Abstract

The Interrelationship of Hepatic Encephalopathy and Motor Functioning in Cirrhosis

Cirrhosis is a late stage of liver disease characterized by scarring of the liver. It is one of the leading causes of mortality worldwide, with cognitive impairment and physical frailty among the most debilitating symptoms. Cognitive dysfunction occurs due to hepatic encephalopathy, a neurotoxic complication of liver disease. These symptoms are often subtle and go undetected. Complications of hepatic encephalopathy and motor weakness are associated with increased hospitalizations and mortality in this population. The relationship between domains of cognitive functioning and motor performance has a strong base in the aging literature and several disease populations, however, this association has not been well demonstrated in cirrhosis. Thus, the current study examined the impact of cognitive functioning on motor performance in cirrhosis in order to target these modifiable risk factors and improve patient health. Disease severity was then analyzed as a moderator between cognitive and motor performance. Finally, we explored the impact of dual-task performance on gait speed and cognitive accuracy, and the moderating effects of disease severity and neuropsychological performance on this relationship. A sample of 38 participants were prospectively enrolled from an ambulatory transplant clinic and completed a battery of physical tasks (i.e., Short Physical Performance Battery (SPPB), Liver Frailty Index (LFI)), neuropsychological tests (i.e., Test of Premorbid Functioning, Golden Stroop, Controlled Oral Word Association Test, Animal fluency, Repeatable Battery for the Assessment of

Neurological Status Figure Copy and Recall, Hopkins Verbal Learning Test – Revised, and Psychometric Hepatic Encephalopathy Score), and a dual-task paradigm with three experimental conditions: Single Task Walking (STW), Single Task Counting backward by 3's (STC), and Dual Task Walking (DTW). Gait velocity was measured using a 40-foot walkway and cognitive accuracy was defined as the rate of numbers subtracted correctly per minute. Results indicated that attention/processing speed was associated with total SPPB performance, gait speed, and handgrip strength. Executive functioning was related to gait speed, handgrip strength and total LFI score. Visuospatial processing was associated with total LFI score. When the attentional system was taxed with the additional demands of DTW, gait speed was reduced. Cognitive accuracy was quantitatively lower but did not reach statistical significance. There was an interaction effect between dual-task performance and cognitive capacity, but not disease severity. In sum, results support the limited existing literature on the relationship between cognitive and motor functioning in cirrhosis. To our knowledge, this is the first study to examine dual task performance in this population. Understanding this relationship can lead to earlier detection of compromised cognitive and motor functioning, and introduction of novel interventions to prevent cirrhosis-related complications.

The Interrelationship of Hepatic Encephalopathy and Motor Functioning in Cirrhosis

By:

Shonna J. Schneider, M.A.

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The Committee for this doctoral dissertation consists of:

Roee Holtzer, Ph.D., Chairperson
Professor, Clinical Psychology (Health Emphasis) Program
Ferkauf School of Graduate Psychology, Yeshiva University
Professor, The Saul R. Korey Department of Neurology, Albert Einstein College of Medicine

David M. Masur, Ph.D.
Director, Division of Neuropsychology, The Saul R. Korey Department of Neurology. Montefiore Medical Center
Professor, Department of Neurology, Albert Einstein College of Medicine
Assistant Professor, Department of Psychiatry & Behavioral Sciences, Albert Einstein College of Medicine

Samuel H. Sigal, M.D.
Clinical Director, Hepatology, Moses Division, Montefiore Medical Center
Associate Professor, Department of Medicine (Hepatology), Albert Einstein College of Medicine

Frederick W. Foley, Ph.D. (Reader)
Professor, Clinical Psychology (Health Emphasis) Program
Ferkauf School of Graduate Psychology, Yeshiva University

Vance Zemon, Ph.D. (Reader)
Professor, Clinical Psychology (Health Emphasis) Program
Ferkauf School of Graduate Psychology, Yeshiva University

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Dedication

This work is dedicated to my family and friends, the most wonderful cheerleaders. To my husband, Jordan, thank you for standing by my side every step of the way with encouragement and love. There are no words to express my gratitude. Mom and Dad, I could not have made it this far without your guidance, words of wisdom, and belief in my success. A special thank you to my in-laws for their constant support and assistance. To my daughters, Tehilla and Baylie, this is dedicated to you with all my love.

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CHAPTER I

Introduction and Overview

The following background will provide an overview of cirrhosis and two of the main components that impact patient morbidity, hospitalization, and quality of life: cognitive functioning and physical functioning. Within cognitive functioning, a literature review of hepatic encephalopathy will be provided. Regarding physical functioning, an overview of frailty in cirrhosis will be discussed followed by aspects of physical functioning that are commonly measured in clinical and research settings as proxies for frailty. This includes balance, gait speed, chair stands, and handgrip strength. Robust evidence indicates the interdependence of physical functioning/motor performance and cognition in the aging population and many disease populations. Emerging literature suggests that parameters of physical functioning may be related to overall cognitive status in cirrhosis, however, the evidence for this is still lacking. As such, we draw from the literature on aging and other disease populations to provide context and rationale to the examination of cognitive and physical function in the current project. Finally, the impact of dual-tasking on gait speed and cognitive accuracy will be discussed.

Overview of Cirrhosis

Cirrhosis, a late stage of liver disease characterized by scarring of the liver, is associated with significantly reduced quality of life and substantial burden on the healthcare industry, with estimated costs of cirrhosis-related hospitalizations approaching 4 billion

dollars annually (Talwalkar, 2006). Trends in the US indicate that these costs will continue to rise as prevalence of patients seeking care for cirrhosis has risen by 59% from 2001 to 2013 (Beste et al., 2015). Cirrhosis is one of the leading causes of mortality worldwide; in 2010 it was the eighth-leading cause of death with over one million cirrhosis-related deaths (Kim et al., 2019). As this problem grows, emphasis on identifying and providing interventions for preventable aspects contributing to the rising burden of cirrhosis is warranted (Ezaz et al., 2018).

Cognition in Cirrhosis: Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a neurotoxic state linked to hyperammonemia and cirrhosis and has a significant and direct negative impact on the quality of life in patients with cirrhosis (Kanwal et al., 2009). The pathophysiology of HE is complex and thought to be related to ammonia accumulation in the brain and overall brain inflammation (Shawcross et al., 2007). Imaging studies indicate hyperintensities in the globus pallidus due to manganese deposition (leading to extrapyramidal symptoms), increased blood flow to the basal ganglia and decreased blood flow to the cortical brain regions (Butterworth, 2019). It is associated with reduced grey matter volume in the insula, thalamus, anterior striatum, basal ganglia, cerebellum (Zhu et al., 2022). Overt HE (OHE) occurs in approximately 30-45% of patients with cirrhosis and Covert Hepatic Encephalopathy (CHE) occurs in 20-60% of individuals with liver disease (Ferenci, 2002).

HE is characterized by grades I through IV. According to the World Congresses of Gastroenterology, using the West Haven Grading criteria (Ferenci, 2002):

- Grade I HE is defined as trivial lack of awareness, euphoria, or anxiety, shortened attention span and impaired performance of addition.
- Grade 2 is characterized by lethargy or apathy, minimal disorientation for time or place, subtle personality change, inappropriate behavior, and impaired performance of subtraction.
- Grade 3 ranges from somnolence to semi stupor, but preserved responsiveness to verbal stimuli, confusion, and gross disorientation.
- Grade 4 is characterized by coma.

Development of an initial episode of HE is associated with future episodes of HE and has been linked to more hospitalizations, falls, morbidity, and mortality (Bale et al., 2018). The most common treatments target inflammation and aim to reduce ammonia in the bloodstream (Bajaj et al., 2012; Bass et al., 2010; Tapper, Jiang, et al., 2015). Typically, HE is only recognized and treated when it is overt, at which point it may be too late to reduce all of its associated symptoms, without liver transplantation (Hadjihambi et al., 2018). It is imperative to detect and treat HE in its subclinical state to prevent progression.

Covert Hepatic Encephalopathy

CHE is known as the mildest form of HE. CHE is defined as the presence of abnormal neuropsychological testing in the absence of clinical symptoms and has been associated with increased morbidity, mortality, and impaired Quality of Life (QOL). The risk of developing overt HE occurs in over 50% of individuals with CHE (Amodio et al., 2008; Bale et al., 2018; Kircheis, 2002). Surprisingly, numerous studies have indicated an indirect

relationship between ammonia accumulation and prevalence and severity of CHE (Shawcross et al., 2007). CHE is known to impact multiple domains of cognitive functioning, including attention, executive functioning, visuospatial abilities, processing speed, memory, and fine motor speed (Bajaj et al., 2009). Use of the West Haven Scale alone to detect and diagnose CHE is insufficient as the criteria are vague and difficult to qualify. Symptoms of CHE often go undetected because presentation is mild, and patients often lack insight into their current state of functioning (Bajaj et al., 2008).

Neuropsychological assessment is an established method of detecting and measuring CHE. Batteries that measure multiple domains of cognitive functioning show greater reliability than tests of single domains and are more strongly associated with functional status. In fact, one study found that neuropsychological testing predicted future HE-related hospitalizations, even in cases when HE was not detected upon clinical examination or bloodwork (Montagnese et al., 2014). There is prognostic benefit to using neuropsychological assessment for detecting HE. That said, there are two batteries most commonly used: the Psychometric Hepatic Encephalopathy Score (PHES) and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Amodio et al., 2008; Randolph et al., 1998). A version of the RBANS has been designed to focus on neurocognitive changes seen in HE and has been shown to be useful in identifying patients with CHE. The RBANS is well-validated and normed in the U.S. and has been normed in the liver population, however, the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) commission indicated the RBANS has only moderate

specificity (38%) when it comes to detecting CHE (Randolph et al., 2009). The PHES is an efficient battery and is considered the "gold standard" in assessment of HE. While the PHES can be used for detection of CHE and is well-validated with high sensitivity and specificity (96%; 100%), it is limited to assessment of aspects of executive functioning, visuomotor abilities, and processing speed, all with a motor component. It does not include assessment of memory, language, or non-motor executive functioning tasks. Given that both batteries are lacking when it comes to assessing all cognitive domains associated with HE, the current study utilizes a battery composed of various neuropsychological measures that are sensitive and specific for detecting impairment.

Physical Functioning in Cirrhosis

Frailty

Frailty is a state of diminished physiological reserve associated with adverse clinical outcomes. This concept originated in the geriatric literature, has since been adapted to describe a state of decompensation in cirrhosis, and is distinct from frailty described in older adults. In patients with cirrhosis it has been shown to be related to increased risk of liver-related death (Lucero & Verna, 2015). The etiology of cirrhosis-related frailty is multifactorial, complex, and not completely understood. Disordered metabolism and inflammation affecting the liver, muscle, adipose, brain, and gut contribute to overall physical debilitation and worse outcomes (Murphy et al., 2020).

Major contributing factors to frailty are sarcopenia, hepatic encephalopathy, malnutrition, ascites, and hyponatremia, thus encompassing physical ability and functional

capacity (Williams et al., 2021; Lucero & Verna, 2015). Sarcopenia refers to a multifactorial process of loss of muscle mass that is commonly seen in the context of aging-related changes and is one of the most common complications of cirrhosis. It is a critical component of medical management in this population as sarcopenia is related to adverse outcomes. The current standard for assessing biomarkers of sarcopenia include measuring muscle mass and muscle strength. The current study utilizes muscle strength testing to represent physical functioning (Warner II & Satapathy, 2022). A number of measures have been validated for assessment of frailty in the liver disease population, the most common of which are the Liver Frailty Index, the Fried Frailty Index, the Short Physical Performance Battery, and the Clinical Frailty Scale (Fried et al., 2001; Lai et al., 2017; Rockwood & Theou, 2020; Treacy & Hassett, 2018). These measures are utilized as proxies for frailty to estimate transplant waitlist mortality.

The Short Physical Performance Battery (SPPB) and the Liver Frailty Index (LFI) are two measures that are well-validated in this population and are included in the current study. These measures include assessment of lower and upper extremity function, are commonly used as proxies of physical frailty, and are better predictors of transplant waitlist mortality than the commonly used Model for End Stage Liver Disease-Na (MELD) (Essam Behiry et al., 2019; Lai et al., 2017). There is significant evidence in the older adult population and other disease populations, as well as emerging evidence in liver disease of strong associations between frailty and cognitive functioning (Berry et al., 2022). Subcomponents of the aforementioned measures include balance testing, gait speed, chair stands, and handgrip

strength. These have each been independently linked to overall poor outcome and have been demonstrated to either co-occur or precede cognitive deficits in the aging population (Montero-Odasso et al., 2019).

Gait Speed

Gait speed is an indicator of functional status when assessing frailty in patients with cirrhosis, similarly to hand grip strength, 6-minute walk test, and chair stands (Dunn et al., 2016; Román et al., 2016). Originally utilized as a marker of phenotypic frailty in the aging population, decrease in gait speed has been evidenced as a powerful indicator of increased risk of cirrhosis-related hospitalization, with each 0.1m/s decrease in gait speed associated with a 22% increase in hospital length (Dunn et al., 2016). Further, slow gait speed while on transplant waitlist was demonstrated as a marker waitlist mortality and post-transplant respiratory complications and (Salim et al., 2020). Dunn and colleagues (2016) noted gait speed to be a stronger predictor of hospitalization than handgrip strength. Recent studies have focused on gait speed training to reduce frailty in individuals with cirrhosis to reduce waitlist mortality, as it is a modifiable risk factor (Duarte-Rojo et al., 2021; Román et al., 2016).

Balance

Deficits in balance are common in patients with cirrhosis and have been studied as a prognostic factor associated with increased frailty and increased mortality (Lai et al., 2017). From a neurological perspective, neurodegeneration has been described in brain regions responsible for balance including the basal ganglia and cerebellum (Kril & Butterworth, 1997; Zhu et al., 2022). Cerebellar dysfunction may contribute to impaired balance and

postural instability, leading to increased falls (Burkhard et al., 2003). While balance has been studied extensively as a component of frailty batteries in this population, there is a scarcity of literature on balance disorders independently. Schmid and colleagues (2008) demonstrated poor postural control in a sample with cirrhosis. There is, however, strong support in the aging and disease literature for balance as a measure of physical performance, which is applied as a basis for balance testing in the cirrhotic population.

Chair Stands

Rising from a chair or bed is a necessary functional activity and can approximate physical capacity. Chair stand assessment is often used as part of physical performance batteries in individuals with cirrhosis, including the SPPB and LFI, to estimate waitlist mortality (Essam Behiry et al., 2019; Lai et al., 2017). It is a known predictor of poor quality of life in this population. In an extensive post-transplant physical rehabilitation study, Mandel (2009) demonstrated the association between chair stands and health-related quality of life. Specifically, improved chair stand performance led to higher report of disease-specific health-related quality of life (Mandel, 2009). While chair stands are well supported as a prognostic factor in the aging population, the literature on the usefulness of chair-stand based lower extremity strength testing in cirrhosis.

Handgrip Strength

Handgrip strength is a strong representative of whole-body strength and is used as a predictor of mortality and disability in community dwelling samples, aging samples, and multiple disease populations, including cirrhosis (Hanai et al., 2019; Soysal et al., 2021). In

individuals with cirrhosis, it is an early indicator of sarcopenia, as it directly measures muscle strength and predicts mortality independently of age, disease etiology, development of hepatocellular carcinoma, serum sodium level, and Child-Pugh score (Hanai et al., 2017). Reduced handgrip strength is a useful measurement of physical decompensation as it can be detected relatively easily in a clinical setting with the use of a handgrip dynamometer.

Physical Functioning and Cognition

While commonly treated as distinct symptoms, mounting evidence supports shared brain mechanisms for cognitive functioning and mobility. This relationship has been demonstrated most robustly in aging studies and there is mounting evidence suggesting that this association exists in individuals with cirrhosis as well (Berry et al., 2022; San Martín-Valenzuela et al., 2020). Impairments in both are known to be associated with adverse outcomes. If treated within a joint conceptual framework, there is potential for novel treatments that can target both cognitive and motor impairments (i.e., cognitive intervention to improve physical functioning, physical intervention to improve cognitive functioning) (Montero-Odasso et al., 2019; Verghese et al., 2010).

Gait Speed and Cognition

Cognitive impairment is one of the leading risk factors for falls in the aging cohort and research suggests that higher order cognitive processes play a role in gait performance (Tinetti & Speechley, 1989). Gait speed has been widely studied in the aging population as an easily accessible, low-cost prognostic assessment. Slow gait speed has been extensively linked to cognitive processes in this population, specifically as a risk factor for development

of mild cognitive impairment (MCI) and conversion to dementia (Montero-Odasso et al., 2014). There have been many studies evidencing this relationship between gait speed and cognition in other disease and neurological populations such Multiple Sclerosis, stroke, and Parkinson's Disease (Bowen, 2001; D′Orio et al., 2012; Mortimer et al., 1982). Specifically, attention, executive functioning, verbal intelligence quotient (IQ) and episodic memory are functions associated with gait speed in older adults (Holtzer et al., 2006; Holtzer, Wang, Lipton, et al., 2012). Indeed, overt gait change (i.e., gait velocity, increased gait variability) may be associated with covert cognitive impairment in this cohort (Soysal et al., 2021). Imaging studies further support this relationship and show associations between slow gait speed and reduced grey matter volume in temporal cortical areas in individuals with MCI, as well as slow gait speed and reduced grey matter volume in frontal areas in healthy older adults (Cosentino et al., 2020).

Emerging research in this area demonstrates that this relationship exists in cirrhosis as well (San Martín-Valenzuela et al., 2020). It is prudent to expand the current understanding and clinical methods for detecting change in gait that may be indicative of underlying cognitive impairment. Clinical studies investigating implications of gait impairment due to cognitive impairment in cirrhosis, however, are lacking.

Balance and Cognition

While the literature on balance and cognition in cirrhosis is limited, a recent study suggests that a relationship exists between balance and verbal fluency and general verbal skills in individuals with CHE (San Martín-Valenzuela et al., 2020). Drawing on the aging

population due to insufficient data in the liver disease population, poor balance has been linked to increased risk for incident dementia. In a meta-analysis of cognitive and motor performance in older adults, Demnitz and colleagues (2017) concluded that balance was associated with cognition in some studies, but not others. Overall, there were far fewer studies that examined associations between balance and cognition compared to other measures of lower extremity functioning (Demnitz et al., 2017). This study will further examine the relationship between balance and cognition in cirrhosis.

Chair Stands and Cognition

There is limited evidence suggesting a relationship between chair stands and cognition in individuals with cirrhosis. This relationship has been demonstrated in the older adult population as well, however, associations between chair stands and cognitive functioning are weaker compared to other parameters of physical functioning (i.e., gait speed and handgrip strength) (Clouston et al., 2013; Demnitz et al., 2017). In a large, community-based sample, processing speed was most strongly related to chair stands compared to other domains of cognitive functioning (Demnitz et al., 2017). Contrastingly, a longitudinal study with a large sample size did not find longitudinal associations between chair stands and cognitive impairment or cognitive decline from baseline (Veronese et al., 2016). Since this area is not well studied in cirrhosis, is worthwhile to examine whether chair stands alone and as an index of composite physical assessments (i.e., SPPB, LFI) are associated with cognitive functioning in cirrhosis.

Handgrip Strength and Cognition

Reduced muscle mass has been linked to HE, however, there is limited research demonstrating the direct relationship of HE and handgrip strength. To our knowledge, there is one published study that demonstrated handgrip strength as a predictor of CHE and overt HE (Miwa et al., 2022). Looking at the aging literature, epidemiological studies show associations between low handgrip strength, general mobility, and impairments in cognition (i.e., executive functions and memory) (Soysal et al., 2021). In a meta-analysis and review, stronger handgrip strength at baseline was a protective factor for cognitive functioning, functional independence, general mobility, and mortality (Rijk et al., 2016). This study aims to further elucidate the relationship between handgrip strength as a representative of physical functioning and cognitive functioning in cirrhosis.

Dual Task Walking

Previously considered an automatic process, walking is a task that requires complex cognitive processes, including attention, executive functioning, self-reference, motor control, and caution (Wickens, 2002; Woollacott & Shumway-Cook, 2002; Yogev-Seligmann et al., 2008). During daily living, the necessity frequently arises to simultaneously engage in more than one task while walking. The capacity to perform a secondary task while walking is an important skill that allows individuals to carry out conversations and assess their environment, requiring constant reallocation or prioritization of attention toward a specific task. Dual tasking refers to the capacity to carry out more than one task at the same time. This has been demonstrated to reduce performance in that task and negatively impact gait

(Huang & Mercer, 2001). This phenomenon is known as dual-task cost. There are several theories that have been proposed to understand the cognitive networks that contribute to dual task cost (e.g., Attentional Resource Theory, Central Bottleneck Theory, 4-dimensional Multiple Response Model) (Navon & Gopher, 1979; Wickens, 2002; Woollacott & Shumway-Cook, 2002).

Dual Task Walk (DTW) paradigms, which have been studied extensively in the literature, are designed to experimentally manipulate attention demands in order to understand the effects of taxing the attention system on gait performance (Huang & Mercer, 2001). The decrease in gait performance and cognitive performance between the single-task condition and dual-task condition is considered a measure of dual-task cost as a result of two tasks competing for the same cognitive resources (Montero-Odasso et al., 2012). The current study utilizes a validated serial subtraction DTW paradigm that requires an individual to simultaneously pay equal attention to walking and a cognitive interference task (Holtzer et al., 2014).

Dual-task paradigms have been used to demonstrate the effect of increased demand of the attention system on motor performance in various disease populations including Parkinson's disease, Multiple Sclerosis, and Huntington's Disease (Delval et al., 2008; Hamilton et al., 2009; O'Shea et al., 2002). Poor performance on DTW tasks is a risk factor for falls, disability, frailty, and mortality in healthy older adults (Ayers et al., 2014; Verghese et al., 2012) and in individuals with MCI (Burton et al., 2009). A meta-analysis of the current aging literature indicated that motor dual task costs during the performance of serial

subtraction tasks and verbal fluency tasks showed a significant difference between healthy controls and people with mild cognitive impairment (MCI) (Bishnoi & Hernandez, 2020).

The impact of divided attention on gait performance has not yet been studied in individuals with cirrhosis. Deficits in dual task performance may indicate early HE-related cognitive or gait changes and could lead to earlier diagnosis and treatment. Understanding this relationship may help target impairment at early stages, preventing fall and HE-related hospitalizations.

Rationale and Hypotheses

Hepatic encephalopathy is a common occurrence in cirrhosis. Often, even in well-compensated cirrhosis, cognitive changes in HE remains undetected and can lead to increased morbidity and mortality (Bale et al., 2018; Gitlin et al., 1986). The literature discusses the nature and course of hepatic encephalopathy, though it has been poorly characterized and comprehensive batteries for assessing HE are lacking. Detailed below, the current study includes neuropsychological tests that encapsulate various cognitive domains known to be impacted by HE and are sensitive and specific for detecting cognitive impairment in this population.

Furthermore, the current literature demonstrates a strong connection between parameters of physical functioning and cognition. It is well established that walking is associated with high attentional and executive functioning demands, and impairment in these cognitive systems can impact various gait parameters (Yogev-Seligmann et al., 2008). Given the link reported in the literature between gait and cognition in other populations, it is

important to investigate if the same relationship will be demonstrated in patients with cirrhosis (Bowen, 2001; D'Orio et al., 2012; Hall et al., 2011; Hamilton et al., 2009; LaPointe et al., 2010; Verghese et al., 2008). Recent literature supports the link between parameters of physical frailty and cognitive impairment in cirrhosis, however the evidence is sparse. Understanding the nature of physical impairment in cirrhosis and how it is impacted by HE will contribute to early detection and intervention to prevent cognitive and physical decompensation in individuals with cirrhosis (Berry et al., 2022; San Martín-Valenzuela et al., 2020). This relationship is important because HE can be treated with medication, and potentially reversed is treated early. Additionally, there is emerging evidence that cognitive training can improve gait and dual-tasking capacity (Chavez-Tapia et al., 2013; Landrigan et al., 2020; Verghese et al., 2010). Preventing its progression is critical for patient health, QOL, preventing falls, and reducing morbidity and mortality (Butterworth, 2012; Gitlin et al., 1986; Kanwal et al., 2009; Yildirim, 2017). Due to the great deficiency in the literature, this study aims to expand the current understanding of physical performance including, gait, balance, chair stands, and handgrip strength, as they relate to cognitive impairment in cirrhosis.

Secondly, when attention demands are greater, gait velocity can be impacted. There is supporting evidence in the literature for the association of gait speed under both single task and dual-task conditions and falls in the aging population (Menant et al., 2014). This association is found in other disease populations with gait and cognitive symptoms. As such, it is suspected that this effect will be present in cirrhosis as well (Creaby & Cole, 2018).

Given the relationship between frailty, morbidity, and hepatic encephalopathy, it is likely that as disease severity increases, cognitive and gait difficulties will increase as well (Murphy et al., 2020). To date, this relationship has not yet been evaluated in the context of dual-task paradigms in this population. It is important to prevent factors contributing to increased morbidity and mortality; thus, the current study aimed to increase the current understanding of elements underlying cognitive impairment and mobility impairment in cirrhosis.

Aims

Aim 1: To examine the relationship between motor performance and cognitive performance in patients with cirrhosis.

Aim 1A: While meaningful association between cognitive and motor function have been established in aging and disease populations, their interrelation in cirrhosis has largely not been examined. The first hypothesis will examine associations between motor functioning and cognitive performance in patients with cirrhosis.

- Hypothesis 1A: Lower neuropsychological scores in domains known to be impacted by hepatic encephalopathy will be associated with worse motor functioning, as measured by the Short Physical Performance Battery (SPPB) and its subtests (Guralnik et al., 1994). The SPPB is a measure of lower extremity physical functioning and is comprised of three components: balance, gait speed, and chair stands. This aim will examine balance (scored with 0-4 points; based on a composite of three balance tasks), gait velocity under single task conditions, (scored 1-4 points, assessed by a 4-meter walk) and repeated chair stands under

timed conditions (scored 0-4 points), as well as the total SPPB score (0-12 points). Handgrip strength, a proxy for upper extremity physical functioning, will be associated with neuropsychological test scores. Additionally, the Liver Frailty Index (LFI) will be examined relative to neuropsychological test scores to determine whether the LFI or SPPB better represents physical frailty. Scores on neuropsychological tests will capture cognitive domains that were derived rationally. See methods and statistical analysis for details.

Aim 1B: To examine the potential moderating effects of disease severity on the relationship between cognitive performance and motor performance in cirrhosis.

- Hypothesis 1B: Given the connection demonstrated between hepatic encephalopathy and disease severity, and motor symptoms and disease severity, it is hypothesized that disease severity, using MELD scores and Child Pugh scores (described in 'Methods'), will be a significant moderator of the relationship between cognitive performance and motor performance in cirrhosis (Bale et al., 2018; Bustamante et al., 1999; Tapper, Finkelstein, et al., 2015). As such, it is expected that in individuals with greater disease severity, the relationship between cognitive functioning and motor functioning will be stronger, while in individuals with less disease severity, the relationship between cognitive and motor functioning will be weaker. Cognitive performance will be measured by scores on neuropsychological tests and motor performance will be

measured by the SPPB total score and its sub-scores. Disease severity will be measured using MELD scores and Child Pugh scores.

Aim 2: To characterize the effect of dual-tasking on gait speed and cognitive accuracy in cirrhosis as well as to examine its potential moderators.

Aim 2A: To examine the change in gait speed from single-task walking (STW) to dual-task walking (DTW) on a 40-foot walk, and the change in cognitive accuracy from single-task (Serial Subtraction) to dual-task on a serial 3's task.

- Hypothesis 2A: Gait speed will decline from STW to DTW and cognitive accuracy will decrease from Serial Subtraction to DTW due to increased attentional demands required when completing two tasks simultaneously.

Aim 2B: To examine the moderating effects of disease severity (measured using MELD scores) on change in gait velocity from STW to DTW and on change in cognitive accuracy from STC (single task count) to DTW.

- Hypothesis 2B: MELD scores will moderate the change in gait velocity from STW to DTW and in cognitive accuracy from STC to DTW. Specifically, worse disease severity will be associated with greater dual task costs (i.e., greater decline in performance from the two single task conditions to the DTW conditions).

Aim 2C: To examine the moderating effects of neuropsychological performance on change in gait velocity from STW to DTW.

- Hypothesis 2C: Cognitive capacity, determined by performance on neuropsychological tests, will moderate change in gait velocity from STW to DTW and in cognitive accuracy from STC to DTW. It is expected that lower cognitive capacity (as assessed by performance on neuropsychological tests) will be associated with greater dual task costs with regard to gait velocity and cognitive accuracy.

CHAPTER II

Methods

Overview and Study Design

The current study is a prospective cross-sectional design that examined ambulatory men and women with cirrhosis at Montefiore Medical Center in Bronx, New York. This study utilized data collected from the study entitled "Hepatic Encephalopathy and Motor Functioning in Cirrhosis: Motor Correlates of Cognitive Functioning," which has been approved by the Albert Einstein College of Medicine (AECOM) Institutional Review Board (IRB #: 2019-11039; PI: Samuel Sigal, M.D.). Enrollment for this study was open for 18 months.

Participants

Patients were prescreened for eligibility prior to the study visit to ensure they met inclusion criteria. Individuals who met inclusion criteria were asked to enroll in the study,

sign an informed consent, and underwent neuropsychological assessment and physical performance assessment using the measures detailed below. In total, we aimed to enroll 46 subjects. Due to the COVID-19 pandemic, there were challenges with enrollment, and 37 participants were enrolled consecutively from the ambulatory Hepatology Service at Montefiore Medical Center in the Bronx, NY. Both males and female participants were included. Enrollment criteria included an age range of 18 – 75 years. Subjects were enrolled without restrictions based on race or ethnic origin. This study did not include vulnerable subjects including prisoners or persons with decisional incapacity. Participants were seen for one study visit, lasting approximately one hour, after which they received compensation in the form of a $25 Visa gift card.

Inclusion Criteria

Subjects with cirrhosis based on radiologic, clinical, and laboratory evaluation as well as liver biopsy if available.

Exclusion Criteria

Subjects were not eligible for the study if they: (1) were unable to participate in handgrip test; (2) were unable to walk (3) were unable to provide informed consent; (4) had received neuropsychological assessment in the last six months (5) had experienced a major head trauma (6) had a diagnosis of cognitive impairment due to another cause or neurological disorder (7) had been diagnosed with Attention Deficit/Hyperactivity Disorder (8) had a diagnosis of a significant psychiatric disorder other than depression or anxiety (9) were

taking psychoactive medications at the time of enrollment (10) had received a liver transplant (11) had advanced kidney disease (12) did not speak English proficiently.

Procedures

This study design is a cross-sectional observational analysis. Patients were prescreened to determine eligibility for inclusion in this study. Information was collected about the patient's medical and psychoeducational history, including use of psychoactive medications, education level, and English proficiency. Upon enrollment, informed consent was thoroughly reviewed and signed. Once enrolled, a chart review was performed to assess liver function in each participant. This included review of their medical records for confirmation of cirrhosis as well as etiology. At enrollment, each patient's Model for End-Stage Liver Disease-Na (MELD) score was calculated based on baseline total bilirubin, creatinine, and international normalized ratio, and sodium levels (Kamath & Kim, 2007). The MELD score is used to predict mortality and disease progression and has become the standard for determining liver donation allocations. MELD scores range from 6 – 40. Higher scores are associated with greater mortality. Child Pugh scores were calculated as well. The Child-Pugh score is an additional representative of disease severity, measured based on degree of ascites, laboratory values (bilirubin, albumin, and prothrombin time), and degree of hepatic encephalopathy. Scores range from 5-15, and are then classified into Classes A, B, and C, ranging from well-compensated to decompensated disease state. Each participant's Liver Frailty Index (LFI) was collected as well, which is a composite measure consisting of chair stands, balance, and handgrip strength.

Physical Assessment

The SPPB (Guralnik et al., 1994) is a well-established test that assesses lower extremity functioning. It is commonly used in clinical trials the liver literature to mark physical performance (Kahn et al., 2018; Tapper, Finkelstein, et al., 2015). It measures gait speed (4-meter walk), balance (through three standing tasks), and lower extremity function and strength (repeated chair stands). Each test was scored on a scale of 0 to 4 points with a total score ranging from 0 to 12 points. It has high specificity and sensitivity for predicting mortality in cirrhosis (Essam Behiry et al., 2019). Gait velocity was determined by the time in which participants complete the 4-meter walk. The walk began prior to the marked 4-meter course and participants continued walking past the marked course to account for acceleration and deceleration. Participants were asked to complete three 10-second balance trials as part of the SPPB. The first trial involved standing with feet together, the second trial involved a semi-tandem stand, and the third trial involved a tandem stand. The three balance trials were scored with 1 point each for completing the feet together and semi-tandem stand and 2 points for completing the tandem stand. The third component of the SPPB is comprised of consecutive chair stands. Participants were instructed to stand from a chair without using their hands, 5 times in a row, as quickly as possible. This was scored from 0-4, depending on speed of completion. The total SPPB score (0-12) as well as SPPB subcomponent scores for balance and chair stands (each ranging from 0-4) were used for the analyses in Aim 1. Handgrip strength was measured, with three trials on each hand using the Jamar dynamometer. Handgrip strength (the average of three trials using the dominant hand), chair

stands, and balance (using the same criteria as the SPPB) were used to generate a composite score well known as the Liver Frailty Index (LFI) using the following calculation ((−0.330 × gender - adjusted grip strength) + (−2.529 × number of chair stands per seconds) + (−0.040 × balance time) + 6) (Lai et al., 2017).

Cognitive Assessment

A neuropsychological assessment battery comprised of well-established measures was used to assess cognitive functioning. The Test of Premorbid Functioning (TOPF) (Wechsler, 2011) was used to assess premorbid functioning. It is a reading list comprised of 50 irregularly spelled words and correlates highly with verbal IQ (Strauss et al., 2006). Verbal abilities generally remain resistant to cognitive decline, thus, assessment of reading abilities in this population provided an estimate of baseline cognitive function prior to disease impact (McGurn et al., 2004). Verbal memory and learning were examined using the Hopkins Verbal Learning Test- Revised (HVLT-R) (Benedict et al., 1998). It consists of a 10-item word list which is read to subjects on three consecutive trials and followed by a delayed trial after 25-30 minutes. This task involves a yes/no recognition trial as well. Other studies have indicated that it is sensitive to memory impairment in HE (Hassanein et al., 2008). To measure verbal phonemic fluency, the Controlled Oral Word Association Test (COWAT) (Benton et al., 1994) was used. This phonemic fluency task taps executive functioning. It requires the participant to provide as many words as they can generate in 60 seconds beginning with a specific letter. This is repeated for two other letters. As a task of

semantic fluency, Animal Naming was used to assess verbal executive abilities. This task requires participants to name as many animals as possible in 60 seconds. Animal Naming has a sensitivity of 89.19% and a specificity of 95.7% for detecting CHE (animals <14) (Taneja et al., 2018). Variations of the Stroop task are commonly used to determine HE (Amodio et al., 2008). The Golden Stroop (Golden, 1976) was used to assess attention, processing speed, inhibition, and set-shifting. To assess visuospatial abilities, planning, and nonverbal memory the Repeatable Battery for the Assessment of Neurological Status (RBANS) Figure Copy and Recall (Randolph et al., 1998) was used. This task involves copying a complex figure and recreating it after a delay.

The PHES, a well-validated assessment of CHE (see above), was administered to categorize the current sample based presence of CHE vs. no HE (Duarte-Rojo et al., 2011; Weissenborn et al., 2001). It consists of four pencil and paper tasks: (1) WAIS III Coding test examines processing speed. It requires visual scanning and discrimination to motorically transcribe a symbol-digit code. (2) Number Connection Tests A and B (NCT-A; NCT-B) is an assessment with two parts, the first of which requires sequential connection of numbers, and the second requires sequential switching between numbers and letters. It is commonly used to assess HE and has high specificity and sensitivity within the current population (Weissenborn et al., 1998). It was used to determine attention, processing speed and set-shifting. (3) Serial Dotting Test measures motor speed and requires participants to place dots

in circles across each row on the page. (4) Line Tracing Test measures visuomotor abilities and requires following a maze-like figure with a pen to determine accuracy.

Dual-Task Paradigm

To examine dual-task costs in gait and cognitive performance, a well-established walking while talking paradigm was used (Holtzer et al., 2012; Verghese et al., 2012). This paradigm includes three conditions: two single-task conditions and one dual-task condition. The first single-task condition is a single task walk (STW) during which participants walked a designated 40-foot course. They were instructed to walk at their normal pace. The second single-task condition is a cognitive interference task using serial subtraction, during which participants were instructed to count backwards from 100 by 3's aloud (i.e., 100, 97, 94…) while standing still. This trial lasted 20 seconds (approximate time to walk the 40-foot course). Responses were recorded by the examiner and a response accuracy ratio was calculated based on correct responses/minute to allow for direct comparison between Serial Subtraction and DTW. This method of quantifying cognitive performance has been used in other studies using this paradigm (Li et al., 2014) or the dual-task paradigm (DTW). Participants were instructed to complete STW and Serial Subtraction simultaneously. In other words, they were asked to walk at their usual pace on the 40-foot walkway while counting backwards from 100 by 3's. Participants were instructed to pay equal attention to both tasks in order to reduce task prioritization (Holtzer et al., 2014; Holtzer, Wang, & Verghese, 2012). The examiner recorded walking time and response accuracy. A response accuracy ratio was calculated. The order of Serial Subtraction and DTW tasks was counterbalanced to account

for practice effects. The first six participants' data was excluded from analyses because a different serial subtraction task was utilized.

Ethics

The current study was approved by the Study was approved by the Albert Einstein College of Medicine Institutional Review Board. All study personnel have received Collaborative Institutional Training Initiative (CITI) training. The study personnel on the study are supervised by licensed medical professionals and licensed psychologists. As detailed above, informed consent was collected during the study visit prior to data collection. During this process, participants were informed of potential benefits and risks, detailed below.

Risks and Benefits

The potential risks and benefits for the current study are outlined in the IRB-approved informed consent. It is believed that this study posed minimal risk to participants as it was non-invasive. The risks associated in taking part in each part of the study were minimal and were related to physical or cognitive fatigue and the confidentiality of information collected as part of patients' medical history and their own individual perceptions about their condition.

Participants may have felt fatigued during the study visit or uncomfortable when answering questions about health status, mood, or quality of life. The researchers mitigated any feelings of discomfort that participants potentially felt, and participants were aware that they could withdraw from the study freely, at any time. While the names of participants were

only collected as part of the informed consent process, other identifying information such as age, sex, ethnicity, and marital status were collected. Patients were assigned a unique subject number upon enrollment to ensure confidentiality. To reduce the risk of a breach of confidentiality, all information was stored in locked file cabinets and/or password protected digital files, only accessible to the study staff. All data will be shredded after being retained for the period of time required by federal and state laws.

Benefits from this study include receiving a $25 Visa gift card for participation and insight into physical and cognitive functioning of patients with cirrhosis. The results from this study will provide useful clinical information regarding the nature of cognitive and motor dysfunction in cirrhosis and potential implications for targeted treatment and intervention (e.g., physical therapy, cognitive rehabilitation) in order to improve patient well-being.

CHAPTER III

Statistical Analysis

IBM SPSS Statistics version 25 was used to perform the analyses. The distribution of the data was examined using descriptive and frequency statistics as well as measures of skewness and kurtosis. Bivariate and univariate variables were inspected using scatterplots. Continuous variables were summarized using means and standard deviations (SD) and categorical data was summarized using frequencies and percentages. Pearson correlations were used to examine the associations between continuous variables in conjunction with non-

parametric correlations (Spearman's rho) if any variables did not meet parameters of normality. All tests were two-tailed. A missing value analysis evaluated the pattern and extent of any missing data.

Covariates include demographic information (i.e., age, sex, and education), and a disease comorbidity summary score (Global Disease Score; GDS) was tallied to control for significant medical comorbidities. This was done using dichotomous scoring (presence or absence) of diabetes, chronic heart failure, arthritis, hypertension, depression, stroke, Parkinson's disease, chronic obstructive lung disease, angina, and myocardial infarction, and scored 1-10. This information was obtained from participants' medical records. Disease severity was analyzed as an additional covariate, using MELD scores or Child Pugh scores.

Aim 1A: To examine the impact of neuropsychological functioning on physical functioning, a composite z-score was calculated for each cognitive domain to determine sample-based normative data. Raw scores from each cognitive measure were z-transformed based on the sample distribution. Composite z-scores are used in the neuropsychology literature and can better represent each cognitive domain as a construct rather than individual neuropsychological tests (Bajaj et al., 2020; Ivnik, 1978; Mercuri & Holtzer, 2020; Proust-Lima et al., 2019). Additionally, composite scores can reduce the probability of Type I error (Proust-Lima et al., 2019).

Each individual neuropsychological test was z-transformed. Four composite cognitive domains were derived rationally. The Attention/Processing speed domain comprised of Golden Stroop Word Reading, Golden Stroop Color Naming, Number Connection Test-A,

WAIS-III Coding, and Serial Dotting Test. Executive Functioning domain was derived from Number Connection Test-B, Golden Stroop Color-Word, Golden Stroop Interference score, and COWAT FAS. The visuospatial domain was represented by RBANS Figure Copy. Finally, the memory domain included HVLT learning trials, HVLT delayed recall, HVLT recognition discriminability, and RBANS figure copy delayed recall.

Hierarchical linear regression analyses were used to examine the cognitive domains associated with physical functioning, including total score from the SPPB, and a score for each subcomponent, representing balance, gait velocity, and chair stands. Each factor was analyzed in a separate regression model with cognitive domain as the predictor and overall motor performance (SPPB total score), balance, gait velocity, and chair stands as the outcome measures. Demographic information and health burden (GDS) were entered in block 1. MELD scores, representing disease severity, were entered in block 2. Standardized beta coefficients were used to report variability in motor functioning due to neuropsychological factors.

Exploratory analyses were run to examine associations between cognitive performance and physical performance that includes upper body strength, as measured by the LFI. First, we looked at the LFI as a composite score. We then analyzed handgrip strength independently, as chair stands and gait speed, the other two contributors to the total LFI score, were previously analyzed in Aim 1A. The LFI composite score and handgrip strength were each analyzed in separate regression models as outcome variables, with cognitive domain as the predictor. Demographic information and GDS were entered in block 1. MELD

scores, representing disease severity, were entered in block 2. Standardized beta coefficients were used to report variability in motor functioning due to neuropsychological factors.

Aim 1B: The neuropsychological composite domains mentioned above were used for the analysis of Aim 1B. To determine the potential moderating effects of disease severity (using MELD scores) on the interrelationship between cognitive and motor performance, Hayes PROCESS macro for SPSS was utilized (Hayes, 2012). Specifically, the moderation was examined as the interaction of cognitive domain score x MELD score, with SPPB total score and its sub-scores as the outcome measures.

Aim 2A: To examine the effect of dual-tasking on gait performance and cognitive accuracy, two separate linear mixed effects models (LMEMs) were used. Task condition served as the two-level within-person repeated-measures fixed variable. Specifically, with gait speed as the outcome variable, the STW and DTW conditions served as the within person two-level repeated measures fixed variable. With cognitive accuracy as the outcome variable, the STC and DTW conditions served as the within person two-level repeated measures fixed variable. Cognitive accuracy was examined as a ratio of correct responses per minute.

Aim 2B: To examine the moderating effect of disease severity on the change in performance in gait velocity and counting accuracy from single to dual-task conditions, a linear mixed effects model was utilized. The moderating effects of disease severity on the change in gait velocity from STW to DTW and on counting accuracy from STC to DTW was tested using two-way interactions of disease severity x task condition in separate LMEMs.

Disease severity was examined using MELD scores and Child Pugh scores. Because of the small sample size, these variables were examined as continuous, categorical (based on clinical cut points), and dichotomous (based on cut points in the literature).

Aim 2C: To examine the moderating effect of cognitive performance on the change in performance in gait velocity and counting accuracy from single to dual-task conditions, a linear mixed effects model was utilized. The moderating effects of cognitive capacity on the change in gait velocity from STW to DTW and on counting accuracy from STC to DTW was tested using two-way interactions of composite cognitive score x task condition in separate LMEMs. Disease severity was examined using MELD scores and Child Pugh scores. Because of the small sample size, these variables were examined as continuous, categorical, and dichotomous, based on clinical cut points in the literature and distribution of this sample. MELD was categorized by 0-10, 11-18, 19-24, and $\geq$25 (Subramanian et al., 2010). MELD was dichotomized by 0-9, $\geq$10. Child Pugh was categorized by class, which represents risk of overall mortality at one year; Class A (5-6 points; 0% mortality), Class B (7-9 points;20% mortality), and Class C (10-15 points;55% mortality). Child Pugh was dichotomized by 0-9, $\geq$10.

Power Analysis

G*power version 3.1.93 software was used to conduct power analyses for correlation analyses. Due to the exploratory nature of this study and lack of previous research in this area, power of 0.8 was used and alpha was set at 0.5. The sample size for this study was

calculated based on the primary analysis, Aim 1. Power was set for a two-tailed correlation: bivariate normal model. To obtain a medium effect size (0.5), a sample size of 46 was required. For this study, we aimed to enroll 46 participants. Due to recruitment limitations, 37 participants were recruited, which limited the power of the analyses. This is discussed at further length in the discussion section.

CHAPTER IV

Results

Sample Characteristics and Descriptive Statistics

A total of 37 participants with a clinical diagnosis of cirrhosis were prospectively enrolled in the study (mean ± SD age = 59.83 ± 8.41 years; mean ± SD education = 13.38 ± 2.89 years; mean ± SD MELD = 11.42 ± 5.32; Male = 62.2%; mean ± SD Child Pugh = 9.71 ± 2.05; Male = 62.2%). Liver disease etiology in most participants was unrelated to alcohol use (ETOH = 24.3%). On average, participants had few comorbid disorders other than liver disease (mean ± SD Global Disease Score 2.05 ± 1.33). Of individuals who were able to complete the PHES, 21 did not have HE, and 13 had at least MHE. 45.9% of the sample reported falls in the past year. On average, individuals with HE had lower muscle mass (mean ± SD 105.99 ± 39.92) compared to those without HE (mean ± SD 123.73 ± 19.63).

Participants reported mild mood symptoms of anxiety and depression (mean ± SD Beck Anxiety Inventory 11.63 ± 13.82; mean ± SD Beck Depression Inventory II 14.23 ± 14.19).

Table 1

On average, participants had estimated premorbid functioning in the low average range (TOPF Standard Score mean ± SD 86.13 ± 12.39). When compared to the general population, on average, participants scored below the mean on all cognitive measures administered (see Table 2).

Table 2

Aim 1A:

Hierarchical linear regression analyses were used to examine associations between cognition and lower extremity physical functioning, using the total SPPB score as the outcome variable. Correlation analyses were run to determine covariate variables for the models in Aim 1. Sex, education, and GDS were associated with total SPPB score ($r = 0.431$, $p < 0.05$, $r = 0.332$, $p < 0.01$; $r = -0.546$, $p < 0.001$), while age and GDS were not. Regarding cognitive domains, age was correlated with attention ($r = 0.407$, $p < 0.05$), education was correlated with executive functioning ($r = -0.367$, $p < 0.05$), and sex was

correlated with memory ($r = 0.336$, $p < 0.05$). Thus, age, sex, education, and GDS were entered as covariates as indicated in the following analyses. See Table 3 for a summary of associations of individual cognitive tests and physical tests.

As seen in Table 4, the first regression was used to assess the association between the composite attention/processing speed and total SPPB scores. Higher attention/processing speed performance was associated with higher SPPB scores ($\beta = 0.454$, $p < 0.01$). The second block included covariates including age, sex, education, and GDS. The relationship between attention/processing speed was then weaker, but still statistically significant ($\beta = 0.354$, $p < 0.05$). When disease severity was entered as a covariate in the third block, the relationship between attention/processing speed and total SPPB score was no longer significant but trended toward significance ($\beta = 0.312$, $p = 0.056$). GDS was associated with total SPPB score ($\beta = -0.262$, $p < 0.01$).

Tables 3-4

The next model examined the association between executive functioning and total SPPB scores. Age, sex, education, GDS, and MELD scores were entered as covariates. Executive functioning was not associated with total SPPB scores, but trended toward significance ($\beta = 0.347$, *$p = 0.052$).* GDS was significantly associated with SPPB scores ($\beta = -0.451$, $p < .05$) (Table 5).

Table 5

We then examined the association between visuospatial functioning and total SPPB scores. Age, sex, education, GDS, and MELD scores were entered as covariates. Visuospatial abilities were not associated with SPPB scores ($\beta = 0.284$ $p = 0.115$). Additionally, sex ($\beta = 0.386$, $p < 0.05$), education **(**$\beta = 0.351$, $p < 0.05$), total health burden ($\beta = -0.481$, $p < 0.01$), and MELD scores ($\beta = -0.381$, $p < 0.05$) were associated with SPPB scores (Table 6).

Table 6

Memory was examined in relation to SPPB scores. Age, sex, education, GDS, and MELD scores were entered as covariates. The relationship between memory and SPPB scores was not significant ($\beta = 0.234$, $p = 0.163$). As seen in other analyses, education ($\beta = 0.305$, $p < 0.05$), total health burden ($\beta = -0.564$, $p < 0.001$), and MELD scores ($\beta = -0.370$, $p < 0.05$) were associated with SPPB scores and sex trended toward significance ($\beta = 0.278$, $p = 0.052$) (See Table 7).

Table 7

Sensitivity analyses where then conducted to understand the relationships between domains of cognitive functioning and independent subscales of the SPPB. Each cognitive domain was examined as an independent variable with balance, gait speed, and chair stands as outcome measures in independent models.

As seen in Table 8, attention/processing speed was not associated with balance (β = 0.252, p =0.151) or chair stands (β = 0.222, p = 0.206), but was associated with gait speed (β = 0.566, p <.001). Higher attention/processing speed performance was associated with higher gait speed scores. When age, sex, education, and GDS were added to the model, the relationship between attention/processing speed and gait speed remained significant (β = 0.484, p <.01). Similarly, the relationship remained significant when MELD scores were added (β = 0.466, p <.05).

Table 8

In the next analysis, executive functioning was associated with balance (β = 0.353, p <0.05). Higher executive functioning performance was associated with higher balance scores. When age, sex, education, GDS variables were added as covariates, the relationship between executive functioning and balance was not significant (β = 0.157, p = 0.427). When MELD

scores were added to the model the relationship was subsequently not significant (β = 0.153, *p* =0.440). The relationship between executive functioning and gait speed was significant (β = 0.490, *p* <0.01). Higher executive functioning scores were associated with higher gait speed scores. When age, sex, education, GDS variables were added as covariates, the relationship between executive functioning and gait speed remained significant (β = 0.433, *p* <0.05). MELD scores were then added as covariates and the relationship between executive functioning and gait speed continued to be significant (β = 0.428, *p* <0.05). Executive functioning was not associated with chair stand performance (β = 0.047, *p* = 0.800) (Table 9).

Table 9

Further analyses demonstrated that visuospatial abilities were not associated with balance, gait speed, or chair stands (β = 0.121, *p* = 0.510*;* β = 0.281, *p* = 0.120*;* β = 0.214, *p* = 0.239). (see Table 10).

Table 10

Memory was similarly not associated with balance, gait, or chair stands (β = 0.166, *p = 0.325;* β = 0.272, *p = 0.103;* β = 0.128, *p = 0.450)* (see Table 11).

Table 11

Exploratory analyses were run to examine associations between cognitive performance and frailty, as measured by the LFI. First, we looked at the LFI as a composite score. We then analyzed handgrip strength independently, as chair stands and gait speed, the other two contributors to the total LFI score, were previously analyzed.

Attention/processing speed was associated with LFI ($\beta = -0.505$, $p < 0.01$). Better attention/processing speed was significantly associated with lower LFI scores (indicating less frailty). When attention, sex, education, and GDS were entered as covariates, this relationship remained significant ($\beta = -0.508$, $p < 0.01$). When disease severity was entered as a covariate using MELD scores, the relationship between attention/processing speed and LFI scores remained significant ($\beta = -0.512$, $p < 0.01$) (see Table 12).

Table 12

Executive functioning was associated with LFI scores ($\beta = -0.529$, $p < 0.01$). Higher executive functioning scores were significantly associated with lower LFI scores. When attention, sex, education, and health comorbidities were entered as covariates, this relationship remained significant ($\beta = -0.487$, $p < 0.01$). When disease severity was entered as a covariate using MELD scores, the relationship between executive functioning and LFI

scores was somewhat weaker, although it remained significant ($\beta = -0.489$, $p < 0.05$) (see Table 13).

Table 13

Visuospatial processing was associated with LFI scores. Higher visuospatial processing scores were significantly associated with lower LFI scores ($\beta = -0.372$, $p < 0.05$). When age, sex, education, and GDS were entered into the model as covariates, this relationship remained significant ($\beta = -0.377$, $p < 0.05$). When MELD scores were entered into the model, the relationship between visuospatial processing and LFI trended toward significance but was no longer statistically significant ($\beta = -0.357$, $p = 0.050$). Female sex was associated with greater LFI scores ($\beta = -0.455$, $p < 0.05$) (see Table 14).

Table 14

Memory performance was not associated with LFI scores ($\beta = -0.307$, $p = 0.072$) (see Table 15).

Table 15

Sensitivity analyses were then conducted to better understand the relationship between handgrip strength and cognitive domain performance. Attention/processing speed was associated with handgrip strength ($\beta = 0.395$, $p < 0.05$). Higher attention/processing speed performance was associated with stronger handgrip strength. This relationship remained significant when age, sex, education, and GDS were entered as covariates ($\beta = 0.378$, $p < 0.05$), and when MELD scores were added as covariates ($\beta = 0.403$, $p < 0.05$) (See Table 16).

Table 16

Executive functioning was associated with handgrip strength ($\beta = 0.457$, $p < 0.05$). Specifically, better executive functioning performance was associated with stronger handgrip strength. When age, sex, education, and GDS were entered as covariates, this relationship remained significant ($\beta = 0.372$, $p < 0.05$). The relationship between executive functioning and handgrip strength was similarly significant when MELD scores were entered as a covariate ($\beta = 0.372$, $p < 0.05$) (See Table 17).

Table 17

Visuospatial processing was not associated with handgrip strength (β = 0.150, *p* =0.428) (see Table 18).

Table 18

Memory was significantly related to handgrip strength (β = 0.372, $p < 0.05$). Higher memory scores were associated with stronger handgrip strength. When covariates were entered into the model, memory was not significantly related to handgrip strength (β = 0.205, $p = 0.178$). Sex was related handgrip strength (β = 0.623, $p < 0.001$) (see Table 19).

Table 19

Aim 1B:

Moderation analyses using Hayes Process Macro (Hayes, 2022) were run to determine whether disease severity moderates the relationship between composite cognitive domains and frailty using the SPPB Total score. Disease severity was defined using MELD scores with clinical cutoff points (see Methods section). Disease severity did not moderate the relationship between attention/processing speed and SPPB scores (β= -0.044, $p = 0.950$) (see Table 20). Similarly, disease severity did not moderate the relationship between executive functioning and SPPB scores (β= -0.506, $p = 0.641$) (see Table 21), visuospatial

processing and SPPB scores (β= -0.303, p = 0.791) (see Table 22) or memory and SPPB scores (β= -0.023, p = 0.42) (see Table 23).

Tables 20-23

Moderation analyses were then computed to determine whether disease severity using MELD scores moderates the relationship between cognitive domains and subscales of the SPPB. There were not significant interaction effects between attention/processing speed and MELD scores when balance (β= -0.046, p = 0.856), gait (β= -0.430, p = 0.950) or chair stands were outcome variables (β= 0.432, p = 0.365) (see Table 24). There were no significant interactions between executive functioning and MELD scores with balance (β= -0.524, p = 0.144), gait (β= -0.426, p = 0.291), or chair stands at outcome variables (β= 0.444, p = 0.548) (see Table 25). No moderation effects were found between visuospatial processing and MELD scores when balance (β= -0.302, p = 0.427), gait (β= -0.328, p = 0.456), or chair stands (β= 0.327, p = 0.557) (see Table 26) were outcome variables. MELD scores did not moderate the relationship between memory and balance (β= -0.157, p = 0.672) or gait (β= -0.313, p = 0.395), but did significantly moderate the relationship between memory and chair stands (β= 0.432, p <0.05) (see Table 27).

Table 24-27

Aim 2A:

Linear mixed effects models were utilized with task as the two-level within person repeated measure to examine the difference in cognitive efficiency and gait speed between single-task and dual-task trials. See Tables 28-30 for summaries of task performances. Gait speed was faster during single task trial than during the dual task trial (estimates = -5.65, $p < 0.001$). While cognitive accuracy was descriptively better on the single task trial than on the dual task trial, this difference was not significant. Cognitive accuracy was analyzed as the rate of correct responses per minute (estimates = 1.885, $p = 0.151$) (see Table 28).

Tables 28 - 30

Aim 2B:

When examining the interaction between disease severity and walking speed, disease severity was looked at in several ways due to its non-normal distribution (see Methods sections). First, MELD score was examined as a continuous variable. Continuous MELD scores did not moderate the change in gait speed between STW and DTW (estimates = -0.120, $p = 0.659$). MELD scores were then examined as a dichotomous variable, with 10 as the cutoff point. The interaction effect was similarly not significant (estimates = -2.212, p =

0.449). Finally, MELD scores were examined as a categorical variable using clinical cut points, which did not indicate a significant interaction (estimates = -0.511, p = 0.804) (see Table 31).

Next, the interaction of disease severity and change in gait speed from STW to DTW was examined using Child Pugh scores to represent disease severity. Child Pugh scores were analyzed in several ways due to the abnormal distribution of the variable. It was first examined as a continuous variable, and the interaction effect was not significant (estimates = -1.030, p = 0.130). Child Pugh scores were then characterized by clinical cut points into categorical groups due to the small sample size. While the results were not statistically significant, the data trended toward a significant relationship (estimates = -5.309, p = 0.051) (Table 31).

Table 31

MELD scores and Child Pugh scores were examined as potential moderators of the change in cognitive accuracy from STC to DTW. Continuous MELD scores did not moderate the change in cognitive accuracy between STC and DTW (estimates = -0.012, p = 0.965). MELD scores were then examined as a dichotomous variable, with 10 as the cutoff point. The interaction effect was similarly not significant (estimates = -1.430, p = 0.598). Finally, MELD scores were examined as a categorical variable using clinical cut points, which did not indicate a significant interaction (estimates = 0.824, p = 0.682) (see Table 32).

Table 32

Next, the interaction of disease severity and change in cognitive accuracy from STC to DTW was examined using Child Pugh scores to represent disease severity. As in prior analyses, Child Pugh scores were analyzed in several ways due to the abnormal distribution of the variable. It was first examined as a continuous variable. No interaction effect was demonstrated (estimates = 0.422, $p = 0.531$). Child Pugh scores were then characterized by clinical cut points into categorical groups. This relationship was not significant (estimates = -0.561, $p = 0.837$) (Table 32).

Aim 2C:

Cognitive capacity, operationalized using a composite cognitive score of all domains assessed, was examined as a moderator of change in gait performance from STW to DTW. Cognitive capacity did not moderate the change in performance from STW to DTW (estimates = 2.559, $p = 0.297$). Cognitive capacity was then examined as a moderator of change in performance from STC to DTW. Overall cognitive capacity did moderate the change in cognitive accuracy from STC to DTW (estimates = -1.130, $p < 0.05$) (see Table 33).

Table 33

CHAPTER V

Discussion

Aspects of physical frailty, including gait speed and handgrip strength, have been linked to increased mortality rate in individuals with cirrhosis (Dunn et al., 2016). Hepatic encephalopathy (HE), a neurocognitive complication of cirrhosis, is independently linked to increased morbidity and mortality (Bustamante et al., 1999). The present study sought to elucidate the relationship between parameters of physical functioning and domains of cognitive functioning to promote earlier detection and intervention of these symptoms. Primary findings demonstrated positive associations between aspects of cognitive functioning and physical functioning. Consistent with the extant literature, attention/processing speed and executive functioning emerged as the areas of cognitive functioning most strongly associated with physical performance, specifically gait speed and handgrip strength. When the attention system was stressed with additional demands using a dual-task paradigm, walking speed was slower and cognitive accuracy decreased.

The relationships between individual domains of cognitive functioning and physical performance (i.e., lower and upper extremity performance), using the SPPB, the LFI, and their subcomponents were examined. The cognitive domains analyzed included attention/processing speed, executive functioning, visuospatial processing, and memory. Better attention/processing speed was associated with improved total SPPB performance, gait speed, and handgrip strength, even after adjustment for demographic covariates. While not associated with total SPPB score, executive functioning was related to gait speed, handgrip strength and LFI. Visuospatial functioning was not associated with individual subtests or SPPB total score but was associated with LFI total score. Results were not significant for associations between memory and parameters of physical functioning, however, analyses with handgrip strength approached significance. Our findings are consistent with the large body of literature on cognition and gait in healthy adults and disease populations evidencing attention, executive functioning and visuospatial processing as the primary cognitive domains associated with mobility and physical strength. Relatedly, most existing studies do not demonstrate a relationship between memory and physical functioning. More notably, our findings build on a recently published large, multi-center study that found strong associations between LFI and NCT-B scores in cirrhosis (Berry et al., 2022).

While HE and MELD scores do not have a linear relationship in the literature, both are well-established predictors of hospitalization and mortality (Butterworth, 2019; Kamath & Kim, 2007). Thus, we examined whether disease severity, measured by MELD scores, moderated the relationship between cognitive domains and physical performance. Findings

demonstrated MELD scores moderated only the relationship between memory performance and chair stands. It is not clear what factors underly this relationship. Perhaps greater interaction effects would have been detected with a larger sample size.

When participants were required to engage in dual-tasking, effects on gait speed were detected at a statistically significant level. Effects on cognitive accuracy were observed, but they did not reach significance. It is likely that the latter analyses were not significant due to the study being underpowered, and with a larger sample size, the effect of dual tasking on cognitive accuracy would reach statistical significance. The dual-tasking effect seen in our study aligns with the robust literature base in this area. The impact of dual-task performance has been demonstrated in other disease populations and in healthy samples, and our findings are the first to support this effect in individuals with cirrhosis.

MELD scores and Child Pugh scores were analyzed as potential moderators of dual task performance. MELD scores did not have significant interaction effects. Child Pugh scores trended toward significance as a moderator between STW and DTW when the variable was categorical, divided by clinical cut points. This finding suggests that overall cognitive capacity impacts the ability to engage in more than one task simultaneously. Cognitive performance was a significant moderator of the change in cognitive accuracy from STC to DTW.

Overall, the results demonstrate a relationship between cognitive and motor symptoms in cirrhosis, suggesting that there are shared neural pathways that impact functioning in these areas, as seen in other disease and healthy aging samples (Demnitz et al.,

2017). While the directionality of the relationship between attention/processing speed, executive functioning and physical symptoms is not clear from the current study, there is a proposed conceptual model of the cyclical relationship of neurotoxicity on both physical and cognitive reserve. The theory proposes a bidirectional relationship between hyperammonemia, neurotoxicity, and muscle depletion (Ney et al., 2018). This is further supported by brain imaging studies that implicate grey matter involvement of the anterior cingulate cortex, insula, and cerebellum in individuals with HE. Moreover, given the established literature on the link between cerebellar changes, motor functioning, and executive control, as well as findings demonstrating that the cerebellum is most susceptible to volume reduction in HE (compared to the cerebral cortex), our findings are well supported (Bellebaum & Daum, 2007; Zhu et al., 2022).

Strengths, Limitations and Future Directions

Strengths and Limitations

The present study offers novel contribution to the literature by expanding the current understanding of cognitive and motor functioning in cirrhosis. To our knowledge, this study was the first to measure cognitive functioning in HE using comprehensive neuropsychological assessment encompassing nearly all domains of cognitive functioning in conjunction with measures of physical functioning. Additionally, our study utilized multiple measures of physical functioning and disease severity.

There were limitations to the study. Primarily, the small sample size limited the power of our analyses. Recruitment was significantly hindered as data collection took place

during the height of the COVID-19 pandemic, and hospital policy did not allow for in-person enrollment for extended periods of time due to patient safety concerns. It is unclear whether the same findings would prove significant in larger studies with higher power, and whether trend-level findings (i.e., $p < 0.06$) would have been statistically significant. For instance, a larger sample size may have produced statistically significant relationships in analyses between attention/processing speed and executive functioning with total SPPB scores when controlling for disease severity, visuospatial processing and LFI when controlling for demographic variables, and Child Pugh scores as a moderator of dual task walking performance.

Further, the data collected in this study was derived from an ambulatory transplant clinic in a large New York City hospital and may not generalize to other settings. While some of the neuropsychological measures have been validated and normed in the cirrhosis population, some have not, which would be helpful for characterization of their sensitivity and specificity. To accommodate for the lack of normative data in this population, the neuropsychological test scores were z-transformed for standardization.

Several limitations pertain to study design, including lack of a control group, which would have allowed for direct comparison of cognitive and physical performance in this sample. Additionally, this study was cross-sectional, and did not measure potential fluctuations in cognitive capacity that can occur in this population.

Moreover, this study's analyses represented cognitive functioning using rationally derived cognitive domains, which utilized composite mean-centered scores of individual

neuropsychological tests. If a larger sample size were recruited, principal component analysis would have been utilized as part of the statistical analysis to reduce individual neuropsychological tests into representative factors. Because the study was underpowered, this analysis was not feasible. Thus, composite cognitive domains were derived based on rational deduction. This poses a limitation because one task may map on to more than one domain. For example, Number Connection Test-A measures processing speed, attention, psychomotor speed, and fine motor abilities, however in our analyses it was represented by the Attention/Processing Speed domain. Perhaps, if domains were created based on PCA, different results would have emerged. This theory warrants further investigation in future studies.

Future Directions

This study examined gait velocity; future research should consider researching additional gait parameters, such as cadence, stride length, posture, and examination of extrapyramidal symptoms to better understand the interaction of cerebellar manganese deposition on cognitive symptoms. Additionally, a longitudinal study would be beneficial to better understand the interplay of cognitive and motor functioning, as well as disease severity in a temporal manner. This would allow for a better understanding of directional relationships. To our knowledge, no such study exists.

Evidence in the literature suggests cognitive training can improve dual-tasking, postural control, and gait (Verghese et al., 2010). There is also indication that physical resistance training can improve executive functioning abilities (Landrigan et al., 2020).

Further research in this area is warranted to see if similar results can be achieved in this population. Additionally, there was demonstrated improvement in a gait syndrome with rifaximin treatment in a patient with cirrhosis (Sousa et al., 2019). Further study of the potential impact of HE-targeting medications (e.g., lactulose, rifaximin) on physical symptoms may help increase understanding of shared networks and improve patient quality of life.

While previous studies suggest that cognitive and physical symptoms do not differ based on liver disease etiology, the current study differentiated HE status based on ETOH liver disease versus non-ETOH, but did not differentiate between non-ETOH etiologies. Results may differ by liver disease etiology. Further, established diagnostic criteria for CHE are nonspecific from a neuropsychological standpoint, which makes CHE difficult to detect and diagnose in a clinical setting. There is a need for more specific diagnostic criteria and standardization of assessment methodology for CHE in the literature.

Clinical Implications

There is a heavy burden associated with implications of cognitive and motor impairments for patients, their families, and the health system. Therefore, it is necessary to enhance understanding of these mechanisms and promote early detection and intervention. This can prevent morbidity, mortality, improve patient quality of life, and reduce healthcare burden. Recommended interventions include the use of cognitive screening measures in outpatient liver clinics to detect subclinical impairment, and referral to neuropsychology and medication treatment, as appropriate. Cognitive rehabilitation is shown to be useful for

treatment of HE. Physical therapy for fall prevention and improvement of postural and gait disturbances, proper nutrition, regular exercise to promote or maintain muscle strength, and cognitive training to reduce attention or executive functioning related incidents. Cognitive training to improve gait may be a feasible intervention for this population (Verghese et al., 2010)

Patients would benefit from increased awareness of subtle physical (i.e., changes in gait and upper extremity strength) and cognitive symptoms that may be present in cirrhosis to prevent risks associated with impairments in these areas. Such risks include, but are not limited to falls, driving accidents, and poor judgement and decision-making (Bajaj et al., 2011; NeSmith et al., 2016).

Conclusion

In sum, the present study offers a unique examination of the interplay between cognitive and physical functioning in individuals with cirrhosis, both of which play crucial roles in overall health and wellbeing in this population. Overall, results indicated significant relationships between attention/processing speed, executive functioning, and physical functioning. Additionally, the impact of dual-task interference on gait speed was noted at the statistically significant level and trends toward significance of dual-task impact on cognitive accuracy were seen.

This study is novel as it comprehensively assesses the relationship between cognitive and physical functioning in cirrhosis by utilizing thorough neuropsychological assessment of various domains of cognition, as well as multiple measures of physical functioning, which, to

our knowledge, has not yet been done. It has meaningfully extended the understanding of important modifiable factors in this population, which has important implications for future research, clinical practice, and public health. By detecting cognitive and physical symptoms that are known to contribute to increased morbidity and mortality, targeted treatment can aim to reduce symptoms and prevent decline. Further research in these areas will be beneficial for gaining further understanding of the effectiveness of these potential interventions.

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TABLES

Table 1

Summary of Sample Characteristics (n = 37)

	Total Mean (SD) & N (%)	No HE Mean (SD) & N (%)	CHE Mean (SD) & N (%)
Participants	37	21*	13*
Sex (Male)	12 (37.8%)	15 (71.4%)	7 (53.8%)
Age	59.83 (8.41)	58.6 (8.9)	63.07 (6.57)
Education	23.38 (2.89)	13.95 (2.85)	12.38 (2.96)
Liver Disease Etiology (ETOH)	9 (24.3%)	6 (24.0%)	3 (25.0%)
MELD Score	11.42 (5.32)	12.04 (5.66)	10 (4.49)
Child Pugh Score	9.71 (2.05)	9.65 (2.25)	9.33 (1.37)
Body Mass Index	31.34 (6.38)	31.05 (4.92)	30.55 (7.75)
Muscle Mass (lbs.)	111.96 (35.55)	123.73 (19.63)	105.99 (39.92)
Bone Mass (lbs.)		6.53 (1.01)	6.15 (1.35)
Disease Comorbidity Score	2.05 (1.33)	1.47 (1.12)	2.69 (1.03)
Diabetes	17 (45.9%)	9 (42.9%)	6 (46.2%)
Chronic Heart Failure	2 (5.4%)	1 (4.8%)	0 (0%)
Arthritis	14 (37.8%)	6 (28.6%)	7 (53.8%)
Hypertension	19 (51.4%)	8 (38.1%)	9 (69.2%)
Depression	.35	4 (19.0%)	7 (53.8%)
Stroke	0 (0%)	0 (0%)	0 (0%)
Parkinson’s Disease	0 (0%)	0 (0%)	0 (0%)
COPD	4 (10.8%)	1 (4.8%)	1 (7.7%)
Angina	5 (13.5%)	1 (4.8%)	4 (30.8%)
Myocardial Infarction	1 (2.7%)	0 (0%)	1 (7.7%)
Falls in last year	17 (45.9%)	9 (42.9%)	6 46.2%)

Table 2

Summaries of Neuropsychological Test Scores

	Population-Based Normed Score Mean (SD)	Raw Score Mean (SD)
TOPF	SS = 86.13 (12.40)	27.38 (13.11)
Attention/Processing Speed		
Digit Symbol Test	Z = -2.61 (1.58)	45.44 (15.82)
Stroop Word	T = 38.44 (8.50)	27.89 (10.03)
Stroop Color	T = 35.81 (9.48)	52.25 (13.05)
Number Connection Test: Part A	Z = -5.96 (1.58)	55.96 (29.12)
Serial Dotting Test (sec)	Z = -2.32 (3.18)	72.91 (28.65)
Executive Functioning		
Stroop Color/Word	T = 40.05 (10.71)	27.92 (9.89)
Stroop Interference	Z = -2.64 (6.52)	6.59 (0.30)
Number Connection Test: Part B	Z = -3.81 (6.92)	169.48 (77.54)
COWAT FAS	Z = -0.82 (1.11)	31.21 (13.19)
Visuospatial/Visuomotor		
Line Tracing Test (seconds + errors)	Z = -0.23 (2.26)	37.783
RBANS Figure copy	ss = 5.03 (3.60)	14.05 (3.98)
Memory		
HVLT Learning Total (3 Trials)	Z = -2.64 (1.56)	18.58 (22.97)
HVLT Delay	Z = -0.74 (1.02)	6.61 (2.83)
HVLT Recognition Discrimination Index	Z = 1.10 (2.94)	8.79 (2.90)
RBANS Figure Recall	ss = 5.73 (3.38)	7.59 (4.32)
Animal Fluency	Z = -0.63 (1.23)	15.47 (5.19)

Note. TOPF = Test of Premorbid Functioning; COWAT = Controlled Oral Word Association Test; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; HVLT = Hopkins Verbal Learning Test.

Table 3

Associations Between Neuropsychological Test Scores and SPPB Scores

	SPPB Total	Balance	Gait Speed	Chair Stands
Attention/Processing Speed				
Digit Symbol Test	-0.23**	0.24	0.51**	0.28
Stroop Word	0.33*	0.14	0.44**	0.20
Stroop Color	0.30	0.13	0.40*	0.18
NCT-A	-0.24	-0.23	-0.57**	-0.41
Serial Dotting Test (sec)	-0.37	-0.11	-0.25	-0.36*
Executive Functioning				
Stroop Color/Word	0.05*	0.29	0.41*	0.11
Stroop Interference	0.16	0.34*	0.15	-0.04
NCT-B	-0.23	-0.002	-0.57**	0.002
COWAT FAS	0.29	0.20	0.28	0.21
Visuospatial/Visuomotor				
Line Tracing Test	-0.16	-0.18	0.06	-0.19
RBANS Figure copy	0.49**	0.37*	0.59**	0.23
Memory				
HVLT Learning Total (3 Trials)	-0.03	-0.07	0.55	-0.40
HVLT Delay	0.10	0.08	0.17	0.008
HVLT Recognition Discrimination Index	0.23	0.27	0.25	0.51
RBANS Figure Recall	0.24	0.21	0.33*	0.08
Animal Fluency	0.14	0.16	0.26	0.16

Note. Associations = Pearson correlations; TOPF = Test of Premorbid Functioning; COWAT = Controlled Oral Word Association Test; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; HVLT = Hopkins Verbal Learning Test; ** = $p < .01$; * = $p < .05$

Table 4

Effects of Attention/Processing Speed and SPPB Total Score

		β	SE	*p*	95% CI
Block 1	(Constant)		28.88	<0.01**	8.66, 9.98
	Attention/PS	0.45	2.88	<0.05*	0.36, 2.10
Block 2	(Constant)		3.02	<0.05*	2.37, 12.34
	Attention/PS	0.35	2.27	<0.05*	0.09, 1.83
	Age	0.08	0.50	0.62	-0.07, 0.11
	Sex	0.27	1.93	0.06	-0.07, 2.41
	Education	0.12	0.71	0.49	-0.15, 0.32
	GDS	-0.35	-2.43	<0.05*	-1.07, -0.10
Block 3	(Constant)		3.31	<0.01*	3.76, 16.03
	Attention/PS	0.31	2.00	<0.05*	-0.02, 1.71
	Age	-0.07	-0.39	0.70	-0.13, 0.10
	Sex	0.28	2.02	0.05	-0.02. 2.44
	Education	0.2	1.16	0.26	-0.11, 0.39
	GDS	-0.45	-2.84	<0.05*	-1.28, -0.21
	MELD	0.62	-1.41	0.17	-2.17, 0.40

Note. PS = processing speed; *b* = unstandardized regression coefficient; β = standardized regression coefficient; CI = confidence interval; GDS = Global Disease Score; MELD = Model for End-Stage Liver Disease; * *p* = <.05

Table 5

Effects of Executive Functioning and SPPB Total Score

		β	SE	*p*	95% CI
Block 1	(Constant)		0.35	<0.01**	8.58, 10.02
	EF	0.35	0.55	0.05	-0.01, 2.22
Block 2	(Constant)		2.32	<0.01**	2.69, 12.23
	EF	0.18	0.57	0.33	-0.61, 1.75
	Age	0.01	0.04	0.94	-0.09, 0.09
	Sex	0.32	0.68	0.05	-0.01, 2.79
	Education	0.2	0.14	0.29	-0.13, 0.42
	GDS	-0.36	0.26	<0.05*	-1.14, -0.05
Block 3	(Constant)		2.84	<0.01**	3.99, 15.68
	EF	0.17	0.56	0.33	-0.60, 1.72
	Age	-0.14	0.05	0.50	-0.14, 0.07
	Sex	0.33	0.67	<0.05*	0.05, 2.81
	Education	0.27	0.14	0.18	-0.09, 0.47
	GDS	-0.45	0.28	<0.05*	-1.31, -0.17
	MELD	-0.28	0.67	0.17	-2.33, 0.44

Note. EF = executive functioning; *b* = unstandardized regression coefficient; β = standardized regression coefficient; CI = confidence interval; GDS = Global Disease Score ; MELD = Model for End-Stage Liver Disease; ** *p* = <.01; * *p* = <.05

Table 6

Effects of Visuospatial Processing and SPPB Total Score

		β	SE	*p*	95% CI
Block 1	(Constant)		0.37	<0.01**	8.56, 10.07
	VP	0.28	0.57	0.11	-0.24, 2.10
Block 2	(Constant)		2.88	<0.01**	3.19, 15.04
	VP	0.24	0.51	0.14	-0.28, 1.84
	Age	-0.1	0.05	0.53	-0.13, 0.07
	Sex	0.38	0.66	<0.05	0.33, 3.06
	Education	0.23	0.12	0.17	-0.07, 0.40
	GDS	-0.34	0.27	<0.05*	-1.15, -0.05
Block 3	(Constant)		3.31	<0.01**	6.41, 20.05
	VP	0.18	0.49	0.23	-0.40, 1.61
	Age	-0.32	0.06	0.09	-0.21, 0.02
	Sex	0.39	0.62	<0.05*	0.42, 2.99
	Education	0.35	0.12	<0.05*	0.01, 0.49
	GDS	-0.48	0.28	<0.05*	-1.42, -0.48
	MELD	-0.38	0.61	<0.05*	-2.56, -0.06

Note. VP = visuospatial processing; β = standardized regression coefficient; CI = confidence interval; GDS = Global Disease Score; MELD = Model for End-Stage Liver Disease; ***p* = <.01;* *p* = <.05

Table 7
Effects of Memory and SPPB Total Score

		β	SE	*p*	95% CI
Block 1	(Constant)		0.39	<0.01**	8.33, 9.93
	Memory	0.23	0.51	0.16	-0.31, 1.77
Block 2	(Constant)		2.34	<0.01**	2.46, 12.00
	Memory	0.13	0.47	0.39	-0.55, 1.36
	Age	-0.03	0.05	0.84	-0.08, 0.10
	Sex	0.25	0.73	0.10	0.26, 2.71
	Education	0.21	0.13	0.17	-0.08, 0.43
	GDS	-0.47	0.26	<0.05*	-1.39, -0.33
Block 3	(Constant)		2.56	<0.01**	5.35, 15.79
	Memory	0.11	0.43	0.44	-0.55, 1.23
	Age	-0.16	0.05	0.35	-0.14, 0.05
	Sex	0.28	0.68	0.05	-0.01, 2.76
	Education	0.30	0.12	0.05	0.01, 0.50
	GDS	-0.56	0.25	<0.01**	-1.54, -0.52
	MELD	-0.37	0.60	<0.05*	-2.72, -0.26

Note. β = standardized regression coefficient; CI = confidence interval; GDS = Global Disease Score; MELD = Model for End-Stage Liver Disease; **p = <.01;* p = <.05

Table 8

Effects of Attention/Processing Speed and SPPB Subscales

		Balance				Gait Speed				Chair Stands			
		β	SE	*p*	*95% CI*	β	SE	*p*	*95% CI*	β	SE	*p*	*95% CI*
Block 1	(Constant)		0.12	<.001**	3.43, 3.90		0.12	<0.001**	3.07, 3.57		0.22	<.001**	1.88, 2.78
	Attention/PS	0.57	0.16	0.15	-0.09, 0.54	0.57	0.16	<0.001**	0.30, 0.95	0.22	0.29	0.21	-0.22, 0.97
Block 2	(Constant)		1.04	<0.01**	1.14, 5.22		1.04	<0.001**	1.275.55		1.78	0.67	-2.88, 4.42
	Attention/PS	0.48	0.18	0.55	-0.25, 0.46	0.48	0.18	<0.05*	0.16, 0.91	0.19	0.31	0.31	-0.32, 0.95
	Age	-0.03	0.02	0.75	-0.04, 0.03	-0.03	0.02	0.86	-0.04, 0.03	0.18	0.03	0.34	-0.03, 0.10
	Sex	0.11	0.26	0.21	-0.19, 0.83	0.11	0.26	0.47	-0.34, 0.72	0.25	0.44	0.14	-0.24, 1.58
	Education	0.09	0.05	0.24	-0.04, 0.15	0.09	0.05	0.59	-0.07, 0.13	0.00	0.08	0.98	-0.17, 0.17
	GDS	-0.26	0.1	0.58	-0.26, 0.15	-0.26	0.1	0.10	-0.38, 0.04	-0.34	0.17	0.05	-0.71, 0.01
Block 3	(Constant)		1.32	<.001**	1.13, 6.29		1.32	<0.05*	1.13, 6.56		2.21	0.30	-2.19, 6.87
	Attention/PS	0.47	0.19	0.65	-0.28, 0.45	0.47	0.19	<0.05*	0.13, 0.90	0.15	0.31	0.44	-0.4, 0.89
	Age	-0.09	0.02	0.51	-0.06, 0.03	-0.09	0.02	0.65	-0.06, 0.04	0.03	0.04	0.90	-0.07, 0.08
	Sex	0.11	0.26	0.21	-0.19, 0.84	0.11	0.26	0.47	-0.35, 0.74	0.26	0.44	0.13	-0.22, 1.60
	Education	0.13	0.05	0.19	-0.03, 0.17	0.13	0.05	0.69	-0.07, 0.15,	0.09	0.03	0.70	-0.15, 0.22
	GDS	-0.3	0.12	0.42	-0.32, 0.14	-0.30	0.12	-1.75	-0.4, 0.044	0.19	-0.45	<0.05*	-0.85, -0.06
	MELD	-0.11	0.28	-0.17	-0.72, 0.35	-0.11	0.28	-0.55	-0.72, 0.42	-0.26	0.46	0.25	-1.49, 0.40

Note. β = standardized regression coefficient; CI = confidence interval; GDS = Global Disease Score ; MELD = Model for End-Stage Liver Disease; ** *p* = <.01; * *p* = <.05

Table 9

Effects of Executive Functioning and SPPB Subscales

		Balance				Gait Speed				Chair Stands			
		β	SE	*p*	95% CI	β	SE	*p*	95% CI	β	SE	*p*	95% CI
Block 1	(Constant)		0.12	<.001**	3.39, 3.87		0.13	<0.001**	3.10, 3.63		0.24	<0.001**	1.82, 2.80
	EF	0.35	0.18	0.05	0.00, 0.76	0.49	0.20	<0.01**	0.21, 1.05	0.05	0.37	0.80	-0.67, 0.86
Block 2	(Constant)		0.85	<.001**	1.61, 5.09		0.98	<0.001**	2.19, 6.23		1.62	0.95	-3.42, 3.22
	EF	0.16	0.21	0.43	-0.26, 0.60	0.43	0.24	<0.05*	0.06, 1.06	-0.07	0.4	0.70	-0.97, 0.67
	Age	-0.15	0.02	0.44	-0.04, 0.02	-0.13	0.02	0.50	-0.05, 0.03	0.18	0.03	0.36	-0.03, 0.09
	Sex	0.27	0.25	0.13	-0.12, 0.90	0.03	0.29	0.85	-0.54, 0.65	0.34	0.48	0.06	-0.04, 1.92
	Education	0.30	0.05	0.16	-0.03, 0.17	0.04	0.06	0.84	-0.11, 0.13	0.13	0.09	0.52	-0.13, 0.25
	GDS	-0.18	0.10	0.32	-0.30, 0.10	-0.23	0.11	0.18	-0.38, 0.07	-0.33	0.18	0.07	-0.72, 0.04
Block 3	(Constant)		1.06	<.001**	1.70, 6.07		1.21	<.001**	2.56, 7.56		2.03	0.66	-3.28, 5.07
	EF	0.15	0.21	0.44	-0.27, 0.60	0.43	0.24	<0.05*	0.06, 1.05	-0.08	0.4	0.69	-0.99, 0.67
	Age	-0.25	0.02	0.28	-0.06, 0.02	-0.27	0.02	0.24	-0.07, 0.02	0.08	0.04	0.73	-0.06, 0.09
	Sex	0.28	0.25	0.12	-0.11, 0.92	0.04	0.29	0.81	-0.52, 0.66	0.35	0.48	0.06	-0.03, 1.94
	Education	0.34	0.05	0.12	-0.02, 0.19	0.1	0.06	0.64	-0.09, 0.15	0.18	0.1	0.42	-0.12, 0.28
	GDS	-0.24	0.10	0.22	-0.34, 0.08	-0.31	0.12	0.10	-0.45, 0.04	-0.38	0.2	0.05	-0.81, 0.01
	MELD	-0.19	0.25	0.41	-0.73, 0.31	-0.25	0.29	0.25	-0.93, 0.25	-0.18	0.48	0.42	-1.39, 0.60

Note.; β = standardized regression coefficient; CI = confidence interval; EF = Executive Functioning; GDS = Global Disease Score; MELD = Model for End-Stage Liver Disease; ** $p = <.01$; *$p = <.05$

Table 10

Effects of Visuospatial Processing and SPPB Subscales

		Balance				Gait Speed				Chair Stands			
		β	SE	*p*	95% CI	β	SE	*p*	95% CI	β	SE	*p*	95% CI
Block 1	(Constant)		0.12	<0.001**	3.43, 3.93		0.14	<.001**	3.06, 3.65		0.24	<.001	1.80, 2.77
	Attention/PS	0.12	0.19	0.51	-0.26, 0.52	0.28	0.22	0.12	-0.10, 0.81	0.21	0.37	0.24	-0.31, 1.20
Block 2	(Constant)		1.11	<0.01**	1.36, 5.94		1.19	<.001**	2.26, 7.15		2.13	0.72	-3.62, 5.14
	Attention/PS	0.08	0.20	0.67	-0.32, 0.49	0.14	0.21	0.40	-0.25, 0.62	0.25	0.38	0.19	-0.27, 1.29
	Age	-0.17	0.02	0.38	-0.06, 0.02	-0.36	0.02	<0.05*	-0.08, 0.00	0.15	0.04	0.43	-0.05, 0.10
	Sex	0.31	0.26	0.10	-0.08, 0.97	0.21	0.27	0.19	-0.19, 0.93	0.31	0.49	0.08	-0.13, 1.89
	Education	0.30	0.04	0.14	-0.02, 0, 0.16	0.38	0.05	<0.05*	0.01, 0.20	-0.02	0.09	0.90	-0.19, 0.16
	GDS	-0.13	0.10	0.46	-0.29, 0.13	-0.26	0.11	0.12	-0.40, 0.05	-0.31	0.20	0.09	-0.75, 0.06
Block 3	(Constant)		1.37	<0.01**	1.54, 7.18		1.40	<.001	3.25, 9.02		2.57	0.30	-2.56, 8.03
	Attention/PS	0.05	0.20	0.78	-0.36, 0.47	0.10	0.21	0.56	-0.30, 0.55	0.21	0.38	0.27	-0.36, 1.21
	Age	-0.28	0.02	0.23	-0.08, 0.02	-0.56	0.02	<0.05*	-0.11, -0.02	-0.01	0.04	0.95	-0.09, 0.09
	Sex	0.31	0.26	0.10	-0.09, 0.98	0.22	0.26	0.17	-0.17, 0.92	0.32	0.48	0.08	-0.11, 1.88
	Education	0.36	0.05	0.09	-0.01, 0.18	0.49	0.05	<0.05*	0.04, 0.24	0.07	0.09	0.73	-0.15, 0.22
	GDS	-0.21	0.11	0.30	-0.36, 0.18	-0.38	0.12	<0.05*	-0.51, -0.03	-0.41	0.21	0.04	-0.91, -0.02
	MELD	-0.20	0.25	0.38	-0.74, 0.11	-0.34	0.26	0.09	-0.99, 0.07	-0.29	0.47	0.20	-1.60, 0.35

Note. β = standardized regression coefficient; CI = confidence interval; GDS = Global Disease Score; MELD = Model for End-Stage Liver Disease; ** p = <.01* p = <.05

Table 11

Effects of Memory and SPPB Subscales

		Balance				Gait Speed				Chair Stands			
		β	SE	*p*	95% CI	β	SE	*p*	95% CI	β	SE	*p*	95% CI
Block 1	(Constant)		0.15	<.001**	3.30, 3.90		0.15	<.001**	3.01, 3.60		0.22	<.001**	1.77, 2.67
	Memory	0.17	0.19	0.32	-0.2, 0.58	0.27	0.19	0.10	-0.07, 0.70	0.13	0.29	0.45	-0.36, 0.80
Block 2	(Constant)		1.01	<0.01**	1.11, 5.22		0.97	<.001**	1.67, 5.62		1.48	0.78	-2.6, 3.44
	Memory	0.05	0.2	0.77	-0.35, 0.47	0.18	0.19	0.30	-0.19, 0.60	0.08	0.3	0.63	-0.46, 0.75
	Age	-0.05	0.02	0.78	-0.05, 0.03	-0.14	0.02	0.42	-0.05, 0.02	0.19	0.03	0.30	-0.03, 0.09
	Sex	0.22	0.31	0.21	-0.24, 1.04	0.1	0.3	0.56	-0.44, 0.79	0.24	0.46	0.17	-0.29, 1.59
	Education	0.23	0.05	0.20	-0.04, 0.18	0.25	0.05	0.15	-0.03, 0.18	0.06	0.08	0.73	-0.13, 0.19
	GDS	-0.32	0.11	0.07	-0.44, 0.01	-0.4	0.11	0.02	-0.49, -0.05	-0.37	0.16	<0.05*	-0.71, -0.04
Block 3	(Constant)		1.15	<.001**	1.90, 0.44		1.12	<.001**	2.26, 6.83		1.71	0.31	-1.71, 5.28
	Memory	0.03	0.2	0.85	-0.36, 0.44	0.16	0.19	0.33	-0.20, 0.58	0.07	0.29	0.69	-0.48, 0.71
	Age	-0.22	0.02	0.29	-0.07, 0.02	-0.28	0.02	0.16	-0.07, 0.01	0.05	0.03	0.81	-0.06, 0.07
	Sex	0.25	0.3	0.15	-0.17, 1.07	0.12	0.3	0.47	-0.39, 0.82	0.26	0.45	0.13	-0.22, 1.64
	Education	0.31	0.05	0.09	-0.01, 0.21	0.31	0.05	0.08	-0.01, 0.20	0.13	0.08	0.47	-0.11, 0.22
	GDS	-0.4	0.11	<0.05*	-0.50, -0.04	-0.47	0.11	<0.05*	-0.54, -0.09	-0.44	0.17	<0.05*	-0.78, 1.64
	MELD	-0.32	0.27	0.09	-1.03, 0.07	-0.27	0.26	0.14	-0.94, 0.14	-0.27	0.40	0.14	-1.44, 0.22

Note. β = standardized regression coefficient; CI = confidence interval; GDS = Global Disease Score; MELD = Model for End-Stage Liver Disease;
** *p* = <.01*; *p* = <.05

Table 12

Effects of Attention/Processing Speed and Liver Frailty Index

		β	SE	*p*	95% CI
Block 1	(Constant)		0.09	<0.001**	-0.11, 0.56
	Attention/PS	-0.51	0.12	<0.05*	-0.31, 0.71
Block 2	(Constant)		0.73	<0.001	-1.03, 3.10
	Attention/PS	-0.51	0.12	<0.05*	-0.05, 0.66
	Age	-0.14	0.01	0.44	-0.07, -0.01
	Sex	-0.32	0.19	0.06	0.96, 1.94
	Education	0.06	0.03	0.72	-0.04, 0.12
	GDS	0.15	0.07	0.36	-0.13, 0.25
Block 3	(Constant)		0.9	<.001**	-1.24, 3.93
	Attention/PS	-0.51	0.13	<0.05*	-0.07, 0.66
	Age	-0.16	0.02	0.47	-0.09, 0.00
	Sex	-0.31	0.2	0.07	0.95, 1.95
	Education	0.08	0.04	0.07	-0.04, 0.14
	GDS	0.14	0.08	0.44	-0.17, 0.26
	MELD	-0.04	0.19	0.86	-0.57, 0.37

Note. PS = processing speed; β = standardized regression coefficient; CI = confidence interval; GDS = Global Disease Score; MELD = Model for End-Stage Liver Disease;** p = <.01; * p = <.05;

Table 13

Effects of Executive Functioning and Liver Frailty Index

		β	SE	*p*	95% CI
Block 1	(Constant)		0.09	<0.001**	3.78, 4.16
	EF	-0.53	0.15	<0.01**	-0.78, -0.18
Block 2	(Constant)		0.62	<0.001**	3.09, 5.67
	EF	-0.49	0.16	<0.05*	-0.77, -0.12
	Age	-0.10	0.01	0.59	-0.03, 0.02
	Sex	-0.31	0.19	0.05	-0.79, 0.01
	Education	0.01	0.04	0.95	-0.07, 0.08
	GDS	0.22	0.07	0.18	-0.05, 0.25
Block 3	(Constant)		0.79	<0.001**	2.63, 5.90
	EF	-0.49	0.16	<0.05*	-0.78, -0.11
	Age	-0.07	0.01	0.76	-0.03, 0.02
	Sex	-0.32	0.20	0.06	-0.81, 0.01
	Education	0.00	0.04	1.00	-0.08, 0.08
	GDS	0.24	0.08	0.18	-0.05, 0.27
	MELD	0.05	0.19	0.80	-0.35, 0.45

Note. EF = executive functioning; β = standardized regression coefficient; CI = confidence interval; GDS = Global Disease Score; MELD = Model for End-Stage Liver Disease;* p = <.05; ** p = <.01

Table 14

Effects of Visuospatial Processing and Liver Frailty Index

		β	SE	*p*	95% CI
Block 1	(Constant)		0.10	<0.001**	3.71, 4.10
	VP	-0.37	0.14	<0.05*	-0.60, -0.01
Block 2	(Constant)		0.80	<0.001**	1.92, 5.23
	VP	-0.38	0.14	<0.05*	-0.60, -0.02
	Age	0.19	0.01	0.27	-0.01, 0.04
	Sex	-0.45	0.20	*0.05*	-0.94, -0.14
	Education	-0.14	0.03	0.43	-0.09, 0.04
	GDS	0.15	0.08	0.39	-0.09, 0.22
Block 3	(Constant)		0.96	<0.001*	1.15, 5.13
	VP	-0.36	0.14	0.05	-0.59, 0.00
	Age	0.29	0.02	0.17	-0.01, 0.06
	Sex	-0.47	0.20	<0.05*	-0.96, -0.15
	Education	-0.19	0.03	0.31	-0.11, 0.03
	GDS	0.2	0.08	0.28	-0.08, 0.26
	MELD	0.17	0.18	0.42	-0.22, 0.52

Note. VP = visuospatial processing; β = standardized regression coefficient; CI = confidence interval; GDS = Global Disease Score; MELD = Model for End-Stage Liver Disease; ** p = <.01; * p = <.05

Table 15

Effects of Memory and Liver Frailty Index

		β	SE	*p*	95% CI
Block 1	(Constant)		0.12	<.001**	3.79, 4.26
	Memory	-0.31	0.15	0.07	-0.59, 0.03
Block 2	(Constant)		0.76	<.001**	2.87, 5.98
	Memory	-0.23	0.15	0.17	-0.52, 0.09
	Age	-0.07	0.01	0.69	-0.04, 0.02
	Sex	-0.23	0.25	0.18	-0.84, 0.17
	Education	-0.08	0.04	0.65	-0.10, 0.06
	GDS	0.38	0.09	<0.05*	0.02, 0.38
Block 3	(Constant)		0.88	<0.001**	2.01, 5.60
	Memory	-0.22	0.15	0.18	-0.51, 0.10
	Age	0.06	0.02	0.76	-0.03, 0.04
	Sex	-0.26	0.25	0.13	-0.89, 0.12
	Education	-0.15	0.04	0.41	-0.12, 0.05
	GDS	0.43	0.09	<0.05*	0.04, 0.40
	MELD	0.25	0.21	0.19	-0.15, 0.72

Note. β = standardized regression coefficient; CI = confidence interval; GDS = Global Disease Score; MELD = Model for End-Stage Liver Disease;* $p = <.05$; ** $p = <.01$

Table 16

Effects of Attention/Processing Speed and Handgrip Strength

		β	SE	*p*	95% CI
Block 1	(Constant)		0.15	0.67	-0.25, 0.38
	Attention/PS	0.39	0.20	<0.05*	0.06, 0.89
Block 2	(Constant)		1.06	0.41	-3.06, 1.30
	Attention/PS	0.38	0.18	<0.05*	0.09, 0.83
	Age	-0.01	0.02	0.95	-0.04, 0.04
	Sex	0.65	0.27	<.001**	0.73, 1.84
	Education	-0.01	0.05	0.97	-0.10, 0.10
	GDS	0.10	0.10	0.49	-0.14, 0.28
Block 3	(Constant)		1.35	0.29	-4.25, 1.32
	Attention/PS	0.40	0.19	<0.05*	0.11, 0.87
	Age	0.07	0.02	0.71	-0.04, 0.06
	Sex	0.65	0.27	<.001*	0.72, 1.85
	Education	-0.05	0.05	0.77	-0.12, 0.09
	GDS	0.15	0.12	0.36	-0.13, 0.35
	MELD	0.13	0.28	0.48	-0.37, 0.77

Note. PS = processing speed; β = standardized regression coefficient; CI = confidence interval; GDS = Global Disease Score; MELD = Model for End-Stage Liver Disease; ** p = <.01;* p = <.05

Table 17

Effects of Executive Functioning and Handgrip Strength

		β	SE	*p*	95% CI
Block 1	(Constant)		0.16	0.77	-0.27, 0.36
	EF	0.46	0.24	<0.05*	0.18, 1.18
Block 2	(Constant)		0.89	0.66	-2.22, 1.43
	EF	0.37	0.22	<0.05*	0.10, 1.00
	Age	-0.08	0.02	0.59	-0.04, 0.02
	Sex	0.62	0.27	<.001**	0.69, 1.79
	Education	0.02	0.05	0.89	-0.10, 0.11
	GDS	0.03	0.10	0.83	-0.19, 0.23
Block 3	(Constant)		1.11	0.68	-2.76, 1.83
	EF	0.37	0.22	<0.05*	0.09, 1.01
	Age	-0.07	0.02	0.70	-0.05, 0.03
	Sex	0.62	0.27	<.001**	0.68, 1.80
	Education	0.02	0.05	0.91	-0.11, 0.12
	GDS	0.04	0.11	0.81	-0.20, 0.25
	MELD	0.02	0.27	0.92	-0.53, 0.58

Note. EF = executive functioning; β = standardized regression coefficient; CI = confidence interval; GDS = Global Disease Score; MELD = Model for End-Stage Liver Disease;** $p = <.01$; * $p = <.05$

Table 18

Effects of Visuospatial Processing and Handgrip Strength

		β	SE	*p*	95% CI
Block 1	(Constant)		0.16	0.19	-0.11, 0.56
	VP	0.15	0.25	0.43	-0.31, 0.71
Block 2	(Constant)		1.00	0.31	-1.03, 3.10
	VP	0.23	0.17	0.09	-0.05, 0.66
	Age	-0.33	0.02	<0.05*	-0.07, -0.01
	Sex	0.76	0.24	<0.001**	0.96, 1.94
	Education	0.15	0.04	0.27	-0.04, 0.12
	GDS	0.09	0.09	0.51	-0.13, 0.25
Block 3	(Constant)		1.25	0.29	-1.24, 3.93
	VP	0.22	0.18	0.11	-0.07, 0.66
	Age	-0.37	0.02	<0.05*	-0.09, 0.00
	Sex	0.76	0.24	<0.001**	0.95, 1.95
	Education	0.17	0.04	0.25	-0.04, 1.14
	GDS	0.06	0.10	0.68	-0.17, 0.26
	MELD	-0.07	0.23	0.67	-0.57, 0.37

Note. VP = visuospatial processing; β = standardized regression coefficient; CI = confidence interval; GDS = Global Disease Score; MELD = Model for End-Stage Liver Disease; ** $p = <.01$; * $p = <.05$.

Table 19

Effects of Memory and Handgrip Strength

		β	SE	*p*	95% CI
Block 1	(Constant)		0.15	0.76	-0.26, 0.36
	Memory	0.34	0.20	0.05	0.00, 0.80
Block 2	(Constant)		0.90	0.60	-2.32, 1.36
	Memory	0.20	0.18	0.18	-0.12, 0.61
	Age	-0.08	0.02	0.63	-0.04, 0.03
	Sex	0.62	0.28	<0.001**	0.66, 1.80
	Education	0.07	0.05	0.65	-0.08, 0.13
	GDS	-0.05	0.10	0.72	-0.24, 0.17
Block 3	(Constant)		1.07	0.87	-2.37, 2.01
	Memory	0.21	0.18	0.17	-0.11, 0.62
	Age	-0.12	0.02	0.51	-0.05, 0.03
	Sex	0.62	0.28	<0.001**	0.65, 1.81
	Education	0.09	0.05	0.58	-0.08, 0.14
	GDS	-0.08	0.11	0.62	-0.27, 0.17
	MELD	-0.09	0.26	0.59	-0.67, 0.39

Note. β = standardized regression coefficient; CI = confidence interval; GDS = Global Disease Score ; MELD = Model for End-Stage Liver Disease; ** $p = <.01$* $p = <.05$;

Table 20

Results of Moderation Analyses with Disease Severity as a Moderator between Attention and SPPB Total

	B	SE	*p*	95%CI
Constant	9.28	0.45	<0.01*	8.37, 10.19
Attention/PS	1.25	0.63	0.06	-0.03, 2.53
MELD	0.09	0.58	0.88	-1.09, 1.27
Attention/PS x MELD	-0.04	0.69	0.95	-1.46, 1.37

Note. PS = processing speed; β = Standardized regression coefficient; CI = Confidence Interval; * = $p < .01$

Table 21

Results of Moderation Analyses with Disease Severity as a Moderator between Executive Functioning and SPPB Total

	B	SE	*p*	95% CI
Constant	9.33	0.49	<.001*	8.32, 10.34
EF	1.42	0.86	0.12	-0.33, 3.17
MELD	0.00	0.63	0.10	-1.30, 1.29
EF x MELD	-0.51	1.07	0.64	-2.70, 1.69

Note. EF = executive functioning; β = standardized regression coefficient; ; CI = confidence interval; * = p <.01

Table 22
Results of Moderation Analyses with Disease Severity as a Moderator between Visuospatial Processing and SPPB Total.

	B	SE *b*	*p*	95% CI
Constant	9.23	0.51	<.01**	<8.18, 10.28
Language	1.12	0.96	0.25	-0.85, 3.10
MELD	0.18	0.67	0.79	-1.19, 1.56
VP x MELD	-0.30	1.13	0.79	-2.62, 2.01

Note. VP = visuospatial processing; β = standardized regression coefficient; ; CI = confidence interval; * = p <.01

Table 23
Results of Moderation Analyses with Disease Severity as a Moderator Between Memory and SPPB Total.

	B	SE	*p*	95% CI
Constant	9.15	0.43	<0.01*	8.28, 10.01
VP	0.13	0.14	0.34	-0.15, 0.41
MELD	0.50	0.08	0.55	-0.12, 0.22
Memory x MELD	-0.02	0.03	0.42	-0.08, 0.03

Note. β = standardized regression coefficient; CI = confidence interval; * = $p < .01$

Table 24

Results of Moderation Analyses with Disease Severity as a Moderator Between Attention and Subscales of the SPPB

	Balance				Chair Stands				Gait Speed			
	B	SE	*p*	95% CI	*B*	SE	*p*	95% CI	*B*	SE	*p*	95% CI
Constant	3.64	0.16	<0.01*	3.32, 3.97	2.14	0.30	<0.01*	1.80, 3.03	3.22	0.16	<0.01	2.89, 3.55
Attention/PS	0.25	0.22	0.27	-0.21, 0.71	0.12	0.42	0.80	-0.76, 0.97	0.89	0.23	<0.01*	0.43, 1.35
MELD	0.05	0.21	0.83	-0.38, 0.47	-0.19	0.39	0.63	-0.99, 0.61	0.23	0.21	0.27	-0.19, 0.66
Attention/PS x MELD	-0.05	0.25	0.86	-0.55, 0.46	-0.43	0.47	0.36	-0.53, 1.39	-0.43	0.25	0.09	-0.94, 0.08

Note. PS = processing speed; *b* = Unstandardized regression coefficient; β = Standardized regression coefficient; CI = confidence interval; ** = $p < .01$; * = p <0.05

Table 25

Results of Moderation Analyses with Disease Severity as a Moderator Between Executive Functioning and Subscales of the SPPB

	Balance				Chair Stands				Gait Speed			
	B	SE	*p*	95% CI	*B*	SE *b*	*p*	95% CI	*B*	SE *b*	*p*	95% CI
Constant	3.59	0.16	<0.01**	3.26, 3.92	2.41	0.33	<0.01*	1.73, 3.09	3.33	-0.18	<0.01**	2.96, 3.70
EF	0.69	0.28	<0.05*	0.12, 1.26	-0.14	0.58	0.81	-1.33, 1.05	0.88	0.32	<0.01**	0.23, 1.52
MELD	0.13	0.20	0.54	-0.29, 0.55	-0.24	0.43	0.59	-1.11, 0.64	0.11	0.23	0.65	-0.37, 0.58
EF x MELD	-0.52	0.35	0.14	-1.24, 0.19	0.44	0.73	0.55	-1.05, 1.94	-0.43	-1.08	0.29	-1.24, 0.39

Note. EF = executive functioning; *b* = unstandardized regression coefficient; β = standardized regression coefficient; CI = confidence interval; ** = $p < 0.01$; * = $p < 0.05$

Table 26

Results of Moderation Analyses with Disease Severity as a Moderator Between Visuospatial Processing and Subscales of the SPPB

	Balance				Chair Stands				Gait Speed			
	B	SE *b*	*p*	95% CI	*B*	SE *b*	*p*	95% CI	*B*	SE *b*	*p*	95% CI
Constant	3.60	0.17	<0.01*	3.26, 3.95	2.40	0.33	<0.01*	1.72, 3.07	3.23	0.20	<0.01*	2.82, 3.63
VP	0.32	0.32	0.32	-0.33, 0.98	0.24	0.62	0.70	01.03, 1.51	0.56	0.37	0.14	-0.20, 1.32
MELD	0.16	0.22	0.47	-0.29, 0.62	-0.23	0.43	0.60	-1.11, 0.65	0.25	0.26	0.34	-0.27, 0.78
VP x MELD	-0.30	0.37	0.43	-1.07, 0.47	0.33	0.73	0.66	-1.16, 1.81	-0.33	0.43	-0.46	-1.22, 0.56

Note. VP = visuospatial processing; *b* = instandardized regression coefficient; β = standardized regression coefficient; CI = confidence interval; ** = $p < 0.01$; * = p <0.05

Table 27

Results of Moderation Analyses with Disease Severity as a Moderator Between Memory and Subscales of the SPPB

	Balance				Chair Stands				Gait Speed			
	B	SE *b*	*p*	95% CI	*B*	SE *b*	*p*	95% CI	*B*	SE *b*	*p*	95% CI
Constant	3.65	0.21	<0.01*	3.22, 4.09	2.30	0.30	<0.01*	1.68, 2.91	3.28	0.21	<0.01*	2.85, 3.71
Memory	0.26	0.28	0.36	-0.31, 0.84	-0.50	0.40	0.22	-1.32, 0.31	0.43	0.28	0.14	-0.14, 0.99
MELD	-0.07	0.26	0.79	-0.61, 0.45	-0.33	0.37	0.38	-1.20, 0.43	0.09	0.26	0.72	-0.44, 0.63
Memory x MELD	-0.16	0.37	0.67	-0.90, 0.59	1.07	0.52	<0.05*	0.01, 2.13	-0.31	0.36	0.40	-1.05, 0.43

Note. b = unstandardized regression coefficient; β = standardized regression coefficient; CI = confidence interval; ** = $p < 0.01$; * = $p < 0.05$

Table 28

Summary of Gait Speed Under Single and Dual-Task Conditions

	M (SD)
STW	13.17 (3.90)
DTW	18.78 (9.94)

Note. Gait speed reported in seconds; STW = single task walking; DTW = dual task walking

Table 29

Summary of Cognitive Performance Under Single and Dual-Task Conditions

	STC M (SD)	DTW M (SD)
Total Responses	9.87 (5.62)	8.25 (2.87)
Total Correct Responses	8.03 (5.07)	5.65 (3.10)
Correct Per Minute	24.42 (15.28)	22.53 (15.17)
Percent Correct	86.75 (23.33)	82.97 (23.06)

Note. DTW = dual task walking; STC = single task counting.

Table 30

Linear Mixed Effects Model for Changes in Gait Speed and Cognitive Accuracy from STW/STC to DTW

	Estimate	SE	*p*	95%CI
STW x DTW	-5.65	1.29	<0.001**	-8.26, -3.03
STC x DTW	1.89	1.28	0.151	-0.72, 4.49

Note. STW = single task walking; DTW = dual task walking; STC = single task counting. ** $p = <.01$

Table 31

Linear Mixed Effects Model for Disease Severity as a Moderator between STW and DTW

	Estimate	SE	*p*	95%CI
MELD Continuous	-0.12	3.27	0.66	-0.67, 0.43
MELD Dichotomous	-2.21	2.89	0.45	-8.08, 3.65
MELD Categorical	-0.51	2.04	0.80	-4.68, 3.65
CP Continuous	-1.03	0.66	0.13	-2.38, 0.32
CP Categorical	-5.31	2.62	0.05	10.64, 0.02

Note. STW = single task walking; DTW = dual task walking; STC = single task counting; MELD = Model for End-Stage Liver Disease; CP = Child Pugh score; ** $p = <.01$

Table 32

Linear Mixed Effects Model for Disease Severity as a Moderator between STC and DTW

	Estimate	SE	*p*	95%CI
MELD Continuous	-0.01	0.27	0.96	-0.55, 0.53
MELD Dichotomous	-0.24	2.91	0.94	-16.80, 6.15
MELD Categorical	0.82	1.99	0.68	-3.23, 4.88
CP Continuous	0.42	0.66	0.53	-0.93, 1.92
CP Categorical	-0.56	2.71	0.84	-6.07, 4.95

Note. STW = single task walking; DTW = dual task walking; STC = single task counting; MELD = Model for End-Stage Liver Disease; CP = Child Pugh score; ** $p = <.01$

Table 33

Linear Mixed Effects Model for Cognitive Capacity as a Moderator between STW/STC and DTW

	Estimate	SE	*p*	95%CI
Cognitive capacity x DTW	2.56	2.41	0.30	-2.37, 7.49
Cognitive capacity x DTC	-0.13	0.06	<0.05*	-0.25, -0.02

Note. STW = single task walking; DTW = dual task walking; STC = single task counting; CC = Cognitive Capacity;
* $p = <.05$