostic Index Based on a Comprehensive Geriatric Assessment Predicts Short-Term Mortality in Older Patients With Heart Failure. *Circ Heart Fail*. 2010;3(1):14-20. doi:10.1161/CIRCHEARTFAILURE.109.865022

68. 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(3):189-198. doi:10.1016/0022-3956(75)90026-6

69. O'Connor DW, Pollitt PA, Hyde JB, et al. The reliability and validity of the Mini-Mental State in a British community survey. *J Psychiatr Res*. 1989;23(1):87-96. doi:10.1016/0022-3956(89)90021-6

70. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695-699. doi:10.1111/j.1532-5415.2005.53221.x

71. Juby A, Tench S, Baker V. The value of clock drawing in identifying executive cognitive dysfunction in people with a normal Mini-Mental State Examination score. *CMAJ Can Med Assoc J J Assoc Medicale Can*. 2002;167(8):859-864.

72. Woodford HJ, George J. Cognitive assessment in the elderly: a review of clinical methods. *QJM Mon J Assoc Physicians*. 2007;100(8):469-484. doi:10.1093/qjmed/hcm051

73. Roccaforte WH, Burke WJ, Bayer BL, Wengel SP. Reliability and validity of the Short Portable Mental Status Questionnaire administered by telephone. *J Geriatr Psychiatry Neurol*. 1994;7(1):33-38.

74. Hajduk AM, Lemon SC, McManus DD, et al. Cognitive impairment and self-care in heart failure. *Clin Epidemiol*. 2013;5:407-416. doi:10.2147/CLEP.S44560