THE QUANTIFICATION OF NEUROCOGNITIVE IMPAIRMENT ACROSS THE SPECTRUM OF KIDNEY DISEASE

by

Jessica A. Vanderlinden

A thesis submitted to the Graduate Program in Neuroscience Studies

in conformity with the requirements for the

Degree of Doctor of Philosophy

Queen's University

Kingston, Ontario, Canada

March, 2021

Dedication

I dedicate this thesis to my parents,

James and Shelly.

Thank you for your unconditional love and support. You

allowed me to reach for the stars and taught me that

nothing in life worth having comes easy.

Abstract

Over the last decade, it has become evident that patients with chronic kidney disease (CKD) are at high risk of developing neurocognitive impairment, which may influence medication/dietary adherence and quality of life. I therefore initiated a program of research that used cutting-edge robotic technology (Kinarm) to precisely and objectively quantify neurocognitive impairments in patients with CKD. To contextualize my work, a systematic review and meta-analysis was performed. Of the one-hundred and forty-eight studies identified, the vast majority used dementia screening tools to identify impairments in patients with CKD. It also demonstrated that patients who were pre-dialysis and dialysis-dependent CKD performed significantly worse than non-CKD controls.

I then performed a prospective observational study that quantified neurocognitive impairment in a cohort of patients with CKD. Forty-nine patients were recruited and assessed with the Kinarm and a traditional neurocognitive screening tool. Although, little impairment was detected by the neurocognitive screening tool, Kinarm detected impairments in up to ~50% of the cohort (task dependent). Additionally, this is the first study to demonstrate that perceptual-motor impairments are common in patients with CKD in addition to attention and executive function impairments.

Next, I characterized neurocognitive impairment in an understudied cohort: patients who experience acute kidney injury (AKI). Twenty-one patients with AKI were compared to healthy controls, and 21 active control patients matched for cardiovascular risk factors. Patients with AKI performed worse than healthy controls on attention, visuomotor, and executive function tasks. Additionally, patients with AKI performed significantly worse on attention and visuomotor domains when compared to active controls. This was the first

study to prospectively investigate neurocognitive impairments after AKI.

Finally, to investigate a potential mechanism of accelerated neurocognitive impairment in patients with end-stage renal disease, I used near-infrared spectroscopy to serially measure cerebral oxygenation during hemodialysis sessions for 1 year. Ultimately, low recruitment rates deemed the study unfeasible, but interesting relationships between cerebral oxygenation, mean arterial pressure, and fluid removal rates were observed. In summary, neurocognitive impairments are common in patients with kidney disease, particularly in perceptual-motor, attention, and executive function domains. Future studies will need to address how these impairments affect quality of life.

Statement of Co-Authorship

The results presented throughout this thesis have been submitted, accepted, and/or published in peer reviewed literature. One manuscript was published in Nephrology, with another in The Journal of Nephrology. Additionally, another manuscript is accepted in Canadian Journal of Kidney Health and Disease. Finally, another manuscript has been submitted with edits, and is pending acceptance at the time of writing. For each manuscript, Jessica A. Vanderlinden was responsible for the curating and collecting the majority of the data, completing the formal analysis which included the construction all the tables and figures, and was responsible for writing the original draft of each manuscript. Final edits were predominately provided by the supervisor and primary investigator Dr. J. Gordon Boyd. Additional edits were provided by the co-authors and peer-reviewers. The manuscripts are listed below and followed by all co-author contributions.

Manuscript 1: **Vanderlinden, J. A.,** Ross-White, A., Holden, R., Shamseddin, M. K., Day, A., & Boyd, J. G. (2019). Quantifying cognitive dysfunction across the spectrum of end-stage kidney disease: A systematic review and meta-analysis. *Nephrology, 24*(1), 5-16.

Co-author Contributions: JGB, KS, and JAV reviewed abstracts to determine study eligibility. ARW performed the literature search and gathered all articles that were assessed for the analysis. JAV and JGB performed the data abstraction and read potential articles for the review. JAV penned the manuscript, performed part of the statistical analysis, and created the tables and figures. ARW assisted with information pertaining the literature search section and flow diagram, along with writing this section. AD assisted in writing the statistical methods, along with performing the final analysis. JGB, RH, KS, & ARW were involved with editing the manuscript.

Manuscript 2: **Vanderlinden, J. A.,** Holden, R. M., Scott, S. H., & Boyd, J. G. (2021). Robotic Technology Quantifies Novel Perceptual-Motor Impairments in Patients with Chronic Kidney Disease. *Journal of Nephrology.* https://doi.org/10.1007/s40620-020-00912-z

Co-author Contributions: JGB and RMH designed the study. SHS developed and designed Kinarm. JAV gathered consent, analyzed, interpreted, and plotted the data, drafted and revised the manuscript. JGB, RMH, & SHS were involved in revising the manuscript.

Manuscript 3: **Vanderlinden, J. A.,** Semrau, J. S., Silver, S. A., Holden, R. M., Scott, S. H., & Boyd, J. G. (2020). Acute Kidney Injury Is Associated With Subtle But Quantifiable Neurocognitive Impairments. Submitted.

Co-author Contributions: JGB, RMH & SAS designed the study. SHS developed and designed Kinarm. JAV gathered consent, arranged the neurocognitive assessments, analyzed, interpreted, and plotted the data, drafted and revised the manuscript. JSS gathered consent, arranged neurocognitive testing, and made the consort diagram with regards to the cardiac control group. JGB, JSS, RMH, SAS, & SHS were involved in revising the manuscript.

Manuscript 4: **Vanderlinden, J. A.,** Holden, R. M., Scott, S. H., & Boyd, J. G. (2021). Cerebral Perfusion In Hemodialysis Patients - A Feasibility Study. Accepted: Canadian Journal of Kidney Health and Disease.

Co-author Contributions: JGB & RMH designed the study. SHS developed and designed Kinarm. JAV gathered consent, was responsible for meeting with the patients weekly for rSO2 monitoring, analyzed, interpreted, and plotted the data, drafted and revised the manuscript. JGB, RMH, & SHS were involved in revising the manuscript.

Acknowledgements

My PhD was conducted at Queen's University from 2015-2021, and was an evolution of my successful Mini-Masters project. Throughout both my Mini-Masters and PhD, the person who was at the forefront in shaping both this project and my career as a scientist was my supervisor Dr. J. Gordon Boyd. Firstly, I would like to express my deepest appreciation and gratitude for your continued guidance, support, and knowledge. I know my project was outside your formal area of training, however your guidance and knowledge was unprecedented and allowed me to explore the fascinating world of clinical neuroscience in a population not routinely investigated by graduate students. Thank you also for the numerous references letters. Dr. Boyd, it was a privilege to learn and work alongside you, and thank you for making me the analytical scientist I am today. Secondly, I would like to thank the members of my thesis committee, Dr. Rachel Holden, Dr. Samuel Silver, and Dr. Stephen Scott. Your eclectic knowledge and expertise into the areas of nephrology, statistics, and robotic technology were invaluable to the completion of this thesis, particularly in manuscript revisions. Thank you also for the numerous reference letters you provided throughout this project. Additionally, thank you Dr. Silver and Dr. Holden for assisting and allowing me to recruit potential patients from your clinics, this certainly was instrumental to the completion of this project. Thirdly, this project would not have been successful if not for the various nephrology doctors, nurses, and staff at Kingston Health Sciences Centre that assisted me in recruitment, eligible patient identification, and navigation of the dialysis ward. Finally, would like to express the deepest thanks to Helen Bretzke, Simone Appaqaq, and Kim Moore of the LIMB Lab. Specifically, thank you Helen for your timely assistance with data management and continued support regarding

the robotic technology used throughout this thesis. Additionally, thank you Simone and Kim for performing the neurocognitive assessments in the majority of my patients. Once again to everyone above sincerely thank you for making my PhD possible.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

3MS: The Modified Mini–Mental State

AIC: Akaike Information Criterion

AKI: Acute Kidney Injury

ANOVA: Analysis of Variance

APM: Arm Position Matching

ATN: Acute Tubular Necrosis

BonB: Ball on Bar

BPM: Beats per Minute

BVMT-R: Brief Visuospatial Memory Test-Revised

C: Celsius

CKD: Chronic Kidney Disease

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

cm: Centimeter

COVID-19: Coronavirus Disease 2019

COWAT: Controlled Oral Word Associations Test

CVLT: California Verbal Learning Test

Cr: Creatinine

CT: Computerized Tomography

dL: Decilitre

DOF: Degree of Freedom

DSM-V: The Diagnostic and Statistical Manual 5

e.g.: Example

eGFR: Estimated Glomerular Filtration Rate

ESKD: End Stage Kidney Disease

F: F-Statistic

FSG: Focal Segmental Glomerulosclerosis

GFR: Glomerular Filtration Rate

HD: Hemodialysis

Hr: Hour

IQR: Interquartile Range

KDIGO: Kidney Disease Improving Global Outcomes

Kg: Kilogram

KINARM: Kinesiological Instrument for Normal and Altered Reaching Movements

L: Litre

MAP: Mean Arterial Pressure

mg: Milligram

mL: Millilitre

mmHg: Millimetre of Mercury

MMSE: The Mini Mental Status Examination

MoCA: Montreal Cognitive Assessment

N/A: Not Applicable

NCT-A: Number Connection Test - A

NIRS: Near-Infrared Spectroscopy

nm: Nanometer

OH: Object Hit

OH+A: Object Hit and Avoid

p: P-value

PD: Peritoneal Dialysis

Pt: Patient

R^2: Coefficient of Determination

RAVLT: Rey Auditory Verbal Learning Test

RBANS: Repeatable Battery for the Assessment of Neuropsychological Status

RCFT: Rey–Osterrieth Complex Figure Test

RRT: Renal Replacement Therapy

RSE: Residual Standard Error

rSO2: Regional Cerebral Oxygenation Saturation

RVGR: Reverse Visually Guided Reaching

SD: Standard Deviation

SS: Spatial Span

Temp: Dialysate Temperature

TMT: Trails Making Test

VGR: Visually Guided Reaching

WAIS: Wechsler Adult Intelligence Scale

Chapter 1

Introduction and Study Objectives

1.1 Introduction

Chronic kidney disease (CKD) has an estimated worldwide prevalence of 13%[1], that increases with age and is particularly prevalent in the elderly[2]. Recent estimates determined that roughly 4 million Canadians are affected by CKD[3]. Due to the complex nature of CKD, patients with CKD create a high burden on the health care system[4], with recent estimates showing that the health care costs for patients with CKD in Canada exceeds 40 billion per year[3].

CKD is defined by the National Kidney Foundation as having structural damage or decreased kidney function for 3 or more consecutive months[4]. Specifically, CKD can be divided into 5 stages according to the glomerular filtration rate (GFR), which is influenced by age, sex, and ethnicity[4]**.** Notably, CKD is considered when the GFR remains constantly below 60 ml/min/1.73m^2 [4]. When the GFR reaches <15 ml/min/1.73m^2, this is classified as stage 5 kidney disease and is also known as kidney failure[4]. Once stage 5 is reached, renal replacement therapy (RRT) in the form of hemodialysis (HD) or peritoneal dialysis (PD) is needed, or a kidney transplantation. RRT becomes essential as it reverses the deleterious effects and symptoms caused by being in a chronic uremic state[5].

CKD is associated with an increased risk of mortality, particularly due to cardiovascular events[6]. Along with cardiovascular disease, comorbidities such as diabetes and hypertension commonly co-occur in patients with CKD[7]. Increased hospitalization rates, neurocognitive impairment, and decreased quality of life[1] have also been demonstrated in those with CKD. Finally, CKD is known to increase the risk of patients having an acute kidney injury (AKI)[8,9], which in turn is known to accelerate or induce CKD[9].

Regardless of the cause of AKI, the Kidney Disease Improving Global Outcomes (KDIGO) is the gold standard for classifying AKI. Specifically, KDIGO states that AKI is diagnosed when there is one of the following: a minimum increase in serum creatinine by 0.3mg/dL in 48 hours, a 1.5 times increase of serum creatinine from baseline, or a decrease in urine volume output[10]. AKI is highly prevalent in patients who are critically ill (1-67%)[11] and those that have undergone cardiac surgery (1-30%)[12]. Additionally, AKI is estimated to affect 1 in 5 hospitalized adults[13]. Similar to CKD, AKI confers an increased risk of morbidity and mortality, regardless of the cause[14].

1.2 Neurocognitive Impairment In Kidney Disease

1.2.1 Chronic Kidney Disease

Neurocognitive impairment has been extensively studied in patients with CKD and those requiring RRT. It has been determined that as patients progress through the different stages of CKD, there is a proportional decrease in neurocognitive performance[15]. Specifically, patients who experience moderate to severe renal failure demonstrate a least a five times elevated risk of developing some degree of neurocognitive impairment[16]. Prevalence estimates of neurocognitive impairment in individuals with renal failure are also three times higher than age-matched controls[17]. Additionally, up to 80% of patients that are receiving HD as their form of RRT have been noted to have some form of neurocognitive impairment[18]. There is however variation in the literature regarding RRT and neurocognitive performance. For example, patients undergoing PD have been shown to have more neurocognitive impairment than healthy controls[19], but have either similar[20] or less neurocognitive impairments when compared to HD patients[21]. Most of these impairments are seen in the domains of attention, memory, and executive function[22,23], and are traditionally assessed by screening tools[24].

The etiology of the impairments seen in CKD and those receiving dialysis remain unknown. However, it has been postulated that it is multifactorial in nature[25]. Many of the risk factors associated with CKD (age, diabetes, and cardiovascular disease) may be involved in the neurocognitive deficits described. In particular, age is known to be associated with both CKD[2] and neurocognitive impairment[26]. Diabetes is known to be the leading cause of CKD[27], and is associated with an increased rate of Alzheimer's disease[27] that is double than the risk to the general public[28]. The risk of neurocognitive impairment

has been found to be up to 143% higher in those with CKD even after accounting for traditional vascular risk factors[29]. Furthermore, cardiovascular disease along with all of its related complications (e.g. cerebral ischemia and cerebrovascular disease) are thought to be a driving force in the cause of neurocognitive impairment in patients with CKD undergoing dialysis[30,31]. For example, intracerebral hemorrhage is twice as likely to occur in those with CKD receiving HD, and are 7.4 times more likely to experience vascular neurocognitive impairment than the general population[32]. Additionally, cerebral atrophy is common in patients with end stage renal failure, which is thought to be caused by the effects of atherosclerosis, and may lead to neurocognitive impairment[32].

1.2.2 Acute Kidney Injury

Although the neurocognitive implications of CKD have been extensively studied, the neurocognitive implications of AKI are largely unknown. Only three studies to date have examined the neurocognitive outcomes of AKI. Of these studies, two were retrospective and used administrative data which demonstrated that AKI was an independent risk factor for dementia[33,34]. The other showed that long-term neurocognitive impairment was associated with AKI in children with severe malaria[35]. The neurocognitive domains that are affected and to what extent in survivors of AKI is currently unknown.

Again like CKD, risk factors such as age, diabetes, hypertension, and cardiovascular disease are common in individuals who develop AKI in the intensive care unit or during cardiovascular surgery[12,36]. Therefore as mentioned above, these baseline risk factors may too play a role in the development of neurocognitive impairment in patients with AKI. Finally, other potential mechanisms that may be involved in the development of neurocognitive impairment in survivors of AKI include: inflammation, uremia, and alterations in blood brain barrier permeability[37].

1.3 Cerebral Hypoperfusion As A Potential Cause of Neurocognitive Impairment In Patients With End Stage Renal Disease

Although the cause of the neurocognitive impairment in patients receiving HD is thought to be multifactorial in nature, repetitive cerebral hypoperfusion could contribute to the accelerated neurocognitive impairment observed in patients with end-stage renal disease. Strategies to monitor cerebral perfusion during HD could include near-infrared spectroscopy (NIRS) which measures the regional saturation of cerebral oxygenation (rSO2), a surrogate marker of cerebral perfusion. This is done by a sensor typically applied to the forehead which emits wavelengths of infrared light (700-1000nm) that pass 2-3 cm through the dermis and skull[38]. NIRS is ideal for this thesis as it provides a real time live capture of the oxygenation status of the cerebral tissue[39], and works on the principle that the absorption of light will change depending on the oxygen status of hemoglobin[40], and is relatively inexpensive, portable, and requires little training in comparison to magnetic resonance imaging[41]. Importantly, NIRS has also been shown to correlate with other measure of cerebral perfusion such as CT perfusion scans[42], and has been extensively used during cardiac surgery[43].

Previous cross sectional studies investigating rSO2 in patients undergoing HD show these patients as having lower rSO2 levels than controls, even before they initiated the dialysis session, with HD and control patient values being 40-55% and 70% respectively[41,44–46]. Furthermore, it has been demonstrated that limb tissue ischemia occurs during dialysis[47], and that there is a negative association between rSO2, diabetes, and blood pH with HD duration[48]. All of the above mentioned studies were cross sectional in nature, indicating there is no longitudinal data on the rSO2 levels of patients undergoing HD. This

represents a major knowledge gap in the understanding of the long-term changes in cerebral oxygenation in patients undergoing HD, and how these changes relate to neurocognitive impairment.

It is important to note that in addition to NIRS there have been, various other imaging modalities that are used to investigate the negative impacts of HD on the brain. The studies demonstrate that there are deficits in the white matter structure integrity, which correlated with neurocognitive deficits[49]. Additionally cerebral blood flow declines have been discovered in those receiving HD, which also correlated with neurocognitive impairment[50]. Table 1 illustrates the different techniques in which one could measure cerebral oxygenation along with each techniques strengths and weaknesses[41].

Table 1: Summary of Techniques used to Monitor Cerebral Oxygenation in Kidney Disease Patients

Method	Mechanism of Action	Advantage	Limitation
Transcranial Doppler	Ultrasound waves are used to determine the mean cerebral blood flow in the cerebral vasculature. Mean blood flow is determined by the difference in frequency of the ultrasound waved emitted and received.	Non-invasive Can be used during HD	Limited to larges cerebral arteries Requires training-operator error is a factor Continuous monitoring is challenging
Positron Emission Tomography Computed Tomography Scan	Intravenous dye that contains oxygen labeled water molecules gives insight into brain areas that are active. Higher active regions show as red indicating a higher uptake of the dye, which is a measure of cerebral blood flow.	Can calculate more than cerebral blood flow (example: cerebral blood volume and metabolic rate) Whole brain can be monitored at one time	Cannot be done in the dialysis unit Expensive Patient movement affects results Training required to operate Radiation exposure
Magnetic Resonance Imaging	Causes a difference in hydrogen proton frequencies in the brain when compared to resting state. This difference is used to image the brian[51].	Dye is not used, therefore not radiation exposure Whole brain can be monitored at one time	Cannot be done in the dialysis unit Expensive Patient movement affects results Training required to operate
NIRS	Near-infrared waves of light pass through the skull, allowing insight into the oxygen status of hemoglobin by using a shallow and deep sensor.	Portable Continuous monitoring Less expensive than other imaging techniques Non-invasive Can be used during HD	Only detects oxygenation status of the frontal lobe and not subcortical areas Majority of the signal is venous

Table 1: Summary of techniques used to monitor cerebral oxygenation in kidney disease patients, along with a description of the mechanism of action, advantages and disadvantages. This table is predominantly reproduced from the information in Wolfgram's 2019 article[41].

1.4 Thesis Components

1.4.1 Thesis Objectives, Aims, and Hypotheses

The main objective of this thesis was to characterize the neurocognitive functioning in patients with kidney disease, with a particular focus on patients with CKD and those who recently experience an episode of AKI. To address this objective, this thesis has the following aims and hypotheses:

1. **Aim**: To provide an up-to-date systematic review and meta-analysis on the neurocognitive assessments used to describe neurocognitive impairment across the spectrum of kidney disease.
2. **Aim**: To use cutting-edge robotic technology to provide objective and quantifiable data describing neurocognitive impairments in patients with CKD and after an episode of AKI.
    - **Hypothesis:** Impairment will be dictated by the severity of kidney disease, in that worse neurocognitive performance will be demonstrated by those with worse renal function. Additionally, robotic technology will provide insight into neurocognitive domains that are not typically measured on traditional clinical assessments.
3. **Aim:** To assess the feasibility of serially recording rSO2 in patients undergoing hemodialysis.
    - **Hypothesis:** Repetitive cerebral hypoperfusion during hemodialysis is contributing to the accelerated neurocognitive impairment seen in individuals with end-stage renal failure undergoing HD.

1.4.2 Neurocognitive Assessments Conducted Throughout The Thesis

Throughout this thesis the neuropsychological battery performed by the various kidney disease cohorts consisted of a standardized dementia screening tool that is proven to measures both cognitive decline and improvement[52]: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and a robotic assessment that quantifies sensory, motor, and cognitive performance of the upper limbs[53]: Kinarm Endpoint Lab (Kinarm)[54]. This neuropsychological assessment took on average 1 hour and 20 minutes to perform, with the RBANS assessment taking 30 minutes, and the Kinarm robotic assessment taking 50 minutes. The assessments were conducted by an individual who was trained to perform this neuropsychological battery.

Regarding the RBANS specifically, it is composed of multiple tasks which are divided into 5 neurocognitive domains: attention, immediate memory, delayed memory, visuospatial, and language. These 5 domains are then complied into a composite score (Total Scale Score), which reflects how the patient performed on the assessment as a whole. The RBANS is standardized by age. The Kinarm in comparison is made up of 9 tasks that measure distinct yet overlapping sensory, motor, and cognitive domains. Each task on the Kinarm is made up of multiple parameters which take into account the movement and accuracy of the patient, and are then compiled into a summary score (Task Score). The Kinarm is standardized by age, sex, and handedness.

Throughout this thesis on both assessments, the 95% confidence interval was selected as the cut-off for impairment. This corresponds to a cut off score of < 75.25 (1.65 standard deviations (SD) below the mean of 100) on the RBANS, and >1.96 on the Kinarm. This 95% cut-off ensured that when impairment was detected in comparison to health age-

matched control data, there was greater certainty that neurocognitive impairment as present. Additionally, some cohorts were asked to perform multiple assessments of this neuropsychological battery. In order to minimize learning effects, each subsequent assessment was performed generally 3 months after the previous one. Furthermore, at each subsequent assessment different RBANS versions were used, along with different variations of some Kinarm tasks (if applicable). Also notably, the Kinarm has been previously shown to have good retest reliability along with minimal practice effects for most tasks in both adults[55] and children[56]. Table 2 describes all the RBANS and Kinarm task components and descriptions, along with hypothesized anatomical areas thought to be involved with regards to the task.

Table 2: RBANS and Kinarm Task Components, Descriptions, and Anatomical Areas

Neurocognitive Test	Domain/Task	Task Components and Description	Anatomical Area Assessed
RBANS	Attention	Digit Span: Patient is asked to repeat a sequence of numbers. The sequence length increases with the previous correct response, up to a max of 9 numbers. Symbol Coding: Numbers 1-9 are represented by a symbol. The patient is asked to fill in as many numbers with their corresponding symbols in 90 seconds. A trial run is performed to ensure the patient understands the task and is matching the correct number to its symbol.	Frontal Lobe
	Immediate Memory	List Learning: A list of 10 unrelated words are given to the patient to recall immediately after the list is given. Four trials of the same word list is performed. Story Memory: A 12 item short story is read to the patient. The patient is asked to immediately recall as much as the story as possible. This story is read 2 times.	Temporal Lobe
	Delayed Memory	List Recall: The patient is asked to recall as many of the 10 words from the list as possible, after they have completed the other domain sections. List Recognition: The patient is give the 10 words from the list along with 10 non-list words and are asked if the word was on the list or not. Story Recall: Patient is asked to recall as much as the story as possible. Figure Recall: The patient is asked to recall as much of the figure as possible. They are instructed that if they can't remember where a shape goes to place it in the figure to receive part marks.	Temporal Lobe
	Visuospatial	Figure Copy: The patient is asked to copy a geometric figure. The figure is available to the patient to view when drawing. Line Orientation: The patient is shown two lines which correspond to 2 of the 13 lines that originate from a single point across 180 degrees figure. The patient is asked to do this 10 times with the 2 lines changing orientations.	Parietal-Occipital Lobe
	Language	Picture Naming: The patient is shown 10 pictures and asked to name them. Semantic Fluency: The patient is given 60 seconds to name as many items related to the prompt as possible. Example: name all the animals you would find in a zoo.	Frontal Lobe, Temporal Lobe (Dominant Hemisphere)

	Total Scale Score	A composite summary score based on the performance of the patient on all the RBANS domains.	Whole Brain
Kinarm	Arm Position Matching	The robot moves one of the patient's arms, and the patients is then asked to mirror match this position with the other arm.	Frontal Lobe, Cerebellum, Parietal Lobe
	Ball on Bar	A bar appears between the patients 2 hands with a ball on top of it. The patient is then asked to move the ball into targets that appear on the screen. This target moves on the screen during the task. There are also three levels of the task which increase in difficulty. The ball goes from being fixed in position to being able to freely move and fall off the bar (depending on how level the patient keeps the bar).	Frontal Lobe, Occipital Lobe, Cerebellum, Basal Ganglia
	Object Hit	Paddles appear at the patients hands and they are instructed to hit as many balls (which fall from the top of the screen) away as possible. As the task progresses the quantity and speed at which the balls fall increases.	Frontal Lobe, Occipital Lobe, Parietal Lobe, Cerebellum, Basal Ganglia
	Object Hit and Avoid	Similar to object hit, but this time two shapes are shown to the patient. They are instructed to hit these two targets while avoiding all the other distractor targets. Again, as the task progresses the quantity and speed at which the targets fall increases.	Frontal Lobe, Occipital Lobe, Parietal Lobe, Cerebellum, Basal Ganglia
	Visually Guided Reaching	A target appears on the screen and the patient is asked to move the dot that represents their hand into the target as quickly and accurately as possible. This target moves around the screen as the task progresses.	Frontal Lobe, Occipital Lobe, Parietal Lobe, Cerebellum, Basal Ganglia
	Reverse Visually Guided Reaching	Similar to visually guided reaching, but the light representing the patient's hand now moves in the opposite direction of the patient's arm movement.	Frontal Lobe, Occipital Lobe, Parietal Lobe, Cerebellum, Basal Ganglia
	Spatial Span	The patient is shown a sequence in a matrix of 4x3 boxes, and is then asked to replicate it. The length of the sequence depends on if the patient got the previous sequence correct or not.	Frontal Lobe, Occipital Lobe, Temporal Lobe, Parietal Lobe, Cerebellum, Basal Ganglia
	Trail Making Test A	The patient is asked to connect the numbers 1-25 in order as quickly as possible. The number arrangement is predetermined and no connecting lines may overlap. A trial run is given to ensure the patient understands the task.	Frontal Lobe, Occipital Lobe, Parietal Lobe, Cerebellum, Basal Ganglia

	Trail Making Test B	Similar to trails making test A, but the patient is now asked to alternate between numbers and letters (1-A-2-B-3) as quickly as possible. The arrangement is predetermined and no connecting lines may overlap, and a trial run is provided like the trails making test A.	Frontal Lobe, Occipital Lobe, Parietal Lobe, Cerebellum, Basal Ganglia

Table 2: RBANS and Kinarm task components, descriptions, and hypothesized anatomical areas that are assessed by each task. RBANS task descriptions were reproduced from Claes et al., 2016[57], and the Kinarm user manual[58].

1.5 Clinical Implications

In summary, neurocognitive impairment is commonly described in patients with CKD and those who are receiving HD, but is unknown in patients who survive an episode of AKI. Additionally, the etiology of this impairment in all cohorts remains unknown. The novelty of this research program is highlighted by the fact that it is the first to 1) quantify neurocognitive impairment using robotic technology in patients with CKD, 2) prospectively assess neurocognitive impairment in adult patients who survive an episode of AKI, and 3) serially monitor rSO2 for an entire year for patients initiating HD. This work is essential to determining the magnitude and scope of the impairment experienced by individuals with either CKD or AKI. It may also assist physicians in devising tailored treatment strategies, in particular how they discuss medication and dietary adherence, along with deciding who may be eligible for at home RRT.

Chapter 2

Literature Review - Quantifying Cognitive Dysfunction Across the Spectrum of End Stage Renal Disease – A Systematic Review and Meta-Analysis

2.1 Abstract

Importance: Neurocognitive dysfunction is reportedly highly prevalent among patients with chronic kidney disease (CKD). A variety of screening tools and neuropsychiatric batteries have been utilized to quantify the magnitude and nature of this dysfunction in patients with CKD.

Objective: To summarize the neurocognitive testing used and determine what degree neurocognitive dysfunction is reported in patients with CKD.

Methods: Articles published in English containing consenting age of majority participants who were either: pre-dialysis, undergoing hemodialysis (HD) or peritoneal dialysis (PD), or renal transplant recipients were considered. If comparative non-CKD control participants were reported, this data was also collected. All study designs were included. The search period encompassed articles from 1980 until May 2018. This review was registered with PROSPERO (CRD42018096568).

Results: Of the 1,711 articles screened, 148 articles were relevant and used in the meta-analysis. Commonly used assessments were: The Mini–Mental State Examination (MMSE), The Modified Mini–Mental State Examination (3MS), the Trails Making Tests (TMT) forms A and B, and components of the Wechsler Adult Intelligence Scale: Digit Span and Digit Symbol. The means for all assessments were adjusted using a random effects model to account for the differences in variance. Adjusted mean MMSE scores were significantly lower for both patients who were pre-dialysis (26.08, n=17,073) and receiving HD (26.31, n=3,314) when compared to non-CKD controls (28.21, n=5,226). Patients receiving either PD (58.01 seconds, n=859) or HD (56.04 seconds, n=2,344) also took significantly longer to complete the TMT-A than non-CKD controls (37.62 seconds,

n=4,809).

Conclusions: Patients with CKD, especially pre-dialysis and those requiring dialysis, are likely to exhibit impairments in cognition that can be identified with specific screening neuropsychological assessments.

2.2 Introduction

Chronic kidney disease (CKD) affects approximately 9% of the population worldwide[59], that increases in prevalence with age[2], creating a high burden on the health care system[4]. Neurocognitive dysfunction is widely believed to occur frequently in patient with CKD, yet the prevalence and nature of this neurocognitive dysfunction is poorly understood. Given that the incidence of CKD is increasing[4] particularly in the elderly, recognizing and understanding neurocognitive dysfunction in patients with CKD has become a research priority[60]. In that characterizing the degree of neurocognitive dysfunction is important for patient-centered care, as neurocognitive impairment may impact an individual's ability to make informed health decisions with regards to the complex fluid and dietary restrictions imposed upon those with CKD[61]. Furthermore, understanding the neurocognitive domains that are predominantly affected by CKD may also be important. For example, impairments in language and executive function may limit a patient's ability to meaningfully participate in complex discussions regarding initiating or ceasing renal replacement therapy (RRT).

Controversy exists regarding the prevalence and magnitude of neurocognitive dysfunction across the CKD spectrum. Declining estimated glomerular filtration rate (eGFR) has been associated with worse neurocognitive dysfunction in individuals with CKD who do not yet require dialysis[62]. Patients with CKD not requiring RRT, have also shown unique neurocognitive deficits when compared to other neurological and medical psychiatric patients[63], suggesting that there is a distinct CKD neurocognitive endotype. In studies of patients undergoing hemodialysis (HD), it has been estimated that 30-80 % of these individuals may have some degree of neurocognitive impairment[61]. In contrast

however, it has also been reported that when comparing elderly patients undergoing HD to age-matched healthy non-CKD controls, there is no significant difference in their neurocognitive abilities[20]. Further controversy exists with respect to the impact of dialysis modality (i.e. HD vs. peritoneal dialysis (PD)) on neurocognitive performance. Compared to patients undergoing HD, patients receiving PD have been shown to have similar[21] or better neurocognitive outcomes[64], but still perform worse than non-CKD controls[19]. These studies are limited by the variability in the description of neurocognitive dysfunction, types of neuropsychological assessments used, and whether or not screening tests or more detailed neurocognitive assessments were performed.

A recent meta-analysis has suggested that patients undergoing HD show deficits in attention and executive function[65], agreeing with previous findings[22,66]. The aim of this study was to complete a comprehensive systematic review and meta-analysis on studies measuring neurocognitive performance by various neuropsychological measures across the CKD spectrum. This in turn will allow us to define the degree of neurocognitive dysfunction across the different CKD populations (patients who were either: pre-dialysis CKD, receiving RRT (HD and PD), transplant recipients, or non-CKD controls).

2.3 Material and Methods

Literature Strategy Search

A three-step search strategy was utilized for this review, based on both the Joanna Briggs and Institute of Medicine standards for systematic review searches[67,68]. An initial limited search of MEDLINE® was undertaken to develop the strategy. This was followed by an analysis of text words and index terms used to describe articles meeting the inclusion criteria to refine the search strategy to ensure a more complete recall. The inclusion criteria was very broad in that it encompassed any article that cited neurocognitive impairment or dysfunction in any age of majority CKD population. Articles were excluded if they predated the 1980s, due to the primary focus of these articles being the interaction between aluminum and dialysis encephalopathy. All study designs were included to ensure the majority of eligible studies were considered for the analysis. A second search using all identified keywords and index terms from the primary search was then undertaken across all included databases. The databases searched included: MEDLINE®, Embase, and PsycInfo, which were chosen for their broad coverage in both the areas of nephrology, neurology, and related disciplines. Index terms that were used in the strategy were: Renal Dialysis; Kidneys, Artificial; Renal Insufficiency, Chronic; Delirium, Dementia, Amnestic, Cognitive Disorders; Mental Status Schedule; Cognition; Neuropsychological Tests and related narrower terms. Thirdly, the reference lists of all identified reports and articles were searched for additional studies. This review only included studies published in English, but there was no language restriction on the neurocognitive assessments. Once all articles were compiled the abstracts were subsequently reviewed independently by at least two reviewers, who ensured the articles used in the systematic review met the

specified inclusion criteria. Any discrepancies between the two reviewers were then resolved by discussion until a consensus was reached in determining if the article was relevant. The literature search encompasses articles up until May 9th 2018, and was registered with PROSPERO (CRD42018096568).

Systematic Review

Once the final list was compiled the articles were read, reviewed, and relevant information pertaining to the meta-analysis was abstracted. Relevant information entailed: author, year of study, funding, study design, country of origin, study population, neurocognitive assessment used, neurocognitive scores, concluding remarks, and study reference. During this process articles were removed if they were a repeat of an article already reviewed, if there was no raw data reported, the article was a review of other studies, if particular populations were excluded (e.g. if they had a score lower than 23 on The Mini–Mental State Examination (MMSE)), or if the neurocognitive assessment used was not in-person (i.e. phone assessments) were not considered in this analysis. In some cases authors were contacted if there was uncertainty regarding the study population being comprised of the same populations in different publications, or if the data was only reported for some of the neuropsychological assessments. If the authors did not reply to our inquiries, our discretion was used, and these articles were removed, or if there was some reported data that was relevant to the meta-analysis only this data was used. As the number connection test (NCT-A), is equivalent to the Trails Making Task A (TMT-A)[69], the data from these tasks were grouped together. Due to the fact the majority of the studies were observational in nature and not clinical trials and used subjective measurement tools, a specific risk of bias assessment for the individual studies was not conducted. At least a

moderate degree of bias was assumed for all studies.

Meta-Analysis and Statistical Analysis

Once data abstraction was complete, all studies were sorted by neuropsychological assessment. If the data was subdivided by another factor such as depressive symptoms, only participants that were as close to control sample were used (i.e. the non-depressed group scores). For prospective studies, only baseline scores were used. If there were any studies that reported their score as a median and interquartile range the data was transformed to a mean and standard deviation (SD) using the equations from Wan et al.[70]. If the study had a large sample size (N>70) the equation used to calculate the means was: (a+2m+b)/4, where a is the minimum value, b is the maximum value, and m is the median[70]. If the sample size was lower than 70 the equation used was: [(a+2m+b)/4] + [(a-2m+b)/4n][70] . For calculating the standard deviation of the studies with a large sample size (N>70) the equation was: (b-a)/6, if the sample size was between 15 and 70 (b-a)/4 was used, and if the sample size was below 15 (b-a)/ square root 12, with a and b again corresponding to the range[70].

Assumptions of normality and variance were both considered to ensure that the correct analysis was performed. These assumptions were investigated by not only graphing the distributions and residuals, but by also performing the Shapiro Wilk Test and the Levene's Test. Once completed, the weighting of the means was taken into account. As the between study variance of the reported means was usually much larger than the within study variance of the mean estimates, a random effects approach was chosen as it accounted for both within and between study variance and treated the study means as the independent units of analysis. The between study variance was estimated by the Dersimonian and Laird

method. The between group mean differences, their confidence intervals, and p-values (compared to a null of no difference) were estimated by applying Welch's two-sample t-test for unequal variance between means to the study level means weighted by the inverse of the studies variance from the random effects model. The degrees of freedom were estimated by a weighted Satterthwaite's approximation as implemented by the T-TEST procedure of SAS (SAS Institute Inc., Cary, NC, USA). We report nominal p-values without adjustment for multiplicity of testing, along with adjusted values using the Bonferroni correction for the number of pairwise comparisons per outcome, to ensure that the type 1 error rate was controlled for (Table 3). Throughout the analysis the reported results from non-CKD controls (eGFR>60 mL/min/1.73 m^2) were used as the reference point to which all other patient populations were compared too. All findings were considered significant if the p-value was <0.05 after applying the correction factor and post hoc testing (Table 3). Heterogeneity was assessed by taking the between study variance and square rooting this estimate in order to obtain Tau (Table 3).

2.4 Results

Study Identification and Commonly Used Cognitive Screening Tests

After screening 1,711 potential article abstracts, 320 were deemed relevant and subsequently read and their content assessed. Of the 320, there were 198 articles whose full content was abstracted, of these 148 articles were relevant for the meta-analysis (Figure 1). Of the 148 articles that were retained, the majority pertained to patients who were either pre-dialysis or receiving HD with: 51 articles assessed patients who were pre-dialysis (n=31,186), 93 assessed patients receiving HD (n=7,117), 19 assessed patients receiving PD (n=1,668), 9 assessed combined modalities (HD and PD not separated) (n=492), 7 assessed transplant recipients (n=215), and 52 had non-CKD controls (n=8,034). The extracted data is summarized in Tables 4-9.

The most commonly used neuropsychological assessments were: The Mini–Mental State Examination (MMSE), The Modified Mini–Mental State Examination (3MS), the Trails Making Tests (TMT) forms A and B, and Digit Span forwards and backwards along with Digit Symbol, which are sub sections of the Wechsler Adult Intelligence Scale (WAIS) (Tables 4-9). Commonly used neuropsychological tests were dictated by which tests had the most study participants or was the most commonly performed (Table 3).

The MMSE is a dementia screening tool that has a maximum score of 30, with normal neurocognitive functioning defined as >24[71]. Across all patients with CKD, the majority of mean MMSE scores were above the traditional cut off of 24 for neurocognitive impairment. However, the studies that had mean MMSE scores below normal were reported for patients receiving HD (n=6), along with pre-dialysis (n=4), combined (n=1), and control populations (n=2) (Figure 2A). Pooled together it was determined that both

patients receiving HD (adjusted mean=26.31, n=3,314, p =0.0015), and who were pre-dialysis (adjusted mean=26.08 n=17,073, p =0.0015) were significantly lower than non-CKD controls (adjusted mean=28.21, n=5,226) (Table 3). Figure 2B illustrates the pooled data with the adjusted means along with the lower and upper confidence levels.

The 3MS is an extended version of the MMSE that is also used to screen for dementia, however unlike the MMSE the 3MS is scored out of 100 instead of 30[72]. The cut off score generally used to identify individuals with neurocognitive impairment is below 78[73]. Only one study reported a 3MS mean score below this cut off of 78, which was for the HD population (Figure 2C). Pooled data with adjusted means and confidence levels are shown in Figure 2D. The mean 3MS scores were not statistically different between the different groups of patients with CKD and non-CKD controls (Table 3).

The Montreal Cognitive Assessment (MoCA) was reported for a few studies (n=17), but was included in the meta-analysis due to its increased use over the past decade. The MoCA is another screening tool that was designed to assess the global neurocognitive function of individuals, and takes approximately 10 minutes to administer[74]. This brief assessment looks to determine mild neurocognitive impairment, which is determined if the score is below 26 out of a possible 30 points[74]. The majority of studies that used the MoCA were with patients receiving HD (n=9), followed by patients who were pre-dialysis (n=3), PD (n=2) and non-CKD controls (n=3) (Table 3). Interestingly to note that all but two studies (non-CKD controls) reported scores below the normative cut off of 26 (Figure 2E). This corresponded to the adjusted mean scores not being significantly different between the CKD populations and non-CKD controls (Table 3). The pooled estimated means for the MoCA along with confidence intervals are shown in Figure 2F.

The TMT-A assesses visuomotor tracking and scanning by asking the patient to connect a sequence of numbers from 1 to 25 in order as quickly as possible[75]. Due to lacking agreement on cut off completion times for the TMT, a study of 911 individuals assessing the TMT across all ages and years of education was averaged to produce the 40-second mean time of completion used in this analysis[76]. As a test of the face validity of the use of the 40-second cut-off for TMT-A completion, the majority of studies that included non-CKD controls documented a mean test duration of less than 40 seconds (Figure 3A and B). In comparison, the majority of the CKD populations were above the average line, indicating worse performance (Figure 3A). Both dialysis groups, patients receiving HD (adjusted mean=58.18, n=2,344, p=0.0015), and PD (adjusted mean=60.90, n=859, p=0.03) took significantly longer to complete the TMT-A than non-CKD controls (adjusted mean=38.77, n=4,809) (Table 3).

In comparison to the TMT-A, the TMT-B is a more cognitive demanding task, because the patient is asked to connect numbers and letters in alternating order (example 1-A-2-B-3-C etc.) which requires thinking flexibility and mental shifting[75]. The mean cut-off time for completion used in this analysis was 94 seconds, again obtained from the population means generated by Tombaugh et al.[76]. The majority of the studies cluster around the blue average line (94 seconds) for all populations completing the TMT-B (Figure 3B). Surprisingly even though the TMT-B is reportedly more cognitively demanding than the TMT-A, there was no significant difference found between the CKD populations and the non-CKD controls. Patients who were pre-dialysis (adjusted mean=164.23, n=7,163, p=0.035), and receiving HD (adjusted mean=135.6, n=3,348, p=0.031) took slightly longer to complete the TMT-B tasks compared to non-CKD controls

(adjusted mean= 97.06, n=4,481). However, these values were not significantly different after controlling for multiple comparisons (Figure 3).

Finally, the subtests of the Wechsler Adult Intelligence Scale (WAIS) Digit Span and Digit Symbol, were also frequently used in the neuropsychological batteries reported. Digit Span is a memory and attention test that requires the participant to repeat back a series of numbers either in the same order (Digit Span forwards) or in reverse order (Digit Span backwards), which increases in length as the test progresses[77]. A normative data study was used in order to determine the cut off values for impairment for this analysis; which corresponded to 5.73 and 4.35 for Digit Span forwards and backwards respectively[78]. The cut off of 5.73 was used for all studies that did not specify which Digit Span test was performed. Figure 4A-F depicts the pooled data and adjusted means and confidence intervals for both Digit Span forwards and backwards, along with all the studies not specifying which Digit Span was performed. The adjusted means demonstrated there were no significant differences with regards to performance on either forwards or backwards tests between the CKD populations and non-CKD controls (Table 3).

In contrast, Digit Symbol is a test of processing speed in which participants are presented with a series of symbols which corresponds to a number legend. They are then asked to fill in as many of the symbols in order without skipping ahead in 120 seconds[79]. A cut off of 59[80] was used for Digit Symbol to indicate impaired performance. Figure 5A demonstrates that the majority of CKD populations (excluding one study of patients who were pre-dialysis) were below the cut off of 59, along with half of the non-CKD controls. Patients undergoing HD (adjusted mean=34.37, n=1,316, p=0.024) may have performed worse than non-CKD controls, but this did not reach significance after controlling for

multiple comparisons.

All other assessments that were considered in this meta-analysis are summarized in Tables 4-9. The majority of these studies assessed the domains of language and memory. There was no significant difference found for any of these neuropsychological assessments when comparing any of the CKD populations to non-CKD controls when pooled together. Interestingly however, when looking at mean cut off values that are reported for the various neuropsychological assessments, there is reported impairment at an individual study level for all populations (Tables 4-9). Therefore, there appears to be a disconnect regarding the pooled data and the neurocognitive impairment reported at an individual study level.

2.5 Discussion

This systematic review and meta-analysis provides an up to date and comprehensive description of the neuropsychological testing performed across the spectrum of CKD populations. This included highlighting the commonly used neuropsychological assessments, along with determining and quantifying the neurological consequences of CKD. Screening assessments for dementia such as the MMSE (pre-dialysis and HD) along with the TMT-A (PD and HD) were able to detect significant differences between these cohorts and non-CKD controls. Pre-dialysis and dialysis populations showed the most significant deviation from non-CKD controls subjects, with deficits noted in global functioning, attention, and processing speed.

Regarding the MMSE, it is interesting to note that even though there was a significant difference between control populations and both pre-dialysis and HD populations, their adjusted mean values (25.13 and 26.31, respectively) are still above the traditional cut-off for neurocognitive impairment (a score <24). This finding is important, as the MMSE may not capture mild neurocognitive impairments in these populations. There is a general consensus that with progression of CKD, there is an increased risk for the development of neurocognitive impairment and dementia[81–83]. Cut off scores on dementia screening tools such as the 3MS and MMSE may not be sensitive enough to detect impairment in these populations. The few studies that performed the MoCA did show promise in detecting impairment in patients with CKD, however non-CKD controls also performed below the traditional cut off for mild neurocognitive impairment. More studies are needed using the MoCA before any conclusions can be made in its ability to detect impairment in CKD populations. Furthermore, these measures were not designed to

investigate impairment specifically in CKD populations. The ability to detect the mild neurocognitive impairment in this population could translate to better monitoring of the progression of this impairment, along with implementing adequate measures to their treatment plans to ensure proper care.

Compared to the TMT-A, the TMT-B adds additional executive neurocognitive load via mental shifting[75]. Given the additional complexity of this task, it was surprising that only the TMT-A took longer to complete for patients receiving RRT (PD and HD) when compared to non-CKD controls. This may suggest that these cohorts may have more broad impairment such as processing speed or visual searching which are known to be tested by the TMT[75]. Cut off values for the TMT are lacking in consensus, and this is problematic for defining impairment. In our analysis, the study cited had a substantial normative data set of 911 participants ranging from ages 18-89, which took into account both age and education, since these impact performance on the TMT[76]. Importantly it is worth nothing that the TMT is not only a measure of attention and executive function[75], it also involves a complex integration of motor capabilities and visual acuity of the participants.

Although this systematic review provides a comprehensive summary of the spectrum of neuropsychological testing across the spectrum of CKD populations there are several key limitations that need to be addressed. The main concern with this analysis was that it was not a typical meta-analysis; in that the studies that were pooled together did not all have control data. This required a novel statistical approach. In order to deal with the unique circumstances of the analysis, it was determined that a mixed effects model would be best, for after testing there was more variance between studies then within studies,

making a fixed effects model not appropriate. It was determined that adjusting and weighting the reported means by the variance was the best course of action (instead of sample size). In doing this we took the most conservative steps in order to retain valid estimates. There was also the issue of having high heterogeneity due to the number of neuropsychological assessments used in the CKD population, along with the majority of the studies having small, uneven sample sizes, and the majority of studies used only had one CKD group and no non-CKD controls. Due to these small sample sizes, subsequent analysis after the commonly used neuropsychological assessments contained few comparisons between the various CKD populations and non-CKD controls. Robust statistical analyses were used to correct for the uneven sample sizes along with implementing a correction factor to decrease the type I error rate. Notably there were significantly fewer transplant and PD studies, thereby limiting the power to detect significant differences between these patient populations. Finally, a barrier to interpreting the degree of neurocognitive impairment among patients with CKD, is the lack of well-defined cut-off scores in appropriate control populations. Although the interpretation of our data may be limited by the absence of these hard criteria, our study highlights the need for future studies to include control groups that are matched for age, sex, and co-morbid illnesses. For example, the majority of neurocognitive testing included in our meta-analysis reports impairments in patients compared to that specific test's intrinsic criteria (likely based on normative data from healthy volunteers), yet our pooled analysis shows no significant neurocognitive impairment.

In summary, our up-to-date and comprehensive meta-analysis of the most commonly used neuropsychological assessments across the spectrum of CKD patients determined that dementia screening tools such as the MMSE and TMT-A may be used identify differences in neurocognitive function between patients with CKD and non-CKD controls. This information may lend itself to the development of a neuropsychological assessment specifically for the CKD population. Higher order neuropsychological testing may demonstrate that patients with CKD perform worse than healthy control individuals, but our findings suggest that future studies will need to address the contribution of other co-morbid illnesses (e.g. hypertension, diabetes) in the development of this neurocognitive impairment.

2.6 Tables

Table 3: Compiled Data for All Patient Populations for the Most Commonly Used Assessments: Meta-Analysis

Patient Population	Test	Number of Studies	N	Unadjusted Mean	SD	Adjusted Mean	Estimated SE	p-Value	Corrected p -Value	Between Study Variance	Between Study Variance Square Root
Pre-Dialysis	3Ms	10	10597	89.80	9.28	89.88	1.29	0.6600	1.0000	5.722	2.392
HD	3Ms	8	1560	86.08	9.68	87.93	1.10	0.9310	1.0000	1.473	1.214
PD	3Ms	4	984	88.51	7.51	88.4	1.46	0.9660	1.0000	3.530	1.879
Combined	3Ms	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Transplant	3Ms	1	28	82.90	15.60	82.9	N/A	N/A	N/A	0.000	0.000
Controls	3Ms	3	304	88.20	7.37	88.24	3.06	Comparison	Comparison	36.397	6.033
Pre-Dialysis	Digit Span-Backwards	8	669	4.28	1.60	4.25	0.37	0.0520	0.5200	0.733	0.856
HD	Digit Span-Backwards	6	279	4.97	1.51	4.95	0.41	0.4910	1.0000	1.003	1.001
PD	Digit Span-Backwards	2	28	4.59	1.57	4.38	0.55	0.2790	1.0000	0.367	0.606
Combined	Digit Span-Backwards	1	20	5.15	1.42	5.15	N/A	N/A	N/A	0.000	0.000
Transplant	Digit Span-Backwards	3	106	5.78	1.73	5.75	0.74	0.6550	1.0000	1.433	1.197
Controls	Digit Span-Backwards	8	1415	5.36	1.56	5.34	0.39	Comparison	Comparison	0.959	0.979
Pre-Dialysis	Digit Span-Forwards	8	669	7.04	1.58	7.01	0.56	0.3720	1.0000	1.512	1.230
HD	Digit Span-Forwards	5	244	6.99	1.68	6.99	0.79	0.4560	1.0000	3.866	1.966
PD	Digit Span-Forwards	1	6	5.83	1.47	5.83	0.82	0.0730	0.7300	0.000	0.000
Combined	Digit Span-Forwards	1	20	5.80	1.40	5.80	N/A	N/A	N/A	0.000	0.000
Transplant	Digit Span-Forwards	3	106	7.42	1.76	7.41	1.39	0.8240	1.0000	4.530	2.128
Controls	Digit Span-Forwards	8	1451	7.81	1.99	7.78	0.63	Comparison	Comparison	1.006	1.003
Pre-Dialysis	Digit Span-Unspecified	4	857	11.81	2.81	11.80	2.27	0.6170	1.0000	15.037	3.878
HD	Digit Span-Unspecified	13	834	9.75	2.73	9.87	0.98	0.1590	0.9540	21.629	4.651
PD	Digit Span-Unspecified	1	51	16.70	3.50	16.70	N/A	N/A	N/A	0.000	0.000
Combined	Digit Span-Unspecified	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Transplant	Digit Span-Unspecified	2	61	8.65	2.00	8.54	1.14	0.0840	0.5040	2.338	1.529
Controls	Digit Span-Unspecified	6	265	13.37	3.33	13.39	2.02	Comparison	Comparison	26.840	5.181
Pre-Dialysis	Digit Symbol	12	3348	40.01	11.76	39.14	5.91	0.1320	1.0000	1568.600	39.606
HD	Digit Symbol	16	1316	33.09	10.24	34.37	5.22	0.0240	0.3600	141.180	11.882
PD	Digit Symbol	3	75	49.67	14.00	50.54	4.84	0.9640	1.0000	40.590	6.371
Combined	Digit Symbol	4	94	49.90	9.57	49.94	4.99	0.8950	1.0000	91.147	9.547
Transplant	Digit Symbol	2	33	42.10	9.78	41.77	5.59	0.3060	1.0000	55.615	7.458
Controls	Digit Symbol	16	1493	50.21	11.23	50.86	4.61	Comparison	Comparison	575.050	23.980
Pre-Dialysis	MMSE	25	17073	25.13	2.78	26.08	0.39	0.0001	**0.0015**	3.582	1.893
HD	MMSE	50	3314	26.29	2.84	26.31	0.28	0.0001	**0.0015**	3.634	1.906
PD	MMSE	7	330	27.37	2.23	27.36	0.58	0.2260	1.0000	5.498	2.345
Combined	MMSE	5	398	26.65	1.77	26.71	1.01	0.2190	1.0000	1.949	1.396
Transplant	MMSE	5	147	28.36	1.66	28.39	0.47	0.7560	1.0000	1.618	1.272
Controls	MMSE	28	5226	28.20	1.42	28.21	0.33	Comparison	Comparison	3.634	1.906
Pre-Dialysis	MoCA	3	198	22.03	2.96	22.05	1.66	0.3810	1.0000	11.588	3.404

HD	MoCA	9	489	23.42	3.49	23.41	0.41	0.5830	1.0000	0.922	0.960
PD	MoCA	2	139	23.76	3.15	23.84	0.76	0.6880	1.0000	1.023	1.011
Combined	MoCA	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Transplant	MoCA	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Controls	MoCA	3	238	25.00	3.20	24.99	2.43	Comparison	Comparison	22.686	4.763
Pre-Dialysis	TMT-A	16	2975	61.19	27.98	59.7	6.31	0.0040	0.0600	860.230	29.330
HD	TMT-A	41	2344	58.18	26.40	56.04	3.03	0.0001	**0.0015**	190.540	13.804
PD	TMT-A	9	859	60.90	21.06	58.01	4.73	0.0020	**0.0300**	43.300	6.580
Combined	TMT-A	5	158	43.75	10.24	43.67	4.83	0.3090	1.0000	233.290	15.274
Transplant	TMT-A	4	117	47.67	17.28	42.40	5.69	0.4750	1.0000	45.823	6.769
Controls	TMT-A	23	4809	38.77	15.10	37.62	2.59	Comparison	Comparison	104.860	10.240
Pre-Dialysis	TMT-B	16	7163	164.23	65.88	155.53	22.36	0.0350	0.3500	2149.600	46.364
HD	TMT-B	36	3348	140.55	69.30	135.60	10.22	0.0310	0.3100	3607.800	60.065
PD	TMT-B	7	949	130.96	42.69	127.12	14.09	0.1440	1.0000	579.410	24.071
Combined	TMT-B	1	20	112.45	51.99	112.45	N/A	N/A	N/A	0.000	0.000
Transplant	TMT-B	4	156	103.93	39.31	103.05	11.39	0.7410	1.0000	787.600	28.064
Controls	TMT-B	14	4481	106.15	46.74	97.06	13.55	Comparison	Comparison	1373.500	37.061

Table 3: Compiled data for all patient populations for the most commonly used assessments, with adjusted means via random effects model, taking into account study variance. Abbreviations used: The Modified Mini–Mental State Examination (3MS), The Mini–Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Trails Making Tests (TMT) forms A and B, N/R: no tests reported for that population, N/A: not enough values to perform statistical analysis. Corrected p-value were determined by a Bonferroni correction between patient populations and controls (used as the comparison group). The square root of between study variance corresponds to the heterogeneity estimate (Tau).

Table 4: Meta-Analysis Pre-Dialysis Studies

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Freedman[84]	193	3Ms	84.70	9.00	78.00[85]	N	Global
Murea[86]	478	3Ms	90.60	7.10	78.00[85]	N	Global
Murray[87]	554	3Ms	94.14	5.40	78.00[85]	N	Global
Palmer[88]	91	3Ms	83.75	9.32	78.00[85]	N	Global
Pi[89]	30	3Ms	92.60	6.20	78.00[85]	N	Global
Slinin[90]	4179	3Ms	94.10	5.00	78.00[85]	N	Global
Kurella[91]	80	3Ms	90.50	8.90	78.00[85]	N	Global
Tamura[15]	3591	3Ms	92.00	8.00	78.00[85]	N	Global
Yaffe*[92]	813	3Ms	91.60	19.60	78.00[85]	N	Global
Yaffe[93]	588	3Ms	84.00	14.30	78.00[85]	N	Global
Lee*[94]	240	Boston Naming Test	10.30	2.90	13.30[95]	Y	Language
Martini[96]	80	Boston Naming Test	7.60	2.50	13.30[95]	Y	Language
Torres[97]	146	Boston Naming Test	34.50	2.70	13.30[95]	N	Language
Yaffe[98]	273	Boston Naming Test	14.20	1.60	13.30[95]	N	Language
Murray[87]	554	COWAT	36.60	11.90	37.50[99]	Y	Language
Torres[97]	146	COWAT	36.00	11.10	37.50[99]	Y	Language
Yeh[100]	230	COWAT	31.24	8.86	37.50[99]	Y	Language
Post[101]	23	COWAT-FAS	30.30	12.10	37.50[99]	Y	Language
Szerlip[102]	437	COWAT-FAS	24.00	10.40	37.50[99]	Y	Language
Post[101]	23	CVLT-Delayed Recall	6.70	2.80	10.38[103]	Y	Memory
Kruella[91]	80	CVLT-Delayed Recall	5.50	2.20	10.38[103]	Y	Memory
Kruella[91]	80	CVLT-Immediate Recall	5.80	1.60	8.60[103]	Y	Memory
Chang[104]	39	Digit Span-Backwards	5.80	2.60	4.35[78]	N	Memory

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Hart[105]	18	Digit Span-Backwards	4.10	0.80	4.35[78]	Y	Memory
Kaya[106]	6	Digit Span-Backwards	4.33	1.50	4.35[78]	Y	Memory
Lee*[94]	240	Digit Span-Backwards	3.50	1.10	4.35[78]	Y	Memory
Paraizo[107]	72	Digit Span-Backwards	3.21	1.12	4.35[78]	Y	Memory
Seidel[108]	84	Digit Span-Backwards	5.50	1.90	4.35[78]	N	Memory
Torres[97]	146	Digit Span-Backwards	4.80	1.40	4.35[78]	N	Memory
Tsai[66]	64	Digit Span-Backwards	3.00	2.40	4.35[78]	Y	Memory
Chang[104]	39	Digit Span-Forwards	9.10	2.20	5.73[78]	N	Memory
Hart[105]	18	Digit Span-Forwards	6.00	1.30	5.73[78]	N	Memory
Kaya[106]	6	Digit Span-Forwards	6.50	0.83	5.73[78]	N	Memory
Lee*[94]	240	Digit Span-Forwards	6.60	1.35	5.73[78]	N	Memory
Paraizo[107]	72	Digit Span-Forwards	4.69	0.94	5.73[78]	Y	Memory
Seidel[108]	84	Digit Span-Forwards	6.90	1.70	5.73[78]	N	Memory
Torres[97]	146	Digit Span-Forwards	6.90	1.40	5.73[78]	N	Memory
Tsai[66]	64	Digit Span-Forwards	9.60	2.90	5.73[78]	N	Memory
Murray[87]	554	Digit Span-Unspecified	9.90	2.80	5.73[78]	N	Memory
Nasser[109]	50	Digit Span-Unspecified	6.90	1.40	5.73[78]	N	Memory
Post[101]	23	Digit Span-Unspecified	12.90	2.40	5.73[78]	N	Memory
Yeh[100]	230	Digit Span-Unspecified	17.53	4.63	5.73[78]	N	Memory

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Chen[110]	26	Digit Symbol	52.00	12.10	59.00[80]	Y	Memory + Processing Speed
Freedman[84]	188	Digit Symbol	47.30	16.90	59.00[80]	Y	Memory + Processing Speed
Hart[105]	18	Digit Symbol	40.80	12.20	59.00[80]	Y	Memory + Processing Speed
Jiang[111]	32	Digit Symbol	51.00	14.00	59.00[80]	Y	Memory + Processing Speed
Lin*[112]	2431	Digit Symbol	69.79	7.05	59.00[80]	N	Memory + Processing Speed
Luo[113]	60	Digit Symbol	58.00	22.00	59.00[80]	Y	Memory + Processing Speed
Nasser[109]	50	Digit Symbol	6.90	0.90	59.00[80]	Y	Memory + Processing Speed
Palmer[88]	91	Digit Symbol	44.22	15.91	59.00[80]	Y	Memory + Processing Speed
Pulignano[114]	52	Digit Symbol	15.90	7.80	59.00[80]	Y	Memory + Processing Speed
Souheaver[63]	24	Digit Symbol	3.29	1.46	59.00[80]	Y	Memory + Processing Speed
Torres[97]	146	Digit Symbol	46.20	12.40	59.0[80]	Y	Memory + Processing Speed
Yeh[100]	230	Digit Symbol	44.76	18.45	59.00[80]	Y	Memory + Processing Speed
Chen[110]	26	Line Tracing Test	59.00	21.00	54.50[115]	Y	Psycho-motor Speed
Jiang[111]	32	Line Tracing Test	58.00	19.00	54.50[115]	Y	Psycho-motor Speed

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Luo[113]	60	Line Tracing Test	57.00	18.00	54.50[115]	Y	Psycho-motor Speed
Afsar[116]	109	MMSE	26.30	1.90	24.00[71]	N	Global
Afsar[117]	247	MMSE	25.90	2.30	24.00[71]	N	Global
Bai*[118]	284	MMSE	21.75	0.75	24.00[71]	Y	Global
Chang[104]	39	MMSE	25.00	4.20	24.00[71]	N	Global
Driessen[119]	11	MMSE	26.60	2.20	24.00[71]	N	Global
Freedman[84]	187	MMSE	26.10	3.00	24.00[71]	N	Global
Helmer[120]	7839	MMSE	27.40	1.90	24.00[71]	N	Global
Hobson[121]	112	MMSE	25.10	4.40	24.00[71]	N	Global
Ito[122]	497	MMSE	26.70	2.00	24.00[71]	N	Global
Lee*[94]	1437	MMSE	24.55	3.25	24.00[71]	N	Global
Lee*[123]	1032	MMSE	25.80	2.68	24.00[71]	N	Global
Madan*[124]	479	MMSE	28.22	1.26	24.00[71]	N	Global
Miwa[125]	600	MMSE	28.00	1.90	24.00[71]	N	Global
Nasser[109]	50	MMSE	23.90	2.10	24.00[71]	Y	Global
Post[101]	24	MMSE	28.90	1.20	24.00[71]	N	Global
Pulignano[114]	52	MMSE	23.30	5.00	24.00[71]	Y	Global
Szerlip[102]	437	MMSE	25.50	4.00	24.00[71]	N	Global
Wang[126]	113	MMSE	13.00	7.50	24.00[71]	Y	Global
Wang[127]	59	MMSE	16.10	5.60	24.00[71]	Y	Global
Wang*[128]	1243	MMSE	28.75	0.50	24.00[71]	N	Global
Wang[129]	71	MMSE	23.05	4.05	24.00[71]	Y	Global
Weng*[130]	958	MMSE	26.33	2.10	24.00[71]	N	Global
Yao*[131]	403	MMSE	27.75	0.50	24.00[71]	N	Global
Yao[132]	560	MMSE	26.70	2.90	24.00[71]	N	Global
Yeh[100]	230	MMSE	27.53	2.21	24.00[71]	N	Global
Iyasere[133]	36	MoCA	25.00	1.00	26.00[74]	Y	Global
Palmer[88]	90	MoCA	19.27	3.73	26.00[74]	Y	Global
Paraizo[107]	72	MoCA	21.83	4.16	26.00[74]	Y	Global
Chen[110]	26	NCT-A	45.70	12.70	40.00[76]	Y	Attention+ Processing Speed

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Jiang[111]	32	NCT-A	42.00	12.00	40.00[76]	Y	Attention+ Processing Speed
Luo[113]	60	NCT-A	50.00	17.00	40.00[76]	Y	Attention+ Processing Speed
Freedman[84]	189	RAVLT-Delayed Recall	6.50	2.30	8.80[134]	Y	Memory
Palmer[88]	89	RAVLT-Delayed Recall	5.43	3.02	8.80[134]	Y	Memory
Tsai[66]	64	RAVLT-Delayed Recall	10.10	2.70	8.80[134]	N	Memory
Kaya[106]	6	RAVLT-Learning	10.67	3.14	44.00[134]	Y	Memory
Murea[86]	478	RAVLT-Learning	41.60	10.20	44.00[134]	Y	Memory
Tsai[66]	64	RAVLT-Learning	49.50	9.60	44.00[134]	N	Memory
Kaya[106]	6	RAVLT-LTM	10.50	2.07	8.80[134]	N	Memory
Seidel[108]	84	RCFT	30.40	5.00	24.50[135]	N	Attention
Kaya[106]	6	RCFT-LTM	16.50	8.24	19.75[135]	Y	Memory
Chen[110]	26	Serial Dotting Test	56.40	17.80	70.00[158]	N	Psycho-motor Speed
Jiang[111]	32	Serial Dotting Test	51.00	18.00	70.00[115]	N	Psycho-motor Speed
Luo[113]	60	Serial Dotting Test	42.00	8.00	70.00[115]	N	Psycho-motor Speed
Post[101]	22	Stroop-Color Reading	45.80	8.10	96.74[136]	Y	Executive Function
Freedman[84]	186	Stroop-Interferences	36.00	16.60	46.49[136]	Y	Executive Function
Seidel[108]	84	Stroop-Interferences	101.80	30.10	46.49[136]	N	Executive Function
Post[101]	23	Stroop-Naming	78.10	13.50	43.49[136]	N	Executive Function
Hart[105]	18	TMT-A	46.80	21.50	40.00[76]	Y	Attention+ Processing Speed

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Kaya[106]	6	TMT-A	58.17	33.05	40.00[76]	Y	Attention+ Processing Speed
Lee*[94]	240	TMT-A	84.55	50.90	40.00[76]	Y	Attention+ Processing Speed
Lee*[123]	1025	TMT-A	23.85	8.80	40.00[76]	N	Attention+ Processing Speed
Pi*[89]	30	TMT-A	46.29	4.83	40.00[76]	Y	Attention+ Processing Speed
Post[101]	24	TMT-A	59.50	24.20	40.00[76]	Y	Attention+ Processing Speed
Ryan[5]	16	TMT-A	143.23	73.00	40.00[76]	Y	Attention+ Processing Speed
Seidel[108]	84	TMT-A	47.80	22.80	40.00[76]	Y	Attention+ Processing Speed
Szerlip[102]	437	TMT-A	63.60	32.40	40.00[76]	Y	Attention+ Processing Speed
Tsai[66]	64	TMT-A	81.60	56.60	40.00[76]	Y	Attention+ Processing Speed
Tsuruya[137]	95	TMT-A	41.00	20.00	40.00[76]	Y	Attention+ Processing Speed
Yaffe[93]	588	TMT-A	77.00	13.10	40.00[76]	Y	Attention+ Processing Speed
Yeh[100]	230	TMT-A	68.02	44.82	40.00[76]	Y	Attention+ Processing Speed
Hart[105]	18	TMT-B	146.70	74.50	94.00[76]	Y	Cognitive Flexibility
Kaya[106]	6	TMT-B	105.00	29.29	94.00[76]	Y	Cognitive Flexibility

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Lee*[94]	240	TMT-B	219.10	77.60	94.00[76]	Y	Cognitive Flexibility
Lee*[123]	1024	TMT-B	48.75	19.30	94.00[76]	N	Cognitive Flexibility
Nasser[109]	50	TMT-B	413.00	79.90	94.00[76]	Y	Cognitive Flexibility
Pi*[89]	30	TMT-B	129.96	10.75	94.00[76]	Y	Cognitive Flexibility
Post[101]	22	TMT-B	157.50	56.80	94.00[76]	Y	Cognitive Flexibility
Ryan[5]	16	TMT-B	383.44	216.25	94.00[76]	Y	Cognitive Flexibility
Seidel[108]	84	TMT-B	127.80	63.80	94.00[76]	Y	Cognitive Flexibility
Slinin[90]	4179	TMT-B	126.70	52.90	94.00[76]	Y	Cognitive Flexibility
Szerlip[102]	437	TMT-B	161.30	79.00	94.00[76]	Y	Cognitive Flexibility
Kruella[91]	80	TMT-B	158.80	74.10	94.00[76]	Y	Cognitive Flexibility
Tsai[66]	64	TMT-B	124.80	75.20	94.00[76]	Y	Cognitive Flexibility
Tsuruya[137]	95	TMT-B	106.00	67.00	94.00[76]	Y	Cognitive Flexibility
Yaffe[93]	588	TMT-B	108.00	18.50	94.00[76]	Y	Cognitive Flexibility
Yeh[100]	230	TMT-B	110.78	59.20	94.00[76]	Y	Cognitive Flexibility
Palmer[88]	91	Verbal Fluency-Animal	15.31	4.55	18.10[138]	Y	Language
Paraizo[107]	72	Verbal Fluency-Animal	13.90	4.07	18.10[138]	Y	Language
Yaffe[98]	273	Verbal Fluency-Category	18.70	4.96	46.90[138]	Y	Language
Chang[104]	39	Verbal Fluency-Not Specified	11.70	3.20	28.60[138]	Y	Language
Kaya[106]	6	Verbal Fluency-Not Specified	7.83	1.47	28.60[138]	Y	Language

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Pulignano[114]	52	Verbal Fluency-Phonemic	16.40	7.60	28.60[138]	Y	Language

Table 4: All scores for patients who were Pre-Dialysis. * denotes data manipulation (median transformed to mean, range to SD). Abbreviations that appear in the table: The Modified Mini–Mental State Examination (3MS), Controlled Oral Word Associations Test (COWAT), California Verbal Learning Test (CVLT), The Mini–Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Number Connection Test- A (NCT-A), Rey Auditory Verbal Learning Test (RAVLT), Rey–Osterrieth Complex Figure Test (RCFT), and Trails Making Tests (TMT) forms A and B. Impairment (Y/N) based off the mean cut off value reported in literature indicated in the cut-off column. Impairment (Y/N) is at an individual study level.

Table 5: Meta-Analysis Hemodialysis (HD) Studies

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Dixon[139]	18	3Ms	88.10	5.70	78.00[85]	N	Global
Kalirao[140]	338	3Ms	88.30	8.60	78.00[85]	N	Global
McAdams-DeMarco[141]	323	3Ms	89.80	7.60	78.00[85]	N	Global
Pi[89]	30	3Ms	87.80	10.30	78.00[85]	N	Global
Shavit[142]	56	3Ms	73.20	23.00	78.00[85]	Y	Global
Tamura*[143]	383	3Ms	89.25	1.83	78.00[85]	N	Global
Kruella[91]	80	3Ms	83.70	12.40	78.00[85]	N	Global
Tamura[144]	332	3Ms	88.50	8.00	78.00[85]	N	Global
Jassal[145]	14	Boston Naming Test	54.60	4.10	13.30[95]	N	Language
Tiffin-Richards[61]	41	Boston Naming Test	14.00	9.00	13.30[95]	N	Language
Kalirao[140]	338	BVMT-R - Delayed Recall	4.70	3.00	8.95[146]	Y	Memory
Murray[147]	28	BVMT-R-Delayed Recall	4.70	0.63	8.95[146]	Y	Memory
Brown[148]	14	COWAT	45.10	15.50	37.50[99]	N	Language
Jassal[145]	14	COWAT	38.90	15.60	37.50[99]	N	Language
Kalirao[140]	338	COWAT	26.40	11.10	37.50[99]	Y	Language
Marsh[149]	18	COWAT	40.50	15.60	37.50[99]	N	Language
Murray[147]	28	COWAT	23.50	1.63	37.50[99]	Y	Language
Oaksford[150]	11	COWAT	34.46	12.21	37.50[99]	Y	Language
Pliskin[151]	16	COWAT	36.80	7.60	37.50[99]	Y	Language
Sarnak[152]	167	COWAT	35.90	11.10	37.50[99]	Y	Language
Tamura[153]	116	COWAT	34.10	13.50	37.50[99]	Y	Language
Wolfgram[154]	39	COWAT	43.10	10.10	37.50[99]	N	Language
Drew[155]	117	COWAT-Animals	16.20	6.00	16.90[99]	Y	Language
Post[101]	27	COWAT-FAS	25.40	9.90	37.50[99]	Y	Language
George[156]	35	COWAT-FAS	36.00	15.00	37.50[99]	Y	Language

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Post[101]	27	CVLT-Delayed Recall	6.60	3.30	10.38[103]	Y	Memory
Tiffin-Richards[61]	41	CVLT-Delayed Recall	11.00	6.00	10.38[103]	N	Memory
Kruella[91]	80	CVLT-Delayed Recall	4.60	2.30	10.38[103]	Y	Memory
Kruella[91]	80	CVLT-Immediate Recall	5.20	1.30	8.60[103]	Y	Memory
Tiffin-Richards[61]	41	CVLT-Immediate Recall	9.00	6.00	8.60[103]	N	Memory
Drew[155]	116	Digit Span-Backwards	5.80	2.50	4.35[78]	N	Memory
George[156]	35	Digit Span-Backwards	4.00	1.00	4.35[78]	Y	Memory
Hart[105]	24	Digit Span-Backwards	4.70	1.10	4.35[78]	N	Memory
Kaya[106]	28	Digit Span-Backwards	3.64	0.73	4.35[78]	Y	Memory
Seidel[108]	35	Digit Span-Backwards	5.70	1.70	4.35[78]	N	Memory
Tiffin-Richards[61]	41	Digit Span-Backwards	6.00	2.00	4.35[78]	N	Memory
Drew[155]	116	Digit Span-Forwards	9.90	2.40	5.73[78]	N	Memory
Hart[105]	24	Digit Span-Forwards	5.80	1.00	5.73[78]	N	Memory
Kaya[106]	28	Digit Span-Forwards	5.36	1.09	5.73[78]	Y	Memory
Seidel[108]	35	Digit Span-Forwards	6.90	1.90	5.73[78]	N	Memory
Tiffin-Richards[61]	41	Digit Span-Forwards	7.00	2.00	5.73[78]	N	Memory
Anwar[157]	50	Digit Span-Unspecified	3.90	1.50	5.73[78]	Y	Memory

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Gallai[158]	20	Digit Span-Unspecified	6.90	1.50	5.73[78]	N	Memory
Jassal[145]	14	Digit Span-Unspecified	10.30	2.90	5.73[78]	N	Memory
Kalirao[140]	338	Digit Span-Unspecified	14.80	3.70	5.73[78]	N	Memory
Nasser[109]	51	Digit Span-Unspecified	8.20	2.10	5.73[78]	N	Memory
Oaksford[150]	11	Digit Span-Unspecified	11.18	3.09	5.73[78]	N	Memory
O'Conner[159]	73	Digit Span-Unspecified	10.73	3.13	5.73[78]	N	Memory
Pliskin[151]	16	Digit Span-Unspecified	7.70	2.00	5.73[78]	N	Memory
Post[101]	27	Digit Span-Unspecified	12.40	3.30	5.73[78]	N	Memory
Ranter[160]	20	Digit Span-Unspecified	6.70	1.50	5.73[78]	N	Memory
Sarnak[152]	165	Digit Span-Unspecified	15.20	3.90	5.73[78]	N	Memory
Umans[161]	10	Digit Span-Unspecified	10.60	4.20	5.73[78]	N	Memory
Wolfgram[154]	39	Digit Span-Unspecified	8.10	2.70	5.73[78]	N	Memory
Chen[110]	32	Digit Symbol	48.60	15.10	59.00[80]	Y	Memory + Processing Speed
Chen[162]	25	Digit Symbol	59.60	10.80	59.00[80]	N	Memory + Processing Speed
Drew[155]	282	Digit Symbol	40.10	17.00	59.00[80]	Y	Memory + Processing Speed
George[156]	32	Digit Symbol	37.00	16.30	59.00[80]	Y	Memory + Processing Speed
Giang[163]	282	Digit Symbol	40.10	17.00	59.00[80]	Y	Memory + Processing Speed

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Hart[105]	24	Digit Symbol	47.00	8.90	59.00[80]	Y	Memory + Processing Speed
Jassal[145]	14	Digit Symbol	9.80	2.80	59.00[80]	Y	Memory + Processing Speed
Jiang[111]	33	Digit Symbol	57.00	14.00	59.00[80]	Y	Memory + Processing Speed
Kong[164]	80	Digit Symbol	54.70	13.90	59.00[80]	Y	Memory + Processing Speed
Nasser[109]	51	Digit Symbol	7.80	1.90	59.00[80]	Y	Memory + Processing Speed
Pereira[165]	25	Digit Symbol	7.70	3.10	59.00[80]	Y	Memory + Processing Speed
Pliskin[151]	16	Digit Symbol	6.60	2.00	59.00[80]	Y	Memory + Processing Speed
Ranter[160]	20	Digit Symbol	7.40	1.90	59.00[80]	Y	Memory + Processing Speed
Tamura[166]	59	Digit Symbol	49.10	19.00	59.00[80]	Y	Memory + Processing Speed
Tamura[166]	141	Digit Symbol	49.90	17.50	59.00[80]	Y	Memory + Processing Speed
Weiner[167]	200	Digit Symbol	7.00	2.60	59.00[80]	Y	Memory + Processing Speed
Chen[110]	32	Line Tracing Test	61.80	22.60	54.50[115]	Y	Psycho-motor Speed
Chen[162]	25	Line Tracing Test	54.20	15.10	54.50[115]	N	Psycho-motor Speed
Jiang[111]	33	Line Tracing Test	47.00	13.00	54.50[115]	N	Psycho-motor Speed

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Anwar[157]	50	MMSE	28.40	7.00	24.00[71]	N	Global
Asfar[168]	135	MMSE	22.00	5.10	24.00[71]	Y	Global
Asfar[169]	65	MMSE	25.00	2.92	24.00[71]	N	Global
Badzek[170]	142	MMSE	24.13	4.39	24.00[71]	N	Global
Bae[171]	15	MMSE	28.70	1.10	24.00[71]	N	Global
Bossola[172]	110	MMSE	23.40	3.60	24.00[71]	Y	Global
Bossola[173]	100	MMSE	25.60	3.40	24.00[71]	N	Global
Chai[174]	42	MMSE	28.00	2.10	24.00[71]	N	Global
Chiu[175]	162	MMSE	24.60	3.80	24.00[71]	N	Global
Costa[176]	47	MMSE	27.40	4.60	24.00[71]	N	Global
Cukor[177]	25	MMSE	27.40	1.70	24.00[71]	N	Global
da Silva[178]	75	MMSE	24.16	4.49	24.00[71]	N	Global
Dahbour[179]	54	MMSE	26.50	2.70	24.00[71]	N	Global
Dixit[180]	30	MMSE	25.80	2.20	24.00[71]	N	Global
Drew[155]	292	MMSE	26.70	2.80	24.00[71]	N	Global
Driessen[119]	28	MMSE	26.50	1.70	24.00[71]	N	Global
Fadili[181]	108	MMSE	25.58	5.58	24.00[71]	N	Global
Fazeka[182]	30	MMSE	22.90	4.00	24.00[71]	Y	Global
Gallai[158]	20	MMSE	25.80	2.10	24.00[71]	N	Global
Gencoz[183]	45	MMSE	26.89	2.48	24.00[71]	N	Global
Grimm[184]	15	MMSE	27.60	2.20	24.00[71]	N	Global
Harciarek[185]	23	MMSE	28.91	1.04	24.00[71]	N	Global
Hsieh[186]	27	MMSE	26.40	3.60	24.00[71]	N	Global
Huertas-Vieco[187]	35	MMSE	26.48	5.30	24.00[71]	N	Global
Jones[188]	36	MMSE	27.30	2.30	24.00[71]	N	Global
Jung[189]	29	MMSE	26.10	3.10	24.00[71]	N	Global
Kim[190]	95	MMSE	27.00	2.60	24.00[71]	N	Global
Kitaguchi*[191]	30	MMSE	27.25	2.35	24.00[71]	N	Global
Kobayashi*[192]	61	MMSE	23.67	5.25	24.00[71]	Y	Global
Kramer[193]	15	MMSE	28.50	2.00	24.00[71]	N	Global
Li C.[194]	20	MMSE	29.20	0.80	24.00[71]	N	Global
Lux[195]	12	MMSE	29.10	1.00	24.00[71]	N	Global
Maugeri[20]	39	MMSE	23.50	1.80	24.00[71]	Y	Global

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Murray[147]	28	MMSE	26.60	0.51	24.00[71]	N	Global
Nasser[109]	50	MMSE	26.50	1.50	24.00[71]	N	Global
O'Conner[159]	73	MMSE	29.44	0.80	24.00[71]	N	Global
Pereira[165]	25	MMSE	27.50	2.30	24.00[71]	N	Global
Post[101]	27	MMSE	28.10	1.80	24.00[71]	N	Global
Prelevic[196]	93	MMSE	21.60	4.70	24.00[71]	Y	Global
Sarnak[152]	314	MMSE	26.70	2.80	24.00[71]	N	Global
Sithinamsuwan[197]	60	MMSE	26.73	2.43	24.00[71]	N	Global
Sorensen[198]	168	MMSE	26.40	2.80	24.00[71]	N	Global
Soysal[199]	121	MMSE	20.50	4.47	24.00[71]	Y	Global
Tasmoc[200]	72	MMSE	25.13	3.47	24.00[71]	N	Global
Tholen[201]	26	MMSE	27.27	1.85	24.00[71]	N	Global
Tholen[202]	26	MMSE	27.27	1.85	24.00[71]	N	Global
Tiffin-Richards[61]	43	MMSE	29.00	2.00	24.00[71]	N	Global
Tilki[203]	25	MMSE	26.00	1.50	24.00[71]	N	Global
Weiner[167]	125	MMSE	26.90	2.70	24.00[71]	N	Global
Zhang[204]	26	MMSE	26.61	3.58	24.00[71]	N	Global
Angermann[205]	151	MoCA	24.09	3.93	26.00[74]	Y	Global
Costa[176]	40	MoCA	23.90	4.60	26.00[74]	Y	Global
Dasgupta[206]	100	MoCA	21.00	4.80	26.00[74]	Y	Global
Iyasere[133]	41	MoCA	23.26	1.75	26.00[74]	Y	Global
Li P. [207]	25	MoCA	23.90	2.50	26.00[74]	Y	Global
Tholen[201]	26	MoCA	23.88	3.21	26.00[74]	Y	Global
Tholen[202]	26	MoCA	24.96	2.84	26.00[74]	Y	Global
Tiffin-Richards[61]	41	MoCA	24.00	4.00	26.00[74]	Y	Global
Wolfgram[154]	39	MoCA	21.80	3.80	26.00[74]	Y	Global
Brown[148]	14	NCT-A	91.80	34.10	40.00[76]	Y	Attention+ Processing Speed
Chen[110]	32	NCT-A	55.60	15.70	40.00[76]	Y	Attention+ Processing Speed

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Chen[162]	25	NCT-A	34.80	8.90	40.00[76]	N	Attention+ Processing Speed
Gallai[158]	20	NCT-A	79.10	29.00	40.00[76]	Y	Attention+ Processing Speed
Jiang[111]	33	NCT-A	42.00	14.00	40.00[76]	Y	Attention+ Processing Speed
Kong[164]	80	NCT-A	42.50	17.10	40.00[76]	Y	Attention+ Processing Speed
Smith[208]	29	NCT-A	80.65	44.60	40.00[76]	Y	Attention+ Processing Speed
Wolcott[19]	14	NCT-A	115.20	47.50	40.00[76]	Y	Attention+ Processing Speed
Oaksford[150]	11	RAVLT-1	7.45	2.81	8.80[134]	Y	Memory
Wolcott[19]	14	RAVLT-1	5.10	2.60	8.80[134]	Y	Memory
Musolino[209]	16	RAVLT-Delayed Recall	35.50	3.00	8.80[134]	N	Memory
Tamura[153]	126	RAVLT-Delayed Recall	8.50	3.70	8.80[134]	Y	Memory
Temple[210]	9	RAVLT-Delayed Recall	6.90	2.90	8.80[134]	Y	Memory
Temple[211]	8	RAVLT-Delayed Recall	7.80	3.60	8.80[134]	Y	Memory
Brown[148]	14	RAVLT-Learning	44.70	15.30	44.00[134]	N	Memory
Griva[212]	77	RAVLT-Learning	39.36	11.94	44.00[134]	Y	Memory
Kaya[106]	28	RAVLT-Learning	10.36	1.89	44.00[134]	Y	Memory
Lux[195]	12	RAVLT-Learning	50.10	10.30	44.00[134]	N	Memory
Lux[195]	12	RAVLT-Learning	49.00	7.00	44.00[134]	N	Memory

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Marsh[149]	18	RAVLT-Learning	43.20	14.70	44.00[134]	Y	Memory
Tamura[153]	126	RAVLT-Learning	40.60	11.00	44.00[134]	Y	Memory
Temple[211]	8	RAVLT-Learning	5.00	1.30	44.00[134]	Y	Memory
Kaya[106]	28	RAVLT-LTM	8.68	2.16	8.80[134]	Y	Memory
Seidel[108]	35	RCFT	29.60	5.10	24.50[135]	N	Attention
Kaya[106]	28	RCFT-LTM	15.63	6.68	19.75[135]	Y	Memory
Oaksford[150]	11	RCFT-Task1	18.95	7.47	24.50[135]	Y	Attention
Chen[110]	32	Serial Dotting Test	51.80	10.50	70.00[115]	N	Psycho-motor Speed
Chen[162]	25	Serial Dotting Test	49.20	10.60	70.00[115]	N	Psycho-motor Speed
Jiang[111]	33	Serial Dotting Test	52.00	19.00	70.00[115]	N	Psycho-motor Speed
Post[101]	26	Stroop-Color Reading	49.90	11.60	96.74[136]	N	Executive Function
Tiffin-Richards[61]	41	Stroop-Color Reading	35.00	14.00	96.74[136]	N	Executive Function
Umans[161]	10	Stroop-Color Reading	47.80	18.50	96.74[136]	N	Executive Function
Kalirao[140]	338	Stroop-Interference	110.40	43.20	46.49[136]	Y	Executive Function
Seidel[108]	35	Stroop-Interference	95.70	25.20	46.49[136]	Y	Executive Function
Tiffin-Richards[61]	41	Stroop-Interference	96.00	49.00	46.49[136]	Y	Executive Function
Post[101]	27	Stroop-Naming	68.40	11.70	43.49[136]	Y	Executive Function
Tiffin-Richards[61]	41	Stroop-Naming	54.00	17.00	43.49[136]	Y	Executive Function
Umans[161]	10	Stroop-Naming	63.00	12.60	43.49[136]	Y	Executive Function

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Anwar[157]	50	TMT-A	97.00	41.00	40.00[76]	Y	Attention+ Processing Speed
Brown[148]	14	TMT-A	51.60	40.90	40.00[76]	Y	Attention+ Processing Speed
Costa[176]	40	TMT-A	60.30	38.30	40.00[76]	Y	Attention+ Processing Speed
Drew[155]	292	TMT-A	61.30	39.00	40.00[76]	Y	Attention+ Processing Speed
Grimm[184]	15	TMT-A	55.00	39.00	40.00[76]	Y	Attention+ Processing Speed
Griva[212]	77	TMT-A	53.73	37.32	40.00[76]	Y	Attention+ Processing Speed
Hart[105]	24	TMT-A	31.20	10.10	40.00[76]	N	Attention+ Processing Speed
Jassal[145]	14	TMT-A	21.30	7.20	40.00[76]	N	Attention+ Processing Speed
Kaya[106]	28	TMT-A	72.39	31.38	40.00[76]	Y	Attention+ Processing Speed
Kramer[193]	15	TMT-A	34.00	10.00	40.00[76]	N	Attention+ Processing Speed
Lux[195]	12	TMT-A	34.70	13.20	40.00[76]	N	Attention+ Processing Speed
McAdams-DeMarco[141]	320	TMT-A	55.40	29.00	40.00[76]	Y	Attention+ Processing Speed
Pi*[89]	30	TMT-A	64.76	7.97	40.00[76]	Y	Attention+ Processing Speed

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Pliskin[151]	8	TMT-A	63.62	30.02	40.00[76]	Y	Attention+ Processing Speed
Post[101]	27	TMT-A	64.70	24.80	40.00[76]	Y	Attention+ Processing Speed
Radić[213]	65	TMT-A	53.54	25.50	40.00[76]	Y	Attention+ Processing Speed
Ranter[160]	20	TMT-A	53.40	18.50	40.00[76]	Y	Attention+ Processing Speed
Ryan*[5]	16	TMT-A	59.50	21.00	40.00[76]	Y	Attention+ Processing Speed
Sarnak[152]	293	TMT-A	61.30	39.60	40.00[76]	Y	Attention+ Processing Speed
Schneider[214]	28	TMT-A	38.89	5.94	40.00[76]	Y	Attention+ Processing Speed
Seidel[108]	35	TMT-A	41.10	14.60	40.00[76]	Y	Attention+ Processing Speed
Shavit[142]	56	TMT-A	79.00	19.00	40.00[76]	Y	Attention+ Processing Speed
Sorensen[198]	146	TMT-A	63.00	44.00	40.00[76]	Y	Attention+ Processing Speed
Tamura[153]	120	TMT-A	46.70	22.50	40.00[76]	Y	Attention+ Processing Speed
Tasmoc[200]	72	TMT-A	103.77	53.13	40.00[76]	Y	Attention+ Processing Speed
Temple*[211]	8	TMT-A	60.50	24.54	40.00[76]	Y	Attention+ Processing Speed

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Tiffin-Richards[61]	43	TMT-A	51.00	38.00	40.00[76]	Y	Attention+ Processing Speed
Umans[161]	10	TMT-A	68.50	48.10	40.00[76]	Y	Attention+ Processing Speed
Weiner[167]	125	TMT-A	49.50	26.60	40.00[76]	Y	Attention+ Processing Speed
Wolcott[19]	14	TMT-A	57.90	28.70	40.00[76]	Y	Attention+ Processing Speed
Wolcott[215]	15	TMT-A	51.50	N/A	40.00[76]	Y	Attention+ Processing Speed
Wolfgram[154]	39	TMT-A	40.60	10.90	40.00[76]	Y	Attention+ Processing Speed
Zhang[204]	26	TMT-A	42.83	5.21	40.00[76]	Y	Attention+ Processing Speed
Anwar[157]	50	TMT-B	194.00	72.00	94.00[76]	Y	Cognitive Flexibility
Brickman[216]	380	TMT-B	120.10	64.80	94.00[76]	Y	Cognitive Flexibility
Brown[148]	14	TMT-B	109.10	56.90	94.00[76]	Y	Cognitive Flexibility
Costa[176]	40	TMT-B	141.30	90.90	94.00[76]	Y	Cognitive Flexibility
Drew[155]	292	TMT-B	136.90	64.70	94.00[76]	Y	Cognitive Flexibility
Griva[212]	77	TMT-B	97.92	51.72	94.00[76]	Y	Cognitive Flexibility
Hart[105]	24	TMT-B	92.80	47.40	94.00[76]	N	Cognitive Flexibility
Jassal[145]	14	TMT-B	57.70	17.00	94.00[76]	N	Cognitive Flexibility
Kaya[106]	28	TMT-B	142.46	49.61	94.00[76]	Y	Cognitive Flexibility

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Lux[195]	12	TMT-B	85.80	25.90	94.00[76]	N	Cognitive Flexibility
Marsh[149]	24	TMT-B	114.40	57.50	94.00[76]	Y	Cognitive Flexibility
McAdams-DeMarco[141]	314	TMT-B	161.00	83.00	94.00[76]	Y	Cognitive Flexibility
Nasser[109]	50	TMT-B	316.00	51.30	94.00[76]	Y	Cognitive Flexibility
Neumann[217]	163	TMT-B	101.50	25.60	94.00[76]	Y	Cognitive Flexibility
O'Conner[159]	73	TMT-B	35.21	15.74	94.00[76]	N	Cognitive Flexibility
Pi*[89]	30	TMT-B	189.54	18.00	94.00[76]	Y	Cognitive Flexibility
Pliskin[151]	8	TMT-B	237.00	209.78	94.00[76]	Y	Cognitive Flexibility
Post[101]	27	TMT-B	169.60	93.60	94.00[76]	Y	Cognitive Flexibility
Ryan*[5]	16	TMT-B	165.55	69.50	94.00[76]	Y	Cognitive Flexibility
Sarnak[152]	289	TMT-B	136.90	64.70	94.00[76]	Y	Cognitive Flexibility
Schneider[214]	28	TMT-B	38.79	7.59	94.00[76]	N	Cognitive Flexibility
Seidel[108]	35	TMT-B	115.40	48.10	94.00[76]	Y	Cognitive Flexibility
Sorensen[198]	114	TMT-B	136.00	63.00	94.00[76]	Y	Cognitive Flexibility
Tamura*[143]	383	TMT-B	177.00	48.33	94.00[76]	Y	Cognitive Flexibility
Kurella[91]	80	TMT-B	218.40	83.90	94.00[76]	Y	Cognitive Flexibility
Tamura[153]	118	TMT-B	127.20	68.80	94.00[76]	Y	Cognitive Flexibility
Tamura[166]	180	TMT-B	162.40	97.20	94.00[76]	Y	Cognitive Flexibility
Tamura[166]	141	TMT-B	130.80	69.80	94.00[76]	Y	Cognitive Flexibility
Tasmoc[200]	72	TMT-B	214.93	112.25	94.00[76]	Y	Cognitive Flexibility

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Tiffin-Richards[61]	43	TMT-B	110.50	96.00	94.00[76]	Y	Cognitive Flexibility
Umans[161]	10	TMT-B	313.00	318.00	94.00[76]	Y	Cognitive Flexibility
Weiner[167]	125	TMT-B	122.50	62.70	94.00[76]	Y	Cognitive Flexibility
Wolcott[19]	14	TMT-B	163.50	94.00	94.00[76]	Y	Cognitive Flexibility
Wolcott[215]	15	TMT-B	108.90	N/A	94.00[76]	Y	Cognitive Flexibility
Wolfgram[154]	39	TMT-B	39.50	11.40	94.00[76]	N	Cognitive Flexibility
Zhang[204]	26	TMT-B	76.17	14.84	94.00[76]	N	Cognitive Flexibility
Wolfgram[154]	39	Verbal Fluency-Animal	46.40	9.70	18.10[138]	N	Language
Lux[195]	9	Verbal Fluency-Category	53.00	8.40	46.90[138]	N	Language
Kaya[106]	28	Verbal Fluency-Not Specified	6.64	1.66	28.60[138]	Y	Language

Table 5: All scores for patients receiving HD. * denotes data manipulation (median transformed to mean, range to SD). Abbreviations that appear in the table: The Modified Mini–Mental State Examination (3MS), Brief Visuospatial Memory Test-Revised (BVMT-R), Controlled Oral Word Associations Test (COWAT), California Verbal Learning Test (CVLT), The Mini–Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Number Connection Test- A (NCT-A), Rey Auditory Verbal Learning Test (RAVLT), Rey–Osterrieth Complex Figure Test (RCFT), and Trails Making Tests (TMT) forms A and B. Impairment (Y/N) based off the mean cut off value reported in literature indicated in the cut-off column. Impairment (Y/N) is at an individual study level.

Table 6: Meta-Analysis Peritoneal Dialysis (PD) Studies

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Dong[218]	458	3Ms	86.70	11.40	78.00[85]	N	Global
Kalirao[140]	51	3Ms	93.00	6.70	78.00[85]	N	Global
Li Y.*[219]	445	3Ms	87.25	3.25	78.00[85]	N	Global
Pi[89]	30	3Ms	87.10	8.70	78.00[85]	N	Global
Kalirao[140]	51	BVMT-R Delayed Recall	6.40	3.60	8.95[146]	Y	Memory
Kalirao[140]	51	COWAT	28.80	11.70	37.50[99]	Y	Language
George[156]	22	COWAT-FAS	32.50	15.50	37.50[99]	Y	Language
George[156]	22	Digit Span-Backwards	4.00	1.30	4.35[78]	Y	Memory
Kaya[106]	6	Digit Span-Backwards	5.17	1.83	4.35[78]	N	Memory
Kaya[106]	6	Digit Span-Forwards	5.83	1.47	5.73[78]	N	Memory
Kalirao[140]	51	Digit Span-Unspecified	16.70	3.50	5.73[78]	N	Memory
George[156]	19	Digit Symbol	40.00	19.00	59.00[80]	Y	Memory + Processing Speed
Jiang[111]	32	Digit Symbol	57.00	11.00	59.00[80]	Y	Memory + Processing Speed
Luo[113]	24	Digit Symbol	52.00	12.00	59.00[80]	Y	Memory + Processing Speed
Jiang[111]	32	Line Tracing Test	55.00	24.00	54.50[115]	Y	Psycho-motor Speed
Luo[113]	24	Line Tracing Test	58.00	22.00	54.50[115]	Y	Psycho-motor Speed
Cukor[177]	6	MMSE	28.12	1.20	24.00[71]	N	Global
Isshiki[220]	18	MMSE	28.00	3.00	24.00[71]	N	Global
Jung[189]	27	MMSE	27.80	2.90	24.00[71]	N	Global
Li J*[221]	81	MMSE	24.25	2.00	24.00[71]	N	Global
Shea[222]	151	MMSE	27.00	4.00	24.00[71]	N	Global
Sithinamsuwan[197]	30	MMSE	27.40	2.18	24.00[71]	N	Global

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Tilki[203]	17	MMSE	29.00	0.30	24.00[71]	N	Global
Iyasere[133]	25	MoCA	24.52	1.00	26.00[74]	N	Global
Shea[222]	114	MoCA	23.00	5.30	26.00[74]	Y	Global
Jiang[111]	32	NCT-A	40.00	11.00	40.00[76]	N	Attention + Processing Speed
Luo[113]	24	NCT-A	41.00	14.00	40.00[76]	Y	Attention + Processing Speed
Wolcott[19]	17	NCT-A	83.50	28.00	40.00[76]	Y	Attention + Processing Speed
Kaya[106]	6	RAVLT-Learning	13.17	1.60	44.00[134]	Y	Memory
Kaya[106]	6	RAVLT-LTM	10.67	1.51	8.80[134]	N	Memory
Kaya[106]	6	RCFT-LTM	24.67	4.50	19.75[135]	N	Memory
Jiang[111]	32	Serial Dotting Test	48.00	13.00	70.00[115]	N	Psycho-motor Speed
Luo[113]	24	Serial Dotting Test	51.00	16.00	70.00[115]	N	Psycho-motor Speed
Kalirao[140]	51	Stroop-Interference	84.40	27.70	46.49[136]	Y	Executive Function
Dong[218]	220	TMT-A	64.25	6.50	40.00[76]	Y	Attention + Processing Speed
Griva[212]	68	TMT-A	50.49	25.98	40.00[76]	Y	Attention + Processing Speed
Kaya[106]	6	TMT-A	80.83	54.84	40.00[76]	Y	Attention + Processing Speed
Li Y.* [219]	445	TMT-A	67.25	11.53	40.00[76]	Y	Attention + Processing Speed
Pi*[89]	30	TMT-A	67.80	6.67	40.00[76]	Y	Attention + Processing Speed
Wolcott[19]	17	TMT-A	53.00	31.00	40.00[76]	Y	Attention + Processing Speed
Dong*[218]	220	TMT-B	145.00	19.67	94.00[76]	Y	Cognitive

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
							Flexibility
Griva[212]	68	TMT-B	99.32	44.74	94.00[76]	Y	Cognitive Flexibility
Kaya[106]	6	TMT-B	167.33	118.94	94.00[76]	Y	Cognitive Flexibility
Li Y.* [219]	445	TMT-B	159.50	31.00	94.00[76]	Y	Cognitive Flexibility
Neumann[217]	163	TMT-B	83.60	40.00	94.00[76]	N	Cognitive Flexibility
Pi*[89]	30	TMT-B	169.66	12.17	94.00[76]	Y	Cognitive Flexibility
Wolcott[19]	17	TMT-B	92.30	32.30	94.00[76]	N	Cognitive Flexibility
Wolcott[19]	17	Verbal Fluency-Animal	6.50	1.50	18.10[138]	Y	Language
Kaya[106]	6	Verbal Fluency-Not Specified	8.17	1.94	28.60[138]	Y	Language

Table 6: All scores for patients receiving PD. * denotes data manipulation (median transformed to mean, range to SD). Abbreviations that appear in the table: The Modified Mini–Mental State Examination (3MS), Brief Visuospatial Memory Test-Revised (BVMT-R), Controlled Oral Word Associations Test (COWAT), The Mini–Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Number Connection Test- A (NCT-A), Rey Auditory Verbal Learning Test (RAVLT), Rey–Osterrieth Complex Figure Test (RCFT), and Trails Making Tests (TMT) forms A and B. Impairment (Y/N) based off the mean cut off value reported in literature indicated in the cut-off column. Impairment (Y/N) is at an individual study level.

Table 7: Meta-Analysis Combined Modalities (HD and PD Not Separated) Studies

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Harciarek[223]	20	BVMT-R-Delayed Recall	9.05	2.37	8.95[146]	N	Memory
Harciarek[223]	20	Digit Span-Backwards	5.15	1.42	4.35[78]	N	Memory
Harciarek[223]	20	Digit Span-Forwards	5.80	1.40	5.73[78]	Y	Memory
Harciarek[223]	20	Digit Symbol	35.20	9.51	59.00[80]	Y	Memory + Processing Speed
Liang[224]	17	Digit Symbol	52.40	10.38	59.00[80]	Y	Memory + Processing Speed
Ni[225]	24	Digit Symbol	57.00	8.67	59.00[80]	Y	Memory + Processing Speed
Zhang[226]	33	Digit Symbol	55.00	9.71	59.00[80]	Y	Memory + Processing Speed
Liang[224]	17	Line Tracing Test	68.43	26.30	54.50[115]	Y	Psycho-motor Speed
Ni[225]	24	Line Tracing Test	53.37	16.49	54.50[115]	N	Psycho-motor Speed
Zhang[226]	33	Line Tracing Test	52.82	18.92	54.50[115]	N	Psycho-motor Speed
Asfar[227]	174	MMSE	26.00	2.18	24.00[71]	N	Global
Frasnelli[228]	64	MMSE	28.40	0.30	24.00[71]	N	Global
Harciarek[229]	49	MMSE	28.57	0.98	24.00[71]	N	Global
Lee[230]	60	MMSE	27.32	2.39	24.00[71]	N	Global
Tyrrell[231]	51	MMSE	22.98	3.00	24.00[71]	Y	Global
Liang[224]	17	NCT-A	37.80	9.78	40.00[76]	N	Attention+ Processing Speed
Ni[225]	24	NCT-A	36.00	6.87	40.00[76]	N	Attention+ Processing Speed
Zhang[226]	33	NCT-A	35.00	8.35	40.00[76]	N	Attention+ Processing Speed
Harciarek[223]	20	RAVLT-Delayed Recall	9.65	2.66	8.80[134]	N	Memory
Harciarek[223]	20	RAVLT-	47.30	6.63	44.00[134]	N	Memory

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
		Learning					
Harciarek[223]	20	RCFT	34.80	1.50	24.50[135]	N	Memory
Harciarek[223]	20	RCFT-Delayed Recall	19.42	4.73	19.75[135]	Y	Memory
Liang[224]	17	Serial Dotting Test	60.86	25.08	70.00[115]	N	Psycho-motor Speed
Ni[225]	24	Serial Dotting Test	53.36	15.08	70.00[115]	N	Psycho-motor Speed
Zhang[226]	33	Serial Dotting Test	55.33	17.05	70.00[115]	N	Psycho-motor Speed
Frasnelli[228]	64	TMT-A	59.30	4.80	40.00[76]	Y	Attention+ Processing Speed
Harciarek[223]	20	TMT-A	50.63	21.38	40.00[76]	Y	Attention+ Processing Speed
Harciarek[223]	20	TMT-B	112.45	51.99	94.00[76]	Y	Cognitive Flexibility

Table 7: All scores for combined modalities. Combined modalities indicates the study did not distinguish between PD and HD. Abbreviations that appear in the table: Brief Visuospatial Memory Test-Revised (BVMT-R), The Mini–Mental State Examination (MMSE), Number Connection Test- A (NCT-A), Rey Auditory Verbal Learning Test (RAVLT), Rey–Osterrieth Complex Figure Test (RCFT), and Trails Making Tests (TMT) forms A and B. Impairment (Y/N) based off the mean cut off value reported in literature indicated in the cut-off column. Impairment (Y/N) is at an individual study level.

Table 8: Meta-Analysis Transplant Studies

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Dixon[139]	28	3Ms	82.90	15.60	78.00[85]	N	Global
Harciarek[223]	22	BVMT-R-Delayed Recall	8.68	2.26	8.95[146]	Y	Memory
Sharma[232]	44	COWAT	36.20	12.90	37.50[99]	Y	Language
Harciarek[223]	22	Digit Span-Backwards	5.41	1.59	4.35[78]	N	Memory
Kaya*[106]	40	Digit Span-Backwards	4.72	1.11	4.35[78]	N	Memory
Sharma[232]	44	Digit Span-Backwards	7.20	2.50	4.35[78]	N	Memory
Harciarek[223]	22	Digit Span-Forwards	6.00	1.75	5.73[78]	N	Memory
Kaya*[106]	40	Digit Span-Forwards	6.07	1.03	5.73[78]	N	Memory
Sharma[232]	44	Digit Span-Forwards	10.20	2.50	5.73[78]	N	Memory
Anwar[157]	50	Digit Span-Unspecified	7.50	1.50	5.73[78]	N	Memory
Gupta[233]	11	Digit Span-Unspecified	9.80	2.50	5.73[78]	N	Memory
Gupta[233]	11	Digit Symbol	47.70	10.90	59.00[80]	Y	Memory + Processing Speed
Harciarek[223]	22	Digit Symbol	36.50	8.66	59.00[80]	Y	Memory + Processing Speed
Anwar[157]	50	MMSE	30.00	1.30	24.00[71]	N	Global
Driessen[119]	20	MMSE	27.20	1.20	24.00[71]	N	Global
Gupta[233]	11	MMSE	28.20	2.60	24.00[71]	N	Global
Harciarek[223]	22	MMSE	28.41	1.18	24.00[71]	N	Global
Sharma[232]	44	MMSE	28.00	2.00	24.00[71]	N	Global
Harciarek[223]	22	RAVLT-Delayed Recall	9.41	2.28	8.80[134]	N	Memory
Harciarek[223]	22	RAVLT-Learning	47.41	8.31	44.00[134]	N	Memory
Kaya*[106]	40	RAVLT-Learning	13.31	1.49	44.00[134]	Y	Memory
Kaya*[106]	40	RAVLT-	11.49	1.59	8.80[134]	N	Memory

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
		LTM					
Harciarek[223]	22	RCFT	35.25	1.35	24.50[135]	N	Memory
Sharma[232]	44	RCFT	32.20	4.20	24.50[135]	N	Memory
Harciarek[223]	22	RCFT-Delayed Recall	20.75	5.79	19.75[135]	N	Memory
Kaya*[106]	40	RCFT-LTM	24.18	5.40	19.75[135]	N	Memory
Sharma[232]	44	RCFT-LTM	17.00	7.80	19.75[135]	Y	Memory
Gupta[233]	11	Stroop-Interferences	38.30	5.90	46.49[136]	Y	Executive Function
Anwar[157]	50	TMT-A	33.70	8.00	40.00[76]	N	Attention + Processing Speed
Gupta[233]	11	TMT-A	50.50	22.30	40.00[76]	Y	Attention + Processing Speed
Harciarek[223]	22	TMT-A	45.82	10.15	40.00[76]	Y	Attention + Processing Speed
Kaya*[106]	40	TMT-A	63.43	34.58	40.00[76]	Y	Attention + Processing Speed
Sharma*[232]	44	TMT-A	30.92	2.08	40.00[76]	N	Attention + Processing Speed
Anwar[157]	50	TMT-B	110.00	28.60	94.00[76]	Y	Cognitive Flexibility
Harciarek[223]	22	TMT-B	110.82	62.66	94.00[76]	Y	Cognitive Flexibility
Kaya*[106]	40	TMT-B	123.16	58.83	94.00[76]	Y	Cognitive Flexibility
Sharma*[232]	44	TMT-B	71.76	7.13	94.00[76]	N	Cognitive Flexibility
Gupta[233]	11	Verbal Fluency-Category	17.60	4.50	46.90[138]	Y	Language
Kaya*[106]	40	Verbal Fluency-Not Specified	7.89	1.82	28.60[138]	Y	Language

Table 8: All scores for patients who received a transplant. * denotes data manipulation (median transformed to mean, range to SD). Abbreviations that appear in the table: The Modified Mini–Mental State Examination (3MS), Brief Visuospatial Memory Test-Revised (BVMT-R), The Mini–Mental State Examination (MMSE), Rey Auditory Verbal Learning Test (RAVLT), Rey–Osterrieth Complex Figure Test (RCFT), and Trails Making Tests (TMT) forms A and B. Impairment (Y/N) based off the mean cut off value reported in literature indicated in the cut-off column. Impairment (Y/N) is at an individual study level.

Table 9: Meta-Analysis Non-Chronic Kidney Disease Control Studies

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Dixon[139]	31	3Ms	85.20	7.60	78.00[85]	N	Global
Murray[234]	101	3Ms	94.30	5.70	78.00[85]	N	Global
Palmer[88]	172	3Ms	85.10	8.80	78.00[85]	N	Global
Lee[94]	286	Boston Naming Test	10.90	2.60	13.30[95]	Y	Language
Martini[96]	60	Boston Naming Test	9.70	1.10	13.30[95]	Y	Language
Tiffin-Richards[61]	42	Boston Naming Test	21.00	10.00	13.30[95]	N	Language
Torres[97]	752	Boston Naming Test	35.00	1.70	13.30[95]	N	Language
Harciarek[223]	30	BVMT-R-Delayed	9.90	1.86	8.95[146]	N	Memory
Kalirao[140]	101	BVMT-R-Delayed	6.80	2.80	8.95[146]	Y	Memory
Kalirao[140]	101	COWAT	43.90	15.80	37.50[99]	N	Language
Pliskin[151]	12	COWAT	33.80	10.70	37.50[99]	Y	Language
Torres[97]	752	COWAT	40.10	11.70	37.50[99]	N	Language
Yeh[100]	92	COWAT	37.93	9.17	37.50[99]	N	Language
Tiffin-Richards[61]	42	CVLT-Delayed	12.50	4.00	10.38[103]	N	Language
Tiffin-Richards[61]	42	CVLT-Immediate	12.50	6.00	8.60[103]	N	Language
Chang[104]	39	Digit Span-Backwards	7.00	2.10	4.35[78]	N	Memory
Harciarek[223]	30	Digit Span-Backwards	5.40	1.38	4.35[78]	N	Memory
Hart[105]	20	Digit Span-Backwards	4.60	1.20	4.35[78]	N	Memory
Lee[94]	286	Digit Span-Backwards	3.70	1.20	4.35[78]	Y	Memory
Seidel[108]	54	Digit Span-Backwards	6.20	1.60	4.35[78]	N	Memory
Tiffin-Richards[61]	42	Digit Span-Backwards	6.00	1.00	4.35[78]	N	Memory
Torres[97]	752	Digit Span-Backwards	5.10	1.50	4.35[78]	N	Memory

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Tsai[66]	192	Digit Span-Backwards	4.90	2.50	4.35[78]	N	Memory
Chang[104]	39	Digit Span-Forwards	11.00	2.10	4.35[78]	N	Memory
Harciarek[223]	30	Digit Span-Forwards	6.10	1.40	5.73[78]	N	Memory
Hart[105]	20	Digit Span-Forwards	5.90	1.40	5.73[78]	N	Memory
Lee[94]	286	Digit Span-Forwards	6.70	1.40	5.73[78]	N	Memory
Seidel[108]	54	Digit Span-Forwards	7.90	1.60	5.73[78]	N	Memory
Tiffin-Richards[61]	42	Digit Span-Forwards	8.00	4.00	5.73[78]	N	Memory
Torres[97]	752	Digit Span-Forwards	7.14	1.20	5.73[78]	N	Memory
Tsai[66]	192	Digit Span-Forwards	9.70	2.80	5.73[78]	N	Memory
Anwar[157]	30	Digit Span-Unspecified	7.90	3.10	5.73[78]	N	Memory
Kalirao[140]	101	Digit Span-Unspecified	18.20	4.20	5.73[78]	N	Memory
Nasser[109]	20	Digit Span-Unspecified	13.70	2.20	5.73[78]	N	Memory
Pliskin[151]	12	Digit Span-Unspecified	8.30	2.20	5.73[78]	N	Memory
Umans[161]	10	Digit Span-Unspecified	12.30	4.10	5.73[78]	N	Memory
Yeh[100]	92	Digit Span-Unspecified	19.79	4.19	5.73[78]	N	Memory
Chen[110]	32	Digit Symbol	62.30	13.00	59.00[80]	N	Memory + Processing Speed
Chen[162]	26	Digit Symbol	62.20	14.20	59.00[80]	N	Memory + Processing Speed
Harciarek[223]	30	Digit Symbol	48.03	11.09	59.00[80]	Y	Memory + Processing Speed
Hart[105]	20	Digit Symbol	48.70	10.50	59.00[80]	Y	Memory + Processing Speed

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Jiang[111]	31	Digit Symbol	65.00	14.00	59.00[80]	Y	Memory + Processing Speed
Kong[164]	80	Digit Symbol	64.40	15.20	59.00[80]	N	Memory + Processing Speed
Liang[224]	20	Digit Symbol	63.22	11.54	59.00[80]	N	Memory + Processing Speed
Luo[113]	24	Digit Symbol	64.00	11.00	59.00[80]	N	Memory + Processing Speed
Nasser[109]	20	Digit Symbol	12.00	0.70	59.00[80]	Y	Memory + Processing Speed
Ni[225]	23	Digit Symbol	62.00	11.82	59.00[80]	N	Memory + Processing Speed
Palmer[88]	171	Digit Symbol	50.20	15.60	59.00[80]	N	Memory + Processing Speed
Pliskin[151]	12	Digit Symbol	7.60	1.90	59.00[80]	Y	Memory + Processing Speed
Pulignano[114]	138	Digit Symbol	19.90	8.30	59.00[80]	Y	Memory + Processing Speed
Torres[97]	752	Digit Symbol	54.10	12.90	59.00[80]	Y	Memory + Processing Speed
Yeh[100]	92	Digit Symbol	57.78	16.04	59.00[80]	N	Memory + Processing Speed
Zhang[226]	22	Digit Symbol	62.00	11.82	59.00[80]	N	Memory + Processing Speed
Chen[110]	32	Line Tracing Test	47.50	14.90	54.50[115]	N	Psycho-motor Speed
Chen[162]	26	Line Tracing Test	55.30	17.60	54.50[115]	Y	Psycho-motor Speed
Jiang[111]	31	Line Tracing Test	53.00	18.00	54.50[115]	N	Psycho-motor Speed
Liang[224]	20	Line Tracing Test	46.56	12.15	54.50[115]	N	Psycho-motor Speed

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Luo[113]	24	Line Tracing Test	45.00	13.00	54.50[115]	N	Psycho-motor Speed
Ni[225]	23	Line Tracing Test	46.50	11.44	54.50[115]	N	Psycho-motor Speed
Anwar[157]	30	MMSE	30.00	0.00	24.00[71]	N	Global
Chai[174]	41	MMSE	29.70	0.50	24.00[71]	N	Global
Chang[104]	39	MMSE	28.40	1.40	24.00[71]	N	Global
Fazekas[182]	30	MMSE	27.90	1.40	24.00[71]	N	Global
Frasnelli[228]	15	MMSE	29.20	0.30	24.00[71]	N	Global
Grimm[184]	50	MMSE	29.60	0.60	24.00[71]	N	Global
Harciarek[223]	30	MMSE	29.00	0.87	24.00[71]	N	Global
Harciarek[185]	25	MMSE	29.24	0.93	24.00[71]	N	Global
Hsieh[186]	27	MMSE	29.20	0.70	24.00[71]	N	Global
Isshiki[220]	60	MMSE	28.50	1.40	24.00[71]	N	Global
Jones[188]	36	MMSE	28.70	0.90	24.00[71]	N	Global
Kramer[193]	45	MMSE	29.50	0.80	24.00[71]	N	Global
Lee[94]	286	MMSE	25.20	3.00	24.00[71]	N	Global
Lee[123]	3654	MMSE	26.40	2.42	24.00[71]	N	Global
Lee[230]	65	MMSE	27.70	1.75	24.00[71]	N	Global
Li C.[194]	20	MMSE	29.50	0.80	24.00[71]	N	Global
Li J.*[221]	66	MMSE	27.18	1.06	24.00[71]	N	Global
Lux[195]	12	MMSE	29.50	0.90	24.00[71]	N	Global
Madan[124]	15	MMSE	29.00	0.85	24.00[71]	N	Global
Maugeri[20]	35	MMSE	23.50	0.70	24.00[71]	Y	Global
Nasser[109]	20	MMSE	29.30	0.90	24.00[71]	N	Global
Pulignano[114]	138	MMSE	26.30	3.90	24.00[71]	N	Global
Soysal[199]	270	MMSE	23.90	4.70	24.00[71]	Y	Global
Tiffin-Richards[61]	42	MMSE	29.00	2.00	24.00[71]	N	Global
Tilki[203]	25	MMSE	30.00	0.20	24.00[71]	N	Global
Wang[126]	654	MMSE	13.40	7.10	24.00[71]	Y	Global
Wang[127]	336	MMSE	17.80	6.00	24.00[71]	Y	Global
Wang[129]	30	MMSE	27.10	3.90	24.00[71]	N	Global

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Yeh[100]	92	MMSE	28.59	1.67	24.00[71]	N	Global
Zhang[204]	28	MMSE	28.57	1.10	24.00[71]	N	Global
Li P. [207]	25	MoCA	26.80	2.70	26.00[74]	N	Global
Palmer[88]	171	MoCA	20.20	3.90	26.00[74]	Y	Global
Tiffin-Richards[61]	42	MoCA	28.00	3.00	26.00[74]	N	Global
Chen[110]	32	NCT-A	34.90	9.80	40.00[76]	N	Attention + Processing Speed
Chen[162]	26	NCT-A	37.00	12.90	40.00[76]	N	Attention + Processing Speed
Jiang[111]	31	NCT-A	33.00	12.00	40.00[76]	N	Attention + Processing Speed
Kong[164]	80	NCT-A	36.80	15.10	40.00[76]	N	Attention + Processing Speed
Liang[224]	20	NCT-A	32.28	8.93	40.00[76]	N	Attention + Processing Speed
Luo[113]	24	NCT-A	31.00	8.00	40.00[76]	N	Attention + Processing Speed
Ni[225]	23	NCT-A	34.00	10.48	40.00[76]	N	Attention + Processing Speed
Harciarek[223]	30	RAVLT-Delayed Recall	11.13	1.96	8.80[134]	N	Memory
Lux[195]	12	RAVLT-Delayed Recall	50.50	9.30	8.80[134]	N	Memory
Musolino[209]	10	RAVLT-Delayed Recall	46.70	3.00	8.80[134]	N	Memory
Palmer[88]	170	RAVLT-Delayed Recall	5.40	3.20	8.80[134]	Y	Memory

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Tsai[66]	192	RAVLT-Delayed Recall	11.30	2.50	8.80[134]	N	Memory
Harciarek[223]	30	RAVLT-Learning	52.33	6.03	44.00[134]	N	Memory
Lux[195]	12	RAVLT-Learning	57.90	4.20	44.00[134]	N	Memory
Tsai[66]	192	RAVLT-Learning	47.90	9.50	44.00[134]	N	Memory
Harciarek[223]	30	RCFT	35.10	1.35	24.50[135]	N	Attention
Seidel[108]	54	RCFT	32.70	2.40	24.50[135]	N	Attention
Harciarek[223]	30	RCFT-Delayed Recall	24.62	2.86	19.75[135]	N	Memory
Chen[110]	32	Serial Dotting Test	44.90	14.00	70.00[158]	N	Psycho-motor Speed
Chen[162]	26	Serial Dotting Test	53.30	17.10	70.00[158]	N	Psycho-motor Speed
Jiang[111]	31	Serial Dotting Test	48.00	15.00	70.00[115]	N	Psycho-motor Speed
Liang[224]	20	Serial Dotting Test	45.13	9.87	70.00[115]	N	Psycho-motor Speed
Luo[113]	24	Serial Dotting Test	35.00	9.00	70.00[115]	N	Psycho-motor Speed
Ni[225]	23	Serial Dotting Test	45.11	9.58	70.00[115]	N	Psycho-motor Speed
Tiffin-Richards[61]	42	Stroop-Color Reading	32.00	6.00	96.74[136]	N	Executive Function
Umans[161]	10	Stroop-Color Reading	57.50	15.70	96.74[136]	N	Executive Function
Kalirao[140]	101	Stroop-Interference	71.20	23.80	46.49[136]	Y	Executive Function
Seidel[108]	54	Stroop-Interference	90.00	17.50	46.49[136]	Y	Executive Function
Tiffin-Richards[61]	42	Stroop-Interference	86.00	28.00	46.49[136]	Y	Executive Function
Tiffin-Richards[61]	42	Stroop-Naming	47.00	12.00	43.49[136]	Y	Executive Function

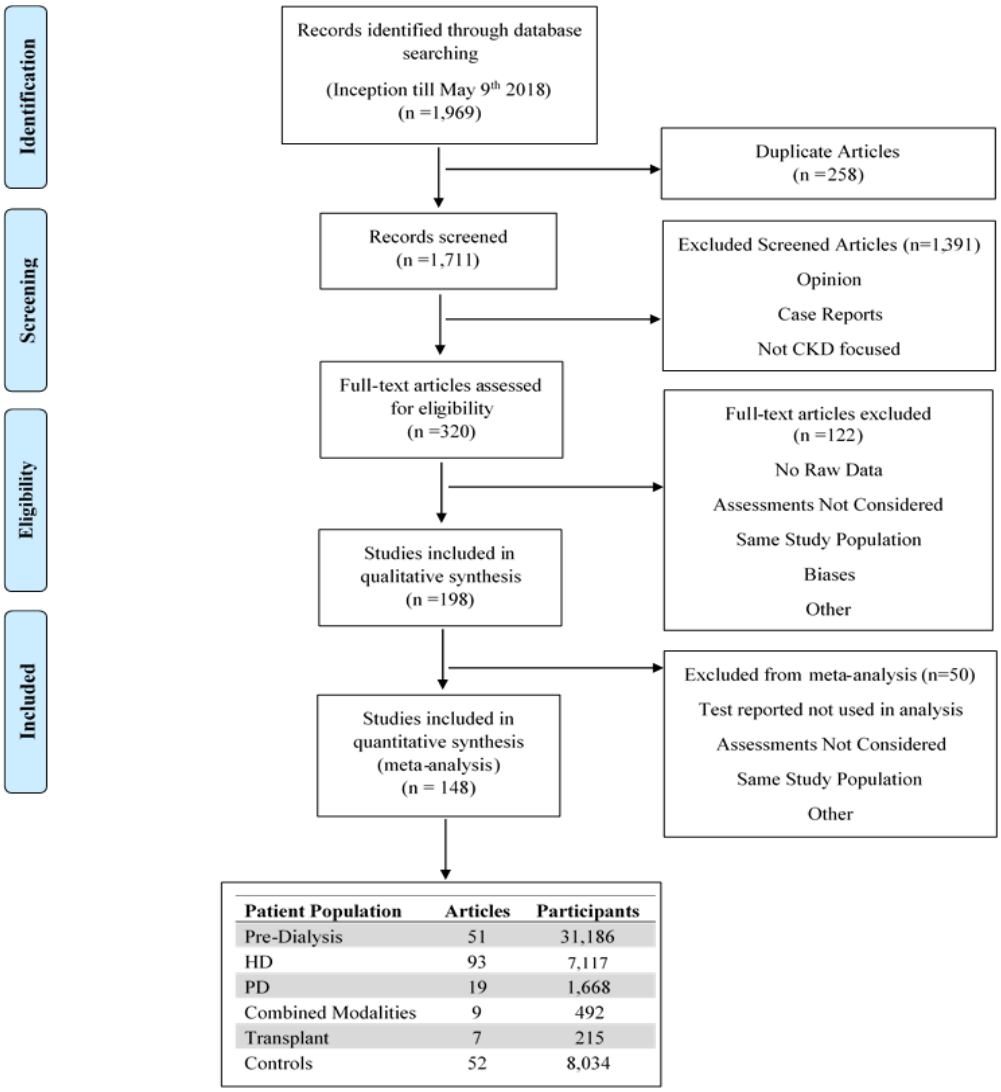
Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Umans[161]	10	Stroop-Naming	76.10	19.00	43.49[136]	Y	Executive Function
Anwar[157]	30	TMT-A	34.70	9.00	40.00[76]	N	Attention + Processing Speed
Frasnelli[228]	15	TMT-A	31.10	1.70	40.00[76]	N	Attention + Processing Speed
Grimm[184]	50	TMT-A	27.00	8.00	40.00[76]	N	Attention + Processing Speed
Harciarek[223]	30	TMT-A	32.90	11.54	40.00[76]	N	Attention + Processing Speed
Hart[105]	20	TMT-A	35.30	13.10	40.00[76]	N	Attention + Processing Speed
Kramer[193]	45	TMT-A	28.00	9.00	40.00[76]	N	Attention + Processing Speed
Lee[94]	286	TMT-A	72.90	46.30	40.00[76]	Y	Attention + Processing Speed
Lee[123]	3647	TMT-A	20.90	6.60	40.00[76]	N	Attention + Processing Speed
Lux[195]	12	TMT-A	25.00	4.50	40.00[76]	N	Attention + Processing Speed
Schneider[214]	20	TMT-A	50.45	8.00	40.00[76]	Y	Attention + Processing Speed
Seidel[108]	54	TMT-A	38.90	16.20	40.00[76]	N	Attention + Processing Speed

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Tiffin-Richards[61]	42	TMT-A	32.50	15.00	40.00[76]	N	Attention + Processing Speed
Tsai[66]	192	TMT-A	69.30	36.80	40.00[76]	Y	Attention + Processing Speed
Umans[161]	10	TMT-A	67.40	57.40	40.00[76]	Y	Attention + Processing Speed
Yeh[100]	92	TMT-A	48.73	20.51	40.00[76]	Y	Attention + Processing Speed
Zhang[204]	28	TMT-A	37.61	6.51	40.00[76]	N	Attention + Processing Speed
Anwar[157]	30	TMT-B	107.00	26.00	94.00[76]	Y	Cognitive Flexibility
Harciarek[223]	30	TMT-B	78.93	23.08	94.00[76]	N	Cognitive Flexibility
Hart[105]	20	TMT-B	81.90	22.90	94.00[76]	N	Cognitive Flexibility
Lee[94]	286	TMT-B	206.50	82.10	94.00[76]	Y	Cognitive Flexibility
Lee[123]	3645	TMT-B	42.60	17.50	94.00[76]	N	Cognitive Flexibility
Lux[195]	12	TMT-B	62.00	20.20	94.00[76]	N	Cognitive Flexibility
Nasser[109]	20	TMT-B	171.00	15.20	94.00[76]	Y	Cognitive Flexibility
Schneider[214]	20	TMT-B	49.35	9.52	94.00[76]	N	Cognitive Flexibility
Seidel[108]	54	TMT-B	92.40	35.80	94.00[76]	N	Cognitive Flexibility
Tiffin-Richards[61]	42	TMT-B	73.50	37.00	94.00[76]	N	Cognitive Flexibility
Tsai[66]	192	TMT-B	119.10	56.00	94.00[76]	Y	Cognitive Flexibility
Umans[161]	10	TMT-B	251.00	252.00	94.00[76]	Y	Cognitive Flexibility

Author	(N)	Test	Mean	SD	Cut Off	Impaired (Y/N)	Cognitive Domain
Yeh[100]	92	TMT-B	92.06	50.54	94.00[76]	N	Cognitive Flexibility
Zhang[204]	28	TMT-B	58.72	6.46	94.00[76]	N	Cognitive Flexibility
Palmer[88]	171	Verbal Fluency-Animal	15.90	4.60	18.10[138]	Y	Language
Tsai[66]	192	Verbal Fluency-Animal	14.80	4.00	18.10[138]	Y	Language
Lux[195]	12	Verbal Fluency-Category	63.60	6.10	46.90[138]	N	Language
Chang[104]	39	Verbal Fluency-Not Specified	10.80	3.10	28.60[138]	Y	Language
Pulignano[114]	138	Verbal Fluency-Phonemic	19.20	7.20	28.60[138]	Y	Language

Table 9: All scores for healthy non-CKD controls. * denotes data manipulation (median transformed to mean, range to SD). Abbreviations that appear in the table: The Modified Mini–Mental State Examination (3MS), Brief Visuospatial Memory Test-Revised (BVMT-R), Controlled Oral Word Associations Test (COWAT), California Verbal Learning Test (CVLT), The Mini–Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Number Connection Test- A (NCT-A), Rey Auditory Verbal Learning Test (RAVLT), Rey–Osterrieth Complex Figure Test (RCFT), and Trails Making Tests (TMT) forms A and B. Impairment (Y/N) based off the mean cut off value reported in literature indicated in the cut-off column. Impairment (Y/N) is at an individual study level.

2.7 Figures



Patient Population	Articles	Participants
Pre-Dialysis	51	31,186
HD	93	7,117
PD	19	1,668
Combined Modalities	9	492
Transplant	7	215
Controls	52	8,034

Figure 1: Systematic review process: Meta-Analysis. Note: Full-text articles excluded encompasses mainly articles that had biases (e.g. looked at participants with only dementia or only used individuals that were above cut off scores on the MMSE). Assessments not considered consisted of telephone surveys. Other indicates the articles that where not CKD focused, case studies, or were a review articles. The table summarizes the number of participants and articles that reported at least one test used in the meta-analysis.

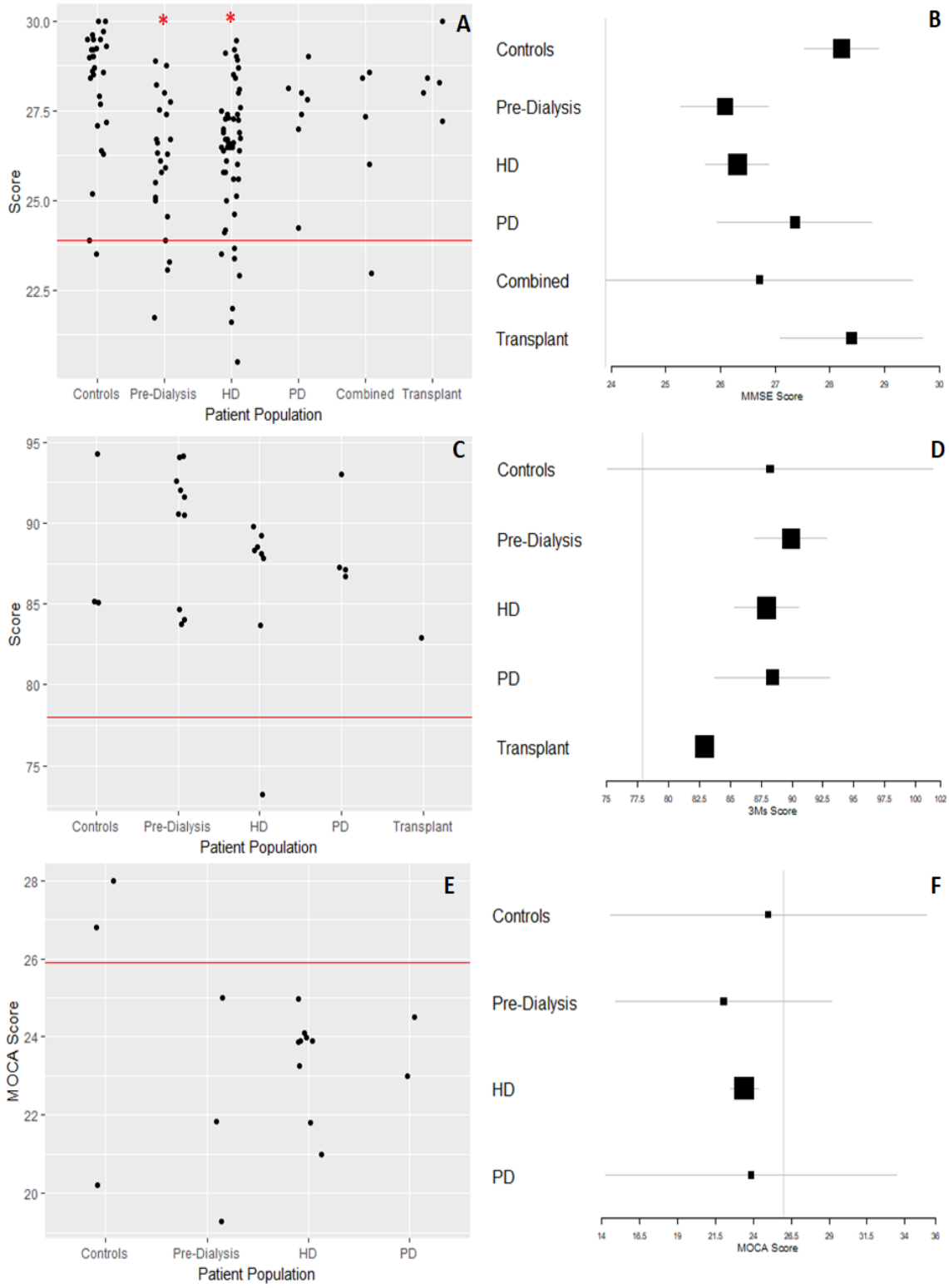

A
Score
30.0
27.5
25.0
22.5
Controls
Pre-Dialysis
HD
PD
Combined
Transplant
Patient Population
B
Controls
Pre-Dialysis
HD
PD
Combined
Transplant
24
25
26
27
28
29
30
MMSE Score
C
Score
95
90
85
80
75
Controls
Pre-Dialysis
HD
PD
Transplant
Patient Population
D
Controls
Pre-Dialysis
HD
PD
Transplant
75
77.5
80
82.5
85
87.5
90
92.5
95
97.5
100
102
3Ms Score
E
MOCA Score
28
26
24
22
20
Controls
Pre-Dialysis
HD
PD
Patient Population
F
Controls
Pre-Dialysis
HD
PD
14
16.5
19
21.5
24
26.5
29
31.5
34
36
MOCA Score

Figure 2: Dementia Screening Test Scores: Meta-Analysis. Figure 2A: All articles reporting The Mini–Mental State Examination (MMSE) scores for all patient populations. Red line indicates the cut off value of 24, anything below indicates impairment. * denotes significantly different from non-CKD controls after Bonferroni correction. Figure 2B: Summary data of MMSE with adjusted means via a random effects model with lower and upper confidence levels. Vertical line indicates the cut off value (24). Figure 2C: All articles reporting The Modified Mini–Mental State Examination (3MS) scores for all patient populations. Red line indicates the cut off value of 78, anything below indicates impairment. Figure 2D: Summary data of 3Ms with adjusted means via a random effects model with lower and upper confidence levels. Vertical line indicates the cut off value (78). Figure 2E: All articles reporting MOCA scores for all patient populations. Red line indicates the cut off value of 26, anything below indicates impairment. Figure 2F: Summary data of MOCA with adjusted means via a random effects model with lower and upper confidence levels. Vertical line indicates the cut off value (26).

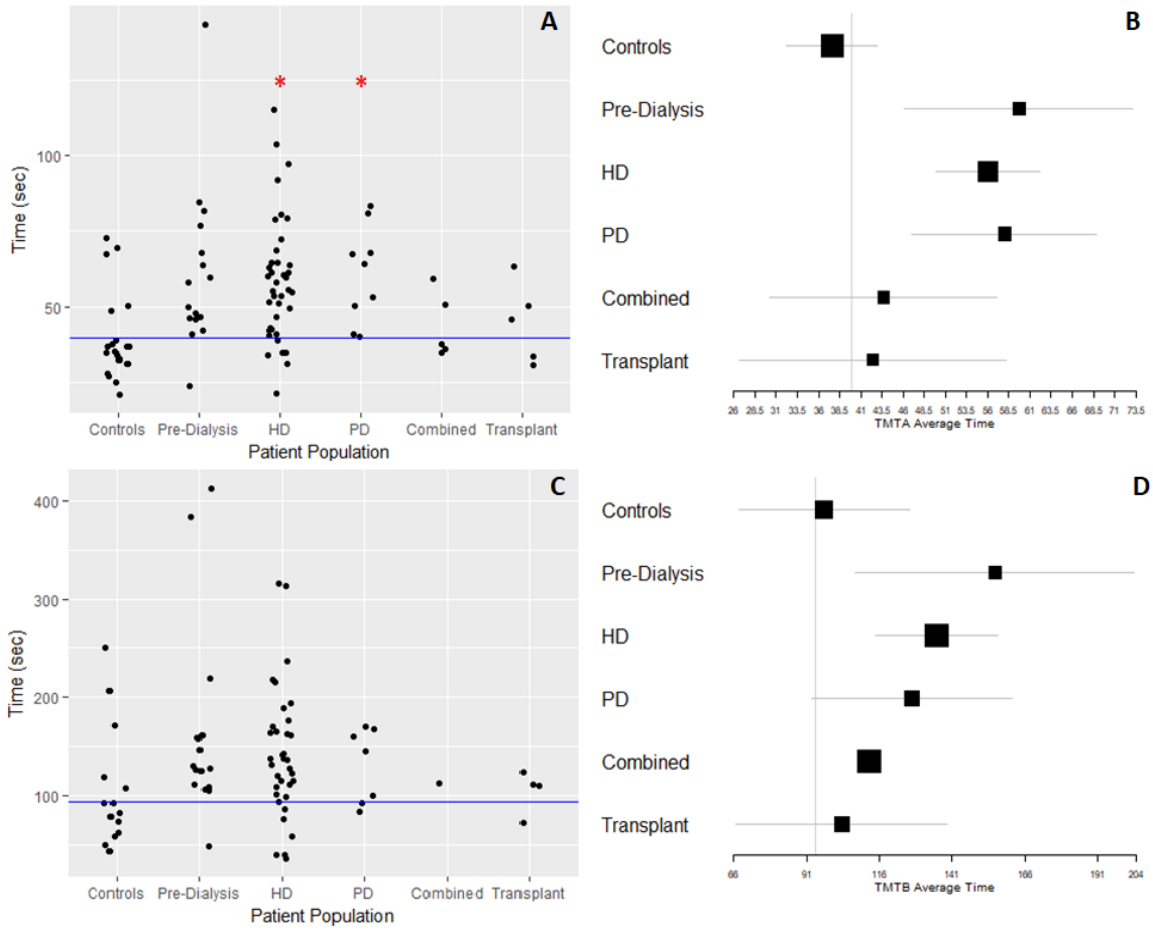


Figure 3: Trails Making Tests and Number Connection Test Scores: Meta-Analysis. Figure 3A: All articles reporting Trails Making Tests (TMT-A) and Number Connection Test (NCT-A) scores for all patient populations. Blue line indicates the average time to complete TMT-A (40 seconds), anything above this line indicates impairment. * denotes significantly different from non-CKD controls after Bonferroni correction. Figure 3B: Summary data of TMT-A with adjusted means via a random effects model with lower and upper confidence levels. Vertical line indicates average time of completion (40 seconds). Figure 3C: All articles reporting TMT-B scores for all patient populations. Blue line indicates the average time to complete the TMT-B (94 seconds), anything above this line

indicates impairment. Figure 3D: Summary data of TMT-B with adjusted means via a random effects model with lower and upper confidence levels. Vertical line indicates average time of completion (94 seconds).

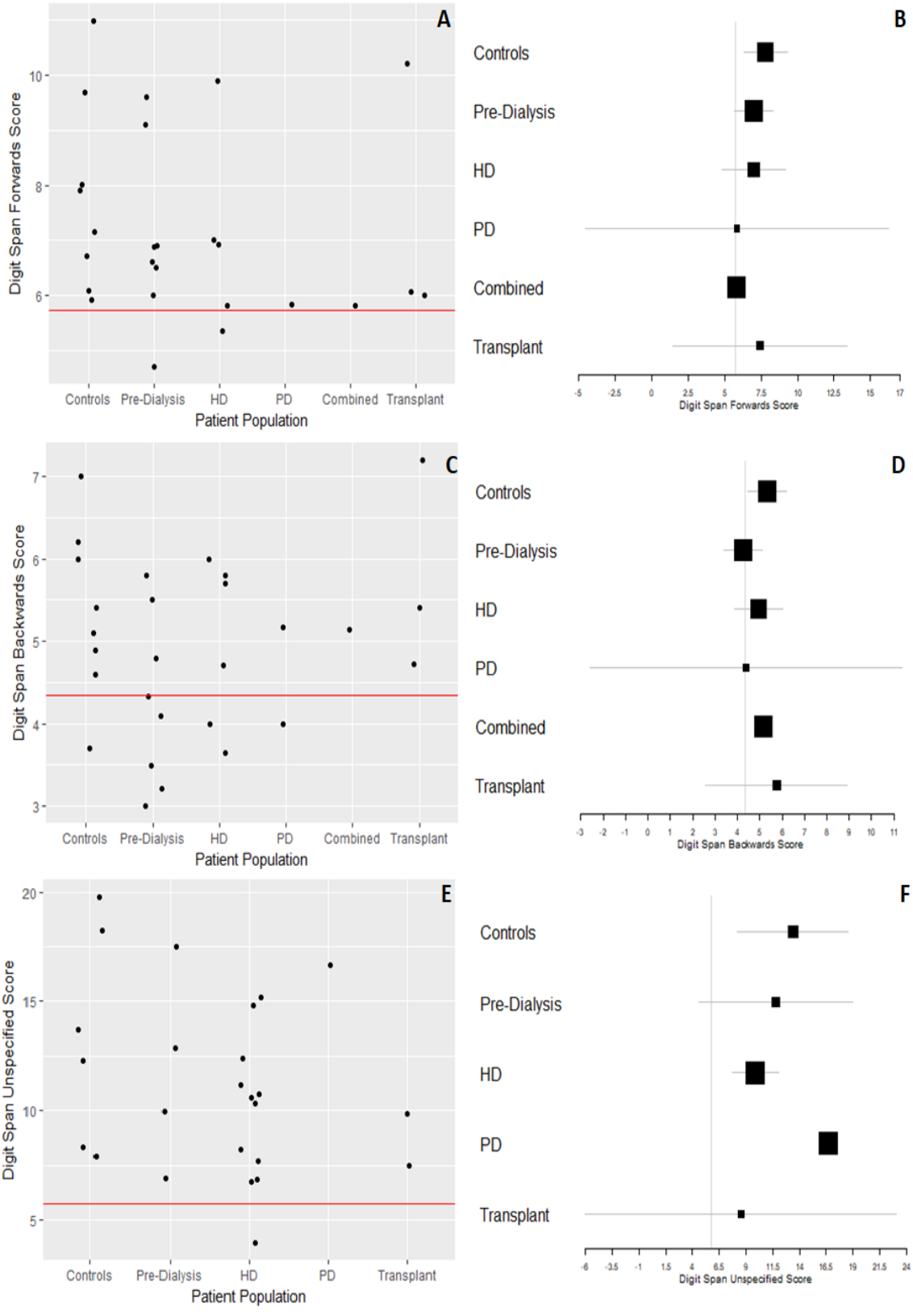

A
Digit Span Forwards Score
10
8
6
Controls
Pre-Dialysis
HD
PD
Combined
Transplant
Patient Population
B
Controls
Pre-Dialysis
HD
PD
Combined
Transplant
-5
-2.5
0
2.5
5
7.5
10
12.5
15
17
Digit Span Forwards Score
C
Digit Span Backwards Score
7
6
5
4
3
Controls
Pre-Dialysis
HD
PD
Combined
Transplant
Patient Population
D
Controls
Pre-Dialysis
HD
PD
Combined
Transplant
-3
-2
-1
0
1
2
3
4
5
6
7
8
9
10
11
Digit Span Backwards Score
E
Digit Span Unspecified Score
20
15
10
5
Controls
Pre-Dialysis
HD
PD
Transplant
Patient Population
F
Controls
Pre-Dialysis
HD
PD
Transplant
-6
-3.5
-1
1.5
4
6.5
9
11.5
14
16.5
19
21.5
24
Digit Span Unspecified Score

Figure 4: Digit Span Forwards and Backwards Scores: Meta-Analysis. Figure 4A: All articles reporting Digit Span Forwards (DSF) scores (part of the WAIS) for all patient populations. Red line indicates the cut off value of 5.73, anything below this line indicates impairment. Figure 4B: Summary data of DSF with adjusted means via a random effects model with lower and upper confidence levels. Vertical line indicates the cut off value (5.73). Figure 2C: All articles reporting Digit Span Backwards (DSB) scores (part of the WAIS) for all patient populations. Red line indicates the cut off value of 4.35, anything below this line indicates impairment. Figure 4D: Summary data of DSB with adjusted means via a random effects model with lower and upper confidence levels. Vertical line indicates the cut off value (4.35). Figure 4E: All articles reporting Digit Span Unspecified (DSU) scores (part of the WAIS) for all patient populations. Red line indicates the cut off value of 5.73, anything below this line indicates impairment. Figure 5F: Summary data of DSU with adjusted means via a random effects model with lower and upper confidence levels. Vertical line indicates the cut off value (5.73).

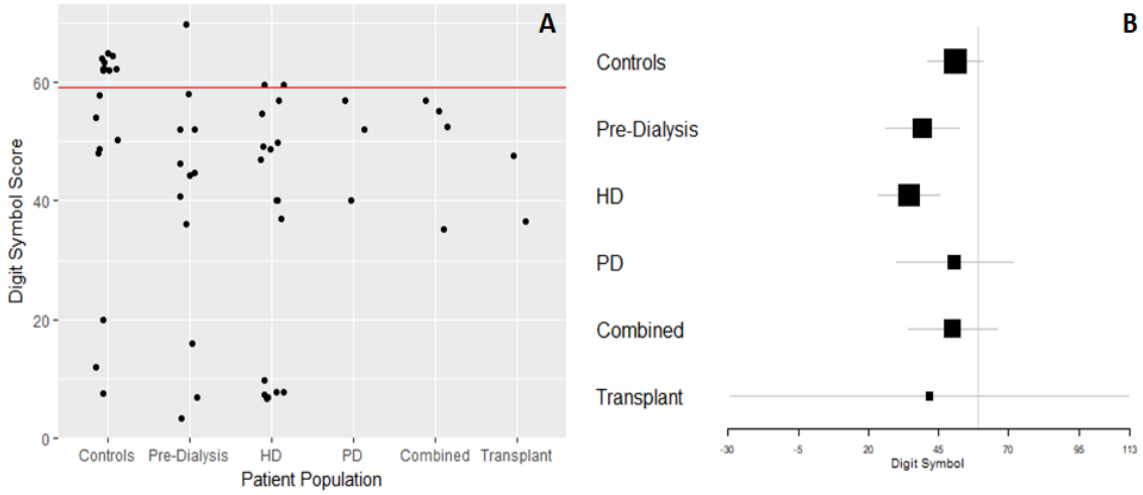


Figure 5: Digit Symbol Scores: Meta-Analysis. Figure 5A: All articles reporting Digit Symbol scores (part of the WAIS) for all patient populations. Red line indicates the cut off value of 59, anything below this line indicates impairment. Figure 5B: Summary data of Digit Symbol with adjusted means via a random effects model with lower and upper confidence levels. Vertical line indicates the cut off value (59).

Chapter 3

Robotic Technology Quantifies Novel Perceptual-Motor Impairments in Patients with Chronic Kidney Disease

3.1 Abstract

Background: Neurocognitive impairment is commonly reported in patients with chronic kidney disease (CKD). The precise nature of this impairment is unclear, due to the lack of objective and quantitative assessment tools used. The feasibility of using robotic technology to precisely quantify neurocognitive impairment in patients with CKD is unknown.

Methods: Patients with stage 4 and 5 CKD with no previous history of stroke or neurodegenerative disease were eligible for study enrollment. Feasibility was defined as successful study enrollment, high data capture rates (>90%), and assessment tolerability. Our assessment included a traditional assessment: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and a robot-based assessment: Kinarm.

Results: Our enrollment rate was 1.6 patients/month. All patients completed the RBANS portion of the assessment, with a 97.8% (range 92%-100%) completion rate on Kinarm. Missing data on Kinarm was mainly due to time constraints. Data from 49 CKD patients' was analyzed. Kinarm defined more individuals as impaired, compared to RBANS, particularly in the domains of perceptual-motor function (17-49% impairment), complex attention (22-49% impairment), and executive function (29-37.5% impairment). Demographic features (sex and education) predicted performance on some, but not all neurocognitive tasks.

Conclusions: It is feasible to quantify neurocognitive impairments in patients with CKD using robotic technology. Kinarm characterized more patients with CKD as impaired, and

importantly identified novel perceptual-motor impairments in these patients, when compared to a traditional assessment.

3.2 Introduction

Neurocognitive impairment in patients with chronic kidney disease (CKD) is frequently reported[235]. The diagnostic and statistical manual (DSM)-V defines 6 neurocognitive domains: complex attention, executive function, learning and memory, language, perceptual-motor function, and social cognition[236]. Of these domains, the most commonly affected in patients with CKD are executive function, complex attention, and memory[22]. The perceptual-motor domain has not routinely been assessed in this cohort, but reflects a broad category related to sensory perception and motor function. The neuropathological mechanisms underlying these neurological impairments is likely multifactorial, and may include the effects of uremic toxins on neurons and neural progenitor cells[237].

The majority of recent studies assessing patients with CKD for neurocognitive impairment have relied on dementia screening tools[24,238]. Using these tools, the prevalence of neurocognitive impairment has been found to vary across the stages of CKD[24]. Although these tools are fast and easy-to-use, they are limited by their lack of objectivity and granularity required to completely define the impairment experienced by patients with CKD. For example, the most commonly used assessment was the Mini-Mental State Examination (MMSE)[24], which lacks sensitivity in detecting mild neurocognitive impairment[239], and does not measure executive function[240]. As such, the use of the MMSE alone is not intended for the assessment of mild neurocognitive impairment[241].

The present study explores the use of robotic technology (Kinarm) to quantify neurocognitive impairments in patients with CKD. The Kinarm robotic platform was initially developed to quantify detailed information on arm sensorimotor control and motor learning in non-human primates[242] and humans[243]. More recently this technology platform is being used to provide a robust, objective, and quantifiable approach to assess a broad range of sensory, motor, and neurocognitive functions associated with neurological disease and injury[54]. Kinarm has quantified impairments in many disorders including: stroke[244], critical illness[245], traumatic brain injury[246], amyotrophic lateral sclerosis[247], and post-cardiac surgery[248]. It has never been used to quantify impairment in patients with CKD. The primary objective of this study is to assess the feasibility of using Kinarm to quantify neurocognitive functioning in patients with CKD. Feasibility was defined as successful study enrollment, safety, tolerability, and data capture rates >90%. Secondary objectives were exploratory in nature and included: 1) comparing impairment identified by Kinarm against a traditional screening tool, and 2) exploring the relationship between patient demographics, clinical characteristics, and neurocognitive impairment. We hypothesized that it is feasible to quantify impairment using Kinarm, and that patients will also exhibit subtle, but measureable neurocognitive deficits.

3.3 Material and Methods

Study Design, Location, Participants, and Data Acquisition

This single-centre cross-sectional study recruited patients from a multidisciplinary CKD clinic at an academic hospital. Patients were considered eligible if they: 1) were >17 years old, 2) had an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2, and 3) had no documented history of stroke or neurodegenerative disease. Patients provided informed consent prior to assessment. Patient data was obtained from the hospital information management system. Demographics, cause of CKD, and co-morbidities were abstracted from the clinic chart. Laboratory values were taken from the closest visit at the time of the patients' neurocognitive assessment. If the eGFR was reported as <15 ml/min/1.73m^2, the CKD-EPI equation was used. Data regarding the patients' highest education and ethnicity were collected at the time of testing. The clinical staff involved in the day-to-day management of these patients were blinded to the results of the neuropsychological testing. The study was approved by Queen's University and Affiliated Hospitals Health Sciences Research Ethics Board.

Neurocognitive Testing

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

The RBANS is an effective screening tool used across a wide age range[249]. It measures five domains: immediate memory, delayed memory, attention, visuospatial, and language. It also produces a composite Total Scale Score, indicative of global performance. All final RBANS scores are standardized by age. Table 10 provides a list of the RBANS subdomains, the tasks involved in each subdomain, and corresponding DSM-V

neurocognitive domains. Traditionally, the RBANS has a normative range of 100 +/- 15 points (with scores <85 indicating impairment). This represents 1 standard deviation (SD) and categorizes ~17% of the population as impaired. We have chosen a more stringent criteria for defining impairment as <1.65 SD (95% below the population norm, equating to a score of <75.25). This allows for a direct comparison between Kinarm and RBANS, and ensures a higher degree of certainty that scores represent true impairment in our cohort.

Kinarm Task Description and Performance Scoring

Kinarm task descriptions, abbreviations, and corresponding DSM-V neurocognitive domains are provided in Table 10, along with a picture of the Kinarm (Figure 6). Specifically, detailed Kinarm task descriptions are below and were adapted from the user guide[58]. Also notably during the assessment the patient was not able to see their arms or hands.

1) Arm Position Matching (APM): Kinarm moves one of the patient's hands to a designated location, then the patient must mirror match this position with their other limb. This is repeated multiple times with Kinarm moving the patients arm to different locations.

2) Ball on Bar (BonB): Patients will observe a bar connecting both their hands with a ball on top of it. They must then move the ball into targets that appear on the screen. There are 3 levels in the task, with each lasting one minute in length. During each level, the friction coefficient between the ball and the bar decreases, such that the ball moves more freely and is more difficult to keep the ball on the bar as the levels increase.

3) Object Hit (OH): Paddles appear at the patient's hands and they must use them to hit away as many balls falling from the top of the screen as possible. As time progresses the amount and speed at which the balls fall increases.

4) Object Hit and Avoid (OH+A): This task is very similar to OH, but now the patient is shown 2 objects in which they must hit away while avoiding all other distractor objects. Again the rate and quantity of the objects that fall increases as time progresses.

5) Visually Guided Reaching (VGR): Patients are instructed to place their hand represented by a dot into a target. This target then moves around the screen. Patients are instructed to reach the target as quickly and accurately as possible when it moves locations.

6) Reverse Visually Guided Reaching (RVGR): Similar to VGR however, now the dot that represents their hand moves in the opposite direction of hand movement.

7) Spatial Span (SS): Patients are instructed to place their hand in a box at the bottom of the screen. They are then shown a light up sequence in a matrix of 3x4 boxes above their hand box. The box in which they place their hand restricts the patients from moving their hand while the sequence is being shown. Once the sequence is complete, the patient may then move their hand and duplicate the sequence. The sequences length is determined if the patients got the previous response correct or not.

8) Trails Making Test A (TMTA): The patient is shown a practice trial consisting of the numbers 1 through 5. They are instructed to connect them as quickly as possible. When the patient completes this, they then move onto the full trial. In the full trial they are asked to connect 1-25 as quickly as possible. The order is predetermined and no lines can intersect.

9) Trails Making Test B (TMTB): Much like TMTA, the TMTB adds complexity by having the patient connect alternating number and letters (ex 1-A-2-B-3. Again, patients receive a trial run followed by the full trial, in which the order is predetermined and no lines can intersect.

Regarding performance on each Kinarm task, a summary score is represented by a task score, which incorporates parameters related to spatial and temporal aspects of movement[58,250]. The task score provides a normalized measure of performance that is generated from a large cohort of healthy individuals (n range = 94 to 494, task dependent). Values for the task parameters from this healthy cohort are used to create a Box-Cox transformations that convert this distribution into a standard normal distribution (mean = 0, standard deviation = 1, distribution symmetric) including regression models to factor out the influence of age, sex, and handedness on performance. These normalized parameters are then aggregated together and transformed into a task score where 0 reflects best performance in the task and values of 1 and 1.96 reflect performance at the 68th and 95th percentile, respectively, for the healthy cohort. These equations are implemented in the software used to run the Kinarm tasks (Dexterit-E, version 3.8[58]) generating a normalized measure of performance for each individual with CKD considering their age, sex, and handedness. Impairments were defined as a task score >1.96, which corresponds to performance beyond the 95th percentile of the healthy cohort.

Data Analysis and Statistical Plan

Descriptive statistics were used to quantify impairment on the RBANS and Kinarm. In order to assess whether the Kinarm and RBANS were measuring similar neurocognitive domains, Pearson correlation plots were created using the p-values with a 95% confidence level. The false discovery rate correction was used, as it is a recommended alternative to the Bonferroni correction for multiple comparisons[251].

To assess the relationship between neurocognitive tasks and clinical variables, multiple linear models were created. Predictor variables were chosen *a priori,* based on their relevance to neurocognitive functioning in patients with CKD. These variables were: age[252], sex[252], education[252], history of cardiovascular disease[30], diabetes[253], and hypertension[253]. Regarding education, a dichotomy of having an education of ≤ grade 12 was used based on previous data[254]. Once the models were created, residuals were plotted, inspected, and normality was tested. The Cook's Distance was also graphed, in order to determine if there were any influential points (Cook's Distance>0.1). The original model and outlier free model were then compared to determine which model was subsequently used. All analyses and graphs were conducted and produced in R Studio[255].

3.4 Results

Feasibility

The study consort diagram is located in Figure 7. Study recruitment was from August 2015-September 2019. Two hundred and sixty-two patients were screened for the study. Of those, 189 were deemed eligible and 76 provided consent. Of those 76 patients: 16 started emergency dialysis before completing their assessment, 4 withdrew consent, and 2 transferred to a satellite clinic. Thus, 54 patients completed the assessment. However, 5 patients were removed from the analysis as 3 were found to have a documented stroke, and 2 had an eGFR >30 ml/min/1.73m^2 at the time of testing. Thus 49 patients were assessed, at an enrolment rate of 1.6 patients/month.

Feasibility was also defined by assessment completion and tolerability. Testing took one hour and twenty minutes to complete, with the RBANS portion taking roughly 30 minutes to complete, and 50 minutes for the Kinarm assessment. All patients completed the RBANS portion of the assessment. However, data capture rates on Kinarm ranged from 92-100% (task dependent). Kinarm tasks that were missing data were: OH+A (N=1), TMTB (N=1), APM (N=2), BonB (N=2), and SS (N=4). Reasons for missing data were fatigue (OH+A) and poor comprehension (TMTB). For APM, BonB, and SS, they were the first tasks to be eliminated in the event the patient could not stay for the full assessment. Importantly, no adverse events were noted, and patients tolerated the testing procedure well.

Patient Characteristics

All participant characteristics are shown in Table 11. The majority of the patients enrolled were Caucasian (43/49, 87.8%) and English was their primary language (47/49, 95.9%). Patient's highest level of education was predominantly grade 12 or above (42/49, 85.7%). The majority were classified with stage 5 CKD (eGFR<15 ml/min/1.73m^2) (39/49, 79.6%), with the primary cause of CKD being attributed by diabetes (25/49, 51%) and/or hypertension (18/49, 36.7%). Cardiovascular disease and sleep apnea were also common co-morbidities.

Kinarm Identifies Novel Neurocognitive Impairments in the DSM-V Perceptual-Motor Domain

Neurocognitive functioning was commonly impaired in our cohort, as a large number of individuals were impaired in both sub-sections of the Trail Making Task (TMTA: 24/49, 49%, and TMTB: 18/48, 37.5%), which measures perceptual motor, complex attention, and executive function neurocognitive domains (Figure 8). RVGR, a variant of the VGR task, requires an individual to move the arm in the opposite direction of the spatial goal, identified a substantive proportion of the cohort as impaired (18/49, 37%). OH+A which requires additional cognitive skills to select objects to hit while avoiding others also identified individuals as impaired (14/48, 29%) (Figure 8). A substantial number of individuals in our cohort also exhibited motor impairments. Particularly, 31% (15/49) of our cohort was impaired on VGR, which is a simple reaching task (Figure 8). Several individuals were also impaired in the other motor skills including rapid motor actions measured by OH (11/49, 22%) and a bimanual range of motion task BonB (8/47, 17%) (Figure 8). Perceptual impairments were also identified in 7/47 (15%)

of our cohort via the APM task. Finally, it was surprising to find only a few individuals were impaired on the working memory task SS (2/45, 4%) (Figure 8).

RBANS Categorizes Few Patients with Global Cognitive Impairment

Eight out of 49 (16%) scored below the 95% cut-off (a score of <75.25) on the Total Scale Score, the composite measure on the RBANS (Figure 9). There was a moderate degree of impairment across the subdomains (visuospatial (13/49, 26.5%), attention (12/49, 24.5%), immediate memory (11/49, 22.5%), and delayed memory (9/49, 18%)) (Figure 9). Only one patient (2%) was impaired on the language subdomain (Figure 9).

Kinarm and RBANS May Assess both Unique and Overlapping Neurocognitive Domains

A correlation matrix assessed the relationship between Kinarm tasks and the RBANS (Figure 10). The correlations were inversely related, which was expected as lower scores on the RBANS indicate worse performance, where the opposite is true for Kinarm. All RBANS subdomains were highly correlated with the RBANS composite score (Total Scale Score). Again, this high degree of correlation was expected, as the RBANS composite score is calculated from the subdomain scores. Performance on Kinarm tasks of TMTA, TMTB, and SS significantly correlated with all RBANS subdomains and the composite score. Performance on Kinarm task OH+A significantly correlated with the RBANS composite score and attention subdomain. Kinarm tasks of RVGR and BonB significantly correlated with only the visuospatial subdomain of the RBANS. Finally, APM, OH, and VGR did not significantly correlate with the RBANS composite score or subdomains.

Education and Sex May Predict Neurocognitive Performance

Although the primary outcome of this study was feasibility, an exploratory analysis was conducted to assess the relationship between clinical and demographic characteristics and neurocognitive performance. These characteristics predicted neurocognitive performance on the composite score on the RBANS (R^2=0.42, F=4.92, p=0.0072), along with the following RBANS subdomains: immediate memory (R^2=0.46, F=5.49, p=0.0004), visuospatial (R^2=0.31, F=3.03, p=0.015), language (R^2=0.43, F=5.09, p=0.0006), and attention (R^2=0.29, F=2.73, p=0.025) (Table 12). Delayed memory was not predicted by these clinical characteristics. When assessing which individual characteristic accounted for the greatest degree of variance in the model, education was a significant predictor for the composite score, along with 3 subdomains (Total Scale Score p=0.0001, immediate memory p=0.0057, visuospatial p=0.0004, language p=0.001, and attention p=0.006) (Table 12). The only other unique predictor was being of male sex for language (p=0.001) (Table 12).

These clinical/demographic characteristics were associated with performance on 5 Kinarm tasks. These tasks were: BonB (R^2=0.34, F=3.20, p=0.012), OH+A (R^2=0.38, F=3.87, p=0.004), OH (R^2=0.30, F=2.75, p=0.03), SS (R^2=0.33, F=3.02, p=0.017), and TMTB (R^2=0.45, F=4.95, p=0.001) (Table 13). Like the RBANS, performance on Kinarm tasks were predicted by both education (BonB p=0.01 and TMTB p=0.001) and being of male sex (BonB p=0.004, OH+A p=0.017 and SS p=0.019). Although the overall model for the task of OH was significant, there were no significant independent predictors (Table 13).

3.5 Discussion

Although it is well known that neurocognitive impairment is prevalent in patients with CKD[235] this impairment is typically described using screening tools[24], which may be limited in their sensitivity. This study was designed to test the feasibility of using Kinarm to provide objective and quantifiable data across multiple neurocognitive domains in patients with CKD. We demonstrated that it was feasible to recruit, enroll, and assess patients with Kinarm and maintain high data capture rates with no issues with safety or tolerability. In comparison to the RBANS, Kinarm assessed both distinct and overlapping domains. Importantly however, it consistently demonstrated perceptual-motor impairments, a domain not previously assessed rigorously in patients with CKD.

Regarding perceptual-motor impairments in patients with CKD, a recent study examined the related concept of hand dexterity with the Moberg's picking-up test in patients with moderate-severe CKD[256]. The authors concluded that GFR predicted time to complete the task in the non-dominant hand with eyes open[256], but the reported time was within published limits[257]. In our study, Kinarm tasks including APM, BonB, VGR, and OH primarily assessed the perceptual-motor domain, and demonstrated frequent and often profound impairments, with some individuals performing at least 6SD away from normative controls. Only one of these tasks (BonB) correlated with the visuospatial domain from the RBANS. Since the majority of the tasks were unrelated to the RBANS, it highlights that existing neurocognitive tools may not adequately capture impairments associated with sensory, perceptual, and motor function. The prevalence and severity of these perceptual-motor impairments may be important considerations for patients with

CKD who may otherwise be eligible for home-base renal replacement therapy, as they may not have the capacity to manage the complexities of home dialysis without assistance.

Visuospatial impairments have only recently been described in patients with CKD, using the Montreal Cognitive Assessment (MoCA)[258]. This screening tool dedicates 5/30 points to the visuospatial and executive domains. Participant scores on many of Kinarm tasks (TMTA/B, SS, BonB, and RVGR) significantly correlated with the visuospatial subdomain of the RBANS. In particular, Kinarm tasks of TMTB and RVGR identified roughly the same amount of impairment (37%). These tasks assessed the neurocognitive domains of perceptual-motor, complex attention, and executive function. Quantifying perceptual and visuospatial deficits in patients with CKD may be clinically relevant, particularly in discussing driving safety. A recent review determined that a better understanding of the relationship between neurocognitive impairments and their effects on driving in patients with CKD is needed[259]. It was noted that roughly 1/3 of patients with CKD are involved in a motor vehicle collision within 1 year of initiating dialysis[259]. There is little data however regarding driving safety in earlier CKD stages.

Intriguingly, only two patients scored outside the normative range on the Kinarm memory task (SS). Lack of memory impairment is inconsistent with the RBANS findings and previous literature[239]. These inconsistencies may be explained by how the task is performed. SS was modeled after the Corsi block-tapping task[58], where patients must repeat a block sequence in the correct order. After they complete the sequence they receive feedback if they correctly reproduced the sequence. It is known that negative feedback has an effect on self-efficacy[260], which in turn affects motivation. Furthermore, low self-

efficacy caused by negative feedback may decrease cognitive resources and ultimately lead to poor performance[261]. Therefore, this task may not truly represent the memory impairment in this population and may need to be redesigned.

In our severe CKD cohort, we found that male sex and lower education were associated with worse performance on some, but not all assessments. Particularly, we found that having a lower education predicted worse performance on all but one subdomain (delayed memory) of the RBANS. In contrast, only 2/9 Kinarm tasks were predicted by level of education (BonB and TMTB). This may be related to the fact that many of Kinarm tasks are more heavily weighted towards attention and perceptual-motor domains, which may be less dependent on level of education.

This study has the following limitations. First, its relatively small sample size and single-centre design limits external generalizability. As there are now dozens of Kinarm labs worldwide, future multi-centre studies will be possible using this technology. Second, this study only assessed predominantly patients with stage 5 CKD. This narrow range of kidney dysfunction precluded our ability to assess whether eGFR was a predictor of neurocognitive performance. Third, our study did not include any imaging or physiological recordings (e.g., functional near-infrared spectroscopy), limiting our ability to draw any conclusions regarding the underlying anatomical or pathophysiological changes that might be responsible for the perceptual motor and visuospatial impairments quantified in our cohort. Fourth, is the lack of a gold-standard neuropsychological assessment as a comparator. Although we did compare Kinarm to a traditional assessment (RBANS), it is not a substitute for a full neuropsychological assessment battery.

In summary, it is feasible to use Kinarm to precisely characterize neurocognitive impairment in patients with CKD. Most subjects demonstrated perceptual-motor impairments, along with difficulties in complex attention and executive function, indicating that CKD affects motor domains along with neurocognitive domains. Future studies using a multi-centre design and larger sample sizes are needed to explore key risk factors for neurocognitive impairment in patients with CKD, as well as a more in-depth understanding of how these impairments affect patient-oriented outcomes such as driving, quality of life, and daily management of CKD.

3.7 Tables

Table 10: Neurocognitive Battery Tasks, Abbreviations, DSM-V Domains: Chronic Kidney Disease

Neurocognitive Test	Task/Domain	Abbreviation	Task Components/ Task Description	Related DSM-V Neurocognitive Domain
RBANS	Attention	N/A	Digit Span, Symbol Coding	Complex Attention
	Immediate Memory	N/A	List Learning, Story Memory	Learning and Memory
	Delayed Memory	N/A	List Recall, List Recognition, Story Recall, Figure Recall	Learning and Memory
	Visuospatial	N/A	Figure Copy, Line Orientation	Perceptual-Motor, Complex Attention
	Language	N/A	Picture Naming, Semantic Fluency	Language
	Total Scale Score	N/A	A summary score based on the performance on all the RBANS domains. Representative of global performance on the RBANS.	Complex Attention, Learning and Memory, Perceptual-Motor, Language
Kinarm	Arm Position Matching	APM	The robot moves one of the patient's arms. Patients are then asked to mirror match this position with the other arm. A measure of proprioception and somatosensory.	Perceptual-Motor
	Ball on Bar	BonB	A bar appears between the patients 2 arms with a ball on top of it. The patient is then asked to move this ball into a target. There are three levels with increasing difficulty, where the ball goes from being fixed in position to being able to freely move and fall off the bar (depending on how level the patient keeps the bar). A measure of visuomotor skill and motor range and coordination.	Perceptual-Motor
	Object Hit	OH	Paddles appear at the patients hands and they are instructed to hit as many balls (which fall from the top of the screen) away as possible. As the task progresses the quantity and speed at which the balls fall increases. A measure of attention and visuomotor.	Perceptual-Motor, Complex Attention
	Object Hit and Avoid	OH+A	Similar to OH, but this time patients are shown 2 shapes which they must hit away while avoiding all the other distractor targets. Again, as the task progresses the quantity and speed at which the targets fall increases. A measure of attention, visuomotor, and executive function.	Perceptual-Motor, Complex Attention, Executive Function
	Visually Guided Reaching	VGR	A target appears on the screen and the patient is asked to move the dot that represents their hand into the appeared target as quickly and accurately as possible. A measure of visuomotor capabilities.	Perceptual-Motor
	Reverse Visually Guided Reaching	RVGR	Similar to VGR, but the light representing the hand now moves in the opposite direction of the arm movement. A measure of visuomotor and executive function.	Perceptual-Motor, Complex Attention, Executive Function
	Spatial Span	SS	The patient is shown a sequence and is then asked to replicate it. The length of the sequence depends on if the patient got the previous sequence correct or not. A measure of working memory.	Learning and Memory

	Trail Making Test A	TMT-A	The patient is asked to connect the numbers 1-25 in order as quickly as possible. The number arrangement is predetermined and no connecting lines may overlap. A measure of visuomotor and attention.	Perceptual-Motor, Complex Attention
	Trail Making Test B	TMT-B	Similar to TMT-A, but the patient is now asked to alternate between number and letters (1-A-2-B-3) as quickly as possible. The arrangement again is predetermined and no connecting lines may overlap. A measure of visuomotor, attention, and executive function.	Perceptual-Motor, Complex Attention, Executive Function

Table 10: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) domains assessed, along with the tasks that make up each domain on the assessment. Additionally, it includes Kinarm task descriptions and abbreviations used throughout the manuscript. Task descriptions were obtained from Kinarm manual[58]. All domains and tasks are related to their corresponding DSM-V neurocognitive domain. N/A is no abbreviation was used in the manuscript for these domains.

Table 11: Patient Characteristics: Chronic Kidney Disease

Patient Characteristic	**Total Cohort N= 49**
Age (Mean, Range)	64.9 (35-86)
Sex (N, %)	
Male Female	32 (65.3) 17 (34.7)
Handedness (N, %)	
Right Left	44 (89.8) 5 (10.2)
English As A Second Language (N, %)	
No	47 (95.9)
Yes	2 (4.1)
Ethnicity (N, %)	
Caucasian	43 (87.8)
Indigenous	3 (6.1)
Caucasian and Indigenous Chinese	1 (2.0) 1 (2.0)
Not Reported	1 (2.0)
Highest Reported Education (N, %)	
Grade 8-11	7 (14.3)
Grade 12	12 (24.5)
College	9 (18.4)
University	16 (32.7)
Masters	4 (8.2)
PhD	1 (2.0)
Cause Of CKD (N, % of Total N)	
Diabetic Nephropathy	25 (51.0)
Hypertension	18 (36.7)
Cardiovascular[a]	10 (20.4)
Polycystic Kidney Disease	6 (12.2)
Focal Segmental Glomerulosclerosis (FSG)	3 (6.1)
Other[b]	9 (18.4)
Co-morbidities (N, % of Total N)	
Diabetes	33 (67.3)
Hypertension	34 (69.4)
Cardiovascular[c]	34 (69.4)
Sleep Apnea	18 (36.7)
Other[d]	34 (69.4)
Stage Of CKD (N, %) mL/min/1.73 m²	
Stage 4 (eGFR 15-29 mL/min/1.73 m²)	10 (20.4)
Stage 5 (eGFR <15 mL/min/1.73 m²)	39 (79.6)
eGFR (Mean, Range) mL/min/1.73 m²	12.6 (5-29)
Creatinine (Mean, Range) umol/L	421 (180-786)
Urea (Mean, Range)[e] mmol/L	24.6 (11.9-47.1)

Table 11: Summary of patient clinical and demographic variables. Abbreviations: CKD - Chronic kidney disease. eGFR - estimated glomerular filtration rate. Note: cause of CKD was multifactorial for the majority of patients, therefore if the cause of CKD was determined to be both diabetes and hypertension it was accounted for in both sections.

[a]Cardiovascular causes of CKD: cardio-renal syndrome (N=4), Vasculitis (N=2), peripheral vascular disease (N=2), and ischemic cardiac disease (N=2).

[b]Other causes of CKD: IgA nephropathy (N=2), Lithium use (N=1), Nephrotic Syndrome (N=1), obstructive uropathy (N=1), and unknown (N=4).

[c]Cardiovascular co-morbidities: coronary heart disease (N=17), peripheral vascular disease (N=7), congestive heart failure (N=4), atrial fibrillation (N=3), myocardial infraction (N=1), pacemaker (N=1), pseudo-aneurysm in coronary artery (N=1).

[d]Other co-morbidities: hyperlipidemia (N=15), gout (N=9), hypothyroidism (N=6), hyperthyroidism (N=4).

[e]Urea values were unavailable for 2 patients.

Table 12: Linear Regression RBANS: Chronic Kidney Disease

RBANS								
Total Scale Score	Standard Error	t value	Pr(>|t|)	RSE	DOF	R^2	F-Statistic	p-value
Age	0.20	1.09	0.284					
Sex (Male)	4.28	-1.37	0.18					
Diabetes (Yes)	4.81	-0.56	0.58					
Hypertension (Yes)	4.98	-0.47	0.64					
Education (Grade 12 and Lower)	4.02	-4.22	**0.0001**					
Cardiovascular (Yes)	4.40	-1.05	0.30					
Final Model	N/A	N/A	N/A	12.96	41	0.42	4.92	**0.0072**
Immediate Memory	Standard Error	t value	Pr(>|t|)	RSE	DOF	R^2	F-Statistic	p-value
Age	0.25	0.94	0.36					
Sex (Male)	5.05	0.11	0.91					
Diabetes (Yes)	5.89	-1.80	0.080					
Hypertension (Yes)	5.44	0.32	0.75					
Education (Grade 12 and Lower)	4.36	-2.93	**0.0057**					
Cardiovascular (Yes)	4.78	-2.79	0.01					
Final Model	N/A	N/A	N/A	13.51	38	0.46	5.49	**0.0004**
Visuospatial	Standard Error	t value	Pr(>|t|)	RSE	DOF	R^2	F-Statistic	p-value
Age	0.27	-0.74	0.47					
Sex (Male)	5.74	-0.19	0.85					
Diabetes (Yes)	6.42	0.11	0.91					
Hypertension (Yes)	6.44	-1.08	0.29					
Education (Grade 12 and Lower)	5.44	-3.86	**0.0004**					
Cardiovascular (Yes)	5.85	-0.13	0.90					
Final Model	N/A	N/A	N/A	17.44	41	0.31	3.03	**0.015**
Language	Standard Error	t value	Pr(>|t|)	RSE	DOF	R^2	F-Statistic	p-value
Age	0.13	-0.71	0.48					
Sex (Male)	2.49	-3.54	**0.0010**					
Diabetes (Yes)	2.75	-0.12	0.91					
Hypertension (Yes)	2.75	0.25	0.80					
Education (Grade 12 and Lower)	2.38	-3.55	**0.001**					
Cardiovascular (Yes)	2.52	0.19	0.85					
Final Model	N/A	N/A	N/A	7.37	40	0.43	5.09	**0.0006**
Attention	Standard Error	t value	Pr(>|t|)	RSE	DOF	R^2	F-Statistic	p-value
Age	0.23	0.41	0.686					
Sex (Male)	4.87	-1.63	0.111					
Diabetes (Yes)	5.44	0.23	0.82					
Hypertension (Yes)	5.46	-0.91	0.371					
Education (Grade 12 and Lower)	4.61	-2.89	**0.006**					
Cardiovascular (Yes)	4.96	-1.06	0.29					
Final Model	N/A	N/A	N/A	14.78	41	0.29	2.73	**0.025**
Delayed Memory	Standard Error	t value	Pr(>|t|)	RSE	DOF	R^2	F-Statistic	p-value
Age	0.25	0.02	0.99					
Sex (Male)	4.85	-0.88	0.39					
Diabetes (Yes)	5.74	-0.91	0.37					
Hypertension (Yes)	5.78	0.92	0.36					
Education (Grade 12 and Lower)	4.35	-2.67	**0.011**					
Cardiovascular (Yes)	4.62	-1.17	0.25					
Final Model	N/A	N/A	N/A	13.60	39	0.26	2.24	0.06

Table 12: Linear regression models for each neurocognitive task of the RBANS. Models were exploratory in nature containing both clinical and demographic variables. Significant findings are represented in bold. Abbreviations in the table: RSE= residual standard error and DOF= degrees of freedom, N/A= not applicable, eGFR= estimated glomerular filtration rate.

Table 13: Linear Regression Kinarm: Chronic Kidney Disease

KINARM								
Arm Position Matching	Standard Error	t value	Pr(>|t|)	RSE	DOF	R^2	F-Statistic	p-value
Age	0.01	0.83	0.41					
Sex (Male)	0.24	1.42	0.16					
Diabetes (Yes)	0.29	1.22	0.23					
Hypertension (Yes)	0.26	-1.50	0.14					
Education (Grade 12 and Lower)	0.21	1.41	0.17					
Cardiovascular (Yes)	0.23	-0.90	0.38					
Final Model	N/A	N/A	N/A	0.67	39	0.19	1.51	0.20
Ball on Bar	Standard Error	t value	Pr(>|t|)	RSE	DOF	R^2	F-Statistic	p-value
Age	0.011337	1.75	0.09					
Sex (Male)	0.22	-3.10	**0.004**					
Diabetes (Yes)	0.28	1.67	0.104					
Hypertension (Yes)	0.26	0.58	0.57					
Education (Grade 12 and Lower)	0.20	2.58	**0.01**					
Cardiovascular (Yes)	0.21	-0.03	0.97					
Final Model	N/A	N/A	N/A	0.61	37	0.34	3.20	**0.012**
Object Hit and Avoid	Standard Error	t value	Pr(>|t|)	RSE	DOF	R^2	F-Statistic	p-value
Age	0.01777	-1.57	0.124					
Sex (Male)	0.30983	2.50	**0.017**					
Diabetes (Yes)	0.37847	0.80	0.43					
Hypertension (Yes)	0.37618	1.50	0.14					
Education (Grade 12 and Lower)	0.26423	0.42	0.68					
Cardiovascular (Yes)	0.29	1.50	0.14					
Final Model	N/A	N/A	N/A	0.81	38	0.38	3.87	**0.004**
Object Hit	Standard Error	t value	Pr(>|t|)	RSE	DOF	R^2	F-Statistic	p-value
Age	0.01581	-1.40	0.170					
Sex (Male)	0.28249	1.81	0.079					
Diabetes (Yes)	0.32924	1.44	0.16					
Hypertension (Yes)	0.31281	-0.25	0.801					
Education (Grade 12 and Lower)	0.24939	0.96	0.34					
Cardiovascular (Yes)	0.2634	0.34	0.74					
Final Model	N/A	N/A	N/A	0.78	39	0.30	2.75	**0.03**
Reverse Visually Guided Reaching	Standard Error	t value	Pr(>|t|)	RSE	DOF	R^2	F-Statistic	p-value
Age	0.01616	1.81	0.08					
Sex (Male)	0.34	0.22	0.83					
Diabetes (Yes)	0.38	1.75	0.09					
Hypertension (Yes)	0.38	-0.47	0.64					
Education (Grade 12 and Lower)	0.32	2.16	**0.04**					
Cardiovascular (Yes)	0.35	-0.49	0.63					
Final Model	N/A	N/A	N/A	1.00	40	0.21	1.72	0.14

Visually Guided Reaching	Standard Error	t value	Pr(>|t|)	RSE	DOF	R^2	F-Statistic	p-value
Age	0.0145	1.91	0.064					
Sex (Male)	0.29	-0.34	0.74					
Diabetes (Yes)	0.34	2.39	**0.021**					
Hypertension (Yes)	0.32	-1.44	0.16					
Education (Grade 12 and Lower)	0.25	1.90	0.06					
Cardiovascular (Yes)	0.28	-0.04	0.97					
Final Model	N/A	N/A	N/A	0.82	41	0.22	1.96	0.09
Spatial Span	Standard Error	t value	Pr(>|t|)	RSE	DOF	R^2	F-Statistic	p-value
Age	0.01	-1.94	0.060					
Sex (Male)	0.16	2.47	**0.019**					
Diabetes (Yes)	0.21	-0.14	0.89					
Hypertension (Yes)	0.20	-0.94	0.35					
Education (Grade 12 and Lower)	0.15	1.90	0.065					
Cardiovascular (Yes)	0.15	0.36	0.72					
Final Model	N/A	N/A	N/A	0.44	36	0.33	3.02	**0.017**
Trails Making Test A	Standard Error	t value	Pr(>|t|)	RSE	DOF	R^2	F-Statistic	p-value
Age	0.02	-0.35	0.73					
Sex (Male)	0.43	1.71	0.09					
Diabetes (Yes)	0.54	-0.18	0.86					
Hypertension (Yes)	0.50	-0.03	0.98					
Education (Grade 12 and Lower)	0.35	1.47	0.15					
Cardiovascular (Yes)	0.40	1.24	0.22					
Final Model	N/A	N/A	N/A	1.14	39	0.19	1.51	0.20
Trails Making Test B	Standard Error	t value	Pr(>|t|)	RSE	DOF	R^2	F-Statistic	p-value
Age	0.02	0.43	0.67					
Sex (Male)	0.29	2.00	0.05					
Diabetes (Yes)	0.36	0.26	0.80					
Hypertension (Yes)	0.33	-0.331	0.74					
Education (Grade 12 and Lower)	0.26	4.40	**0.0001**					
Cardiovascular (Yes)	0.28	-0.01	0.99					
Final Model	N/A	N/A	N/A	0.80	37	0.45	4.95	**0.001**

Table 13: Linear regression models for each neurocognitive task of the Kinarm. Models were exploratory in nature containing both clinical and demographic variables. Significant findings are represented in bold. Abbreviations in the table: RSE= residual standard error and DOF= degrees of freedom, N/A= not applicable, eGFR= estimated glomerular filtration rate.

3.8 Figures

Figure 6: Picture of the Kinarm robot used by patients. Patients place their forehead on the cushioned rest at the top of the machine while seated in a chair (not pictured). Then they are asked to grasp the robotic handles and look at the screen inside. Once seated comfortably, the shield is placed around their neck, so they are unable to see their arms.

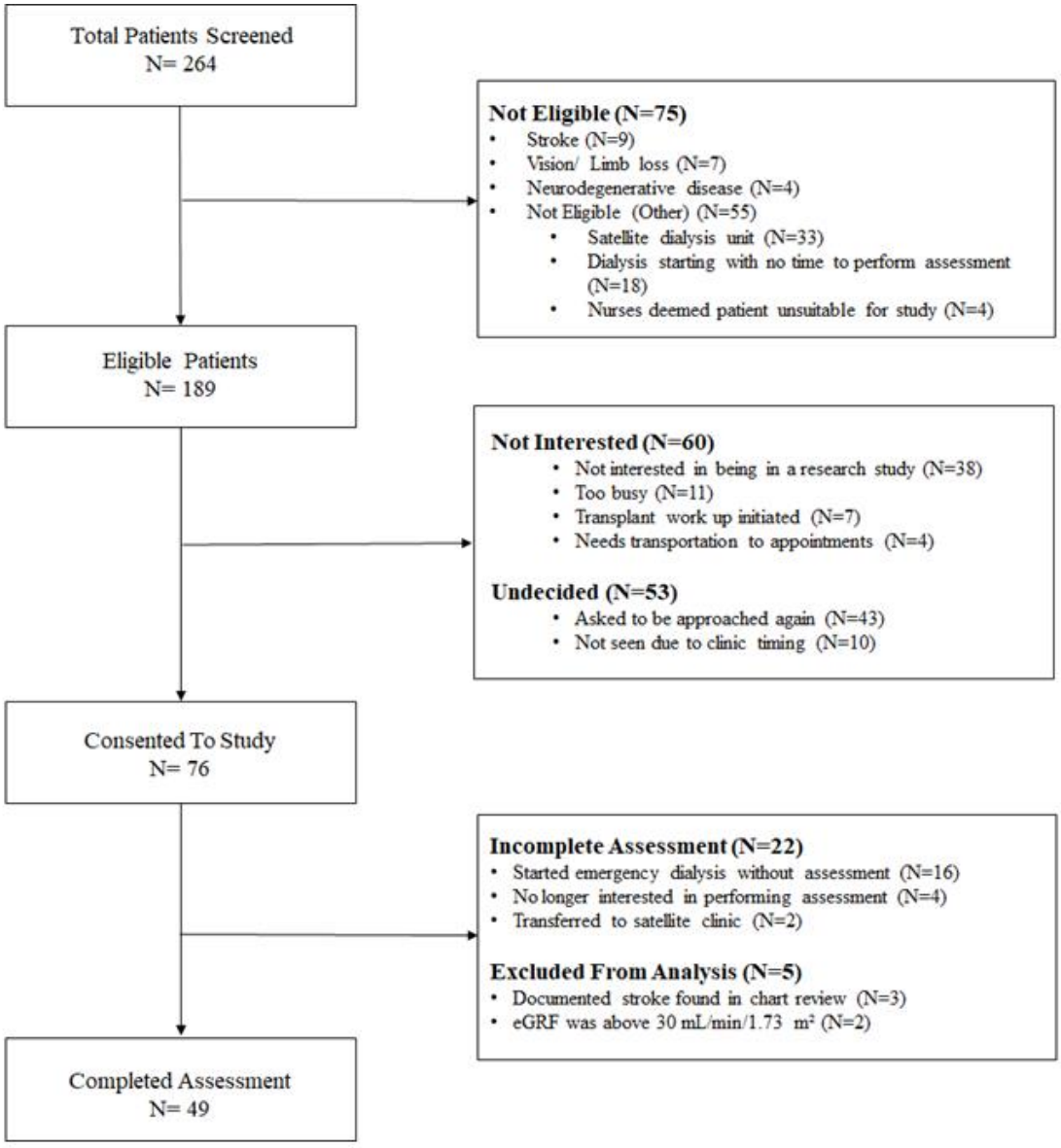


Figure 7: Consort Diagram: Chronic Kidney Disease. For the "not interested" category, any patient that did not specify why they were uninterested in the study was grouped into the "not interested in being in a research study" category. Any patient that was not seen due to clinic timing, or who asked to be approached again were grouped in the undecided approach again category.

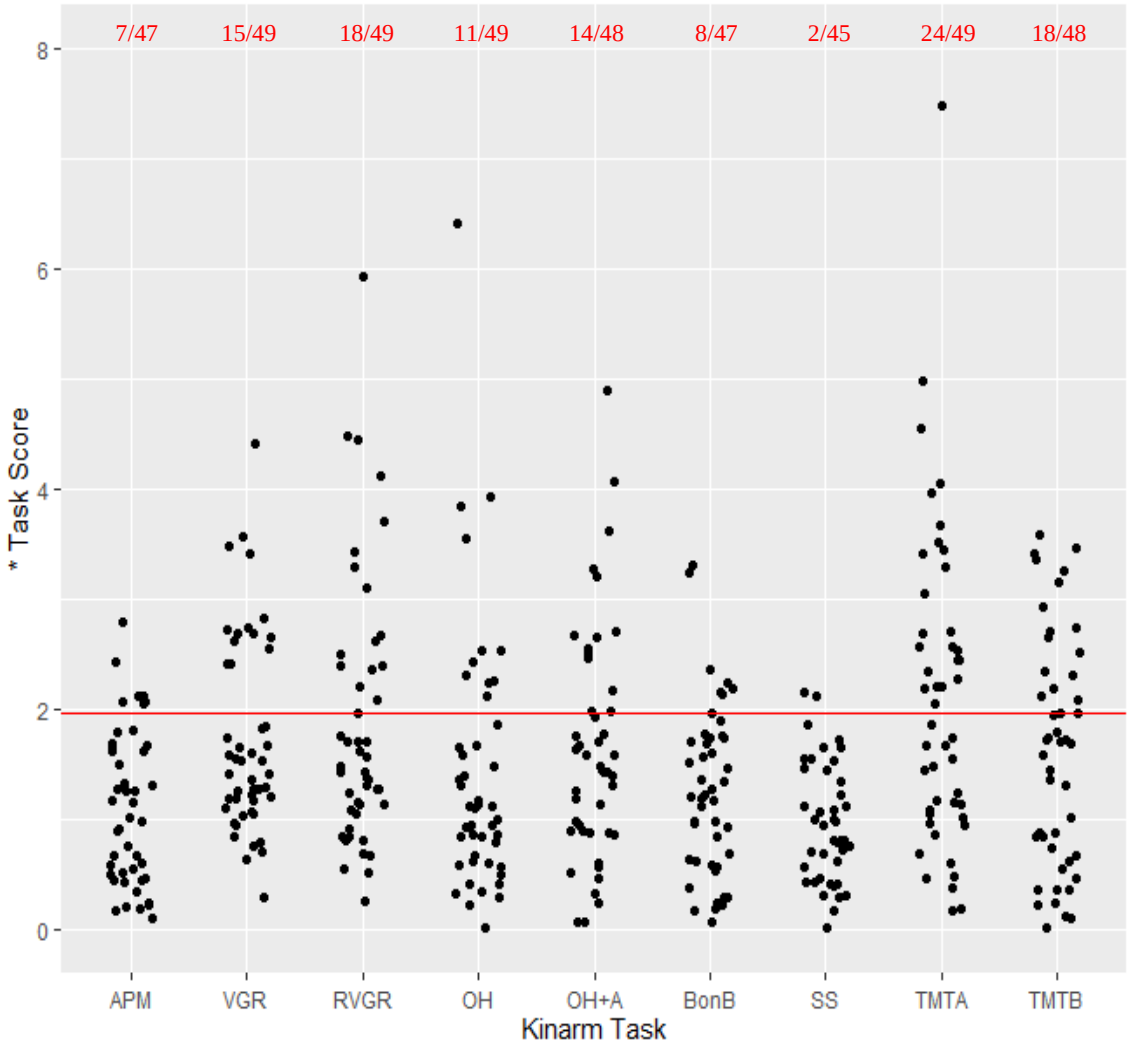


Figure 8: Kinarm Scores: Chronic Kidney Disease. The red line represents the 1.96 SD cut-off. Anything above the red line indicates impairment. Kinarm Task abbreviations are located in Table 10. The red numbers on the top of the graph correspond to the number of patients impaired with respect to the 1.96 SD. Five tasks (APM, OH+A, BonB, TMTB, and SS) had missing data points (N=1 to 4, task dependent) mainly due to testing time constraints.

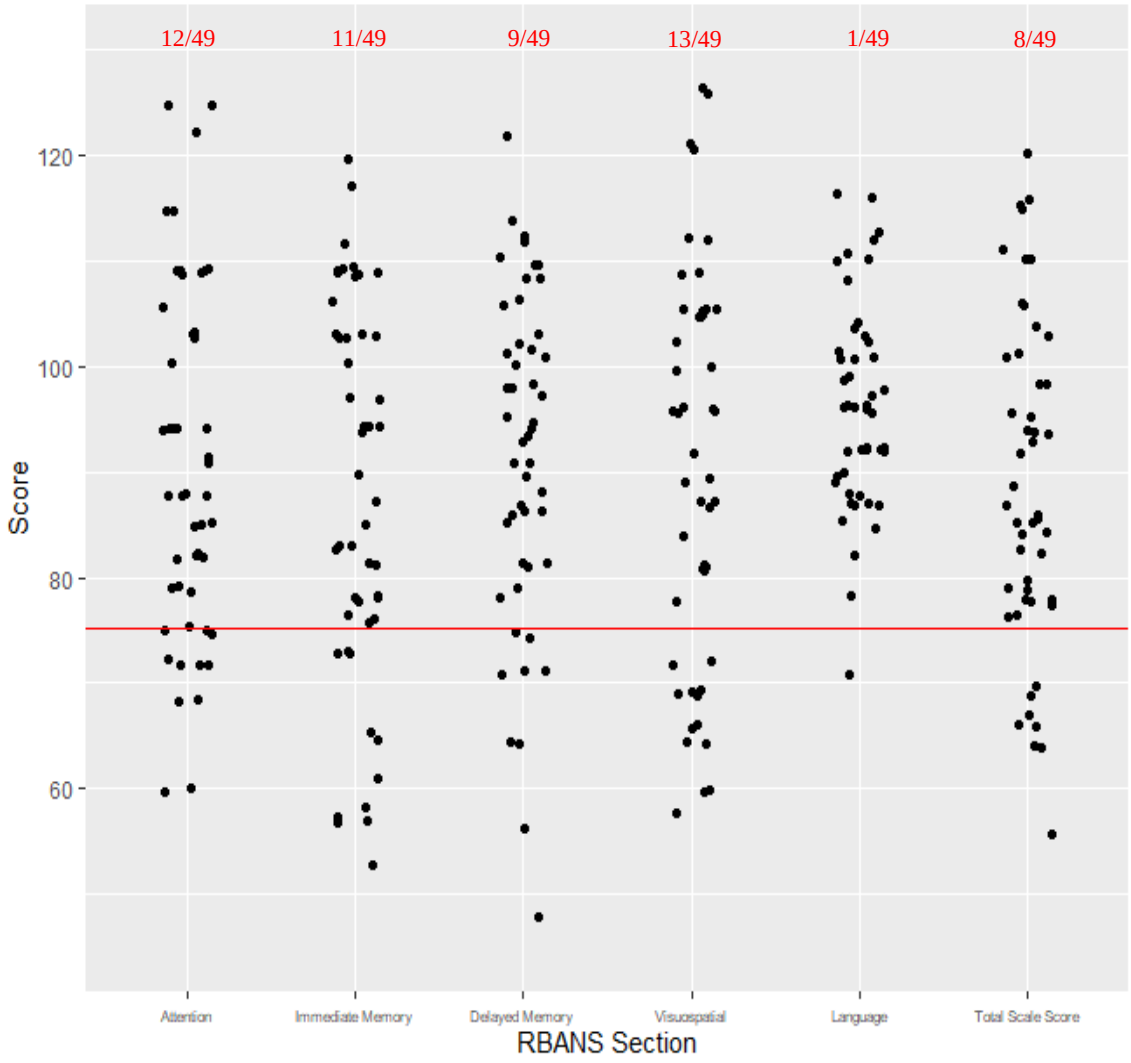


Figure 9: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Scores: Chronic Kidney Disease. The red line represents the 1.65 SD cut-off. Anything below the red line (a score of 75.25) indicates impairment. The red numbers on the top of the graph correspond to the number of patients impaired with respect to the 1.65 SD cut-off.

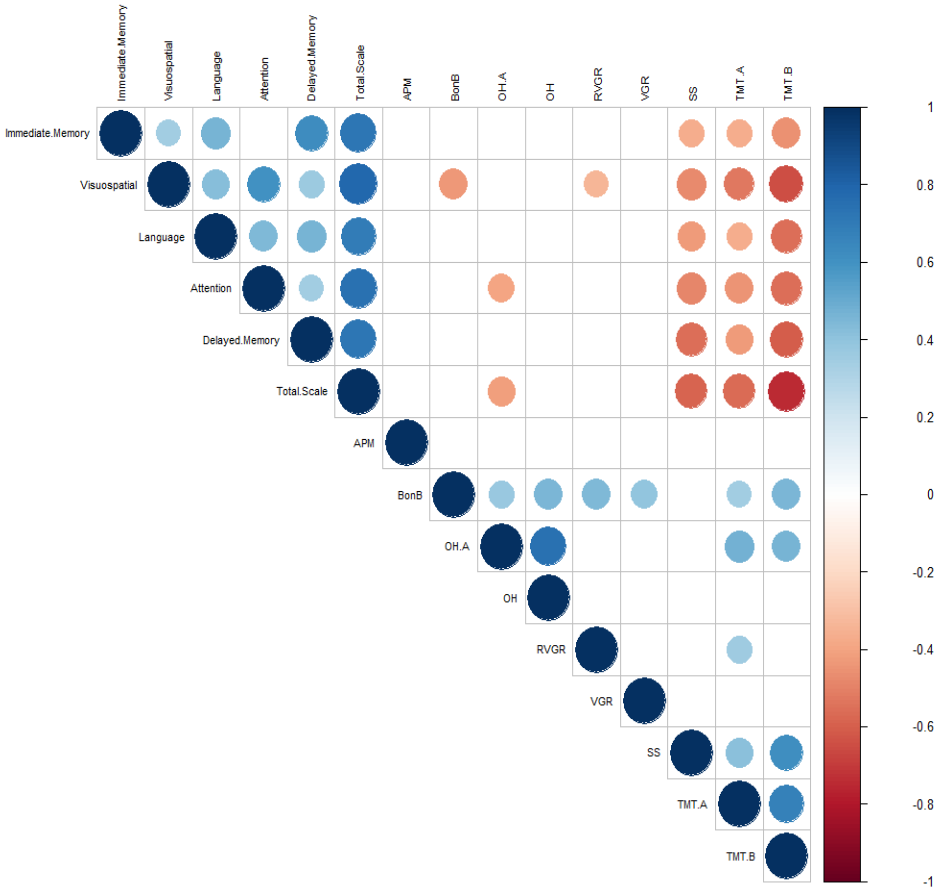


Figure 10: Correlations between RBANS, Kinarm, and linear model predictors: Chronic Kidney Disease. Only the associations that remained significant after the application of the False Discovery Rate for multiple comparisons are shown. Blue represents a positive correlations, whereas red represents a negative one. The color intensity and size of the circle indicates the strength of the association.

Chapter 4

Acute Kidney Injury Is Associated With Subtle But Quantifiable Neurocognitive Impairments

4.1 Abstract

Background: Acute kidney injury (AKI) is associated with long-term morbidity and mortality. The effects of AKI on neurocognitive functioning remain unknown. Our objective was to quantify neurocognitive impairment after an episode of AKI.

Methods: Survivors of AKI were compared to age-matched controls, as well as a convenience sample of patients matched for cardiovascular risk factors with normal kidney function (active control group). Patients with AKI completed two assessments, while the active control group completed one assessment. The assessment included a standardized test: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and a robotic assessment: Kinarm.

Results: The cohort consisted of 21 patients with AKI, 16 of whom completed both assessments, and 21 active control patients. The majority of patients with AKI had Kidney Disease Improving Global Outcomes stage 3 AKI (86%), 57% received dialysis, and 43% recovered to ≤25% of their baseline serum creatinine by their first assessment. Compared to the RBANS which detected little impairment, the Kinarm categorized patients as impaired in visuomotor (10/21, 48%), attention (10/20, 50%), and executive tasks (11/21, 52%) compared to healthy controls. Additionally, patients with AKI performed significantly worse in attention and visuomotor domains when compared to the active controls. Neurocognitive performance was generally not impacted by the need for dialysis or whether kidney function recovered.

Conclusion: Robotic technology identified quantifiable neurocognitive impairment in survivors of AKI. Deficits were noted particularly in attention, visuomotor, and executive domains. Further investigation into the downstream health consequences of these

neurocognitive impairments is warranted.

4.2 Introduction

Acute kidney injury (AKI) defined by the Kidney Disease Improving Global Outcomes (KDIGO) criteria affects 1 in 5 hospitalized adults[13]. AKI is particularly prevalent in patients who undergo cardiovascular surgery[14] or who are critically ill[11]. Regardless of the cause of AKI, patients who experience an episode of AKI have an increased risk of morbidity and mortality[11,12,14].

AKI often occurs in the context of multi-organ dysfunction, either due to the inciting injury affecting multiple organs simultaneously, or as an indirect result of kidney dysfunction[262]. The brain may be particularly vulnerable to dysfunction in the context of AKI. It has been hypothesized that inflammation, uremia, cytotoxicity, osmolality disturbances, and alterations in blood brain barrier permeability are possible mechanisms underlying cerebral dysfunction in patients with AKI[37]. These pathophysiological processes may lead to impaired neurocognitive performance in individuals with AKI.

The neurocognitive outcomes for survivors of AKI have not been extensively studied. Using administrative data, two retrospective studies have demonstrated that a diagnosis of AKI was an independent risk factor for dementia[33,34]. More recently, AKI has been shown to be associated with long-term neurocognitive impairment in children with severe malaria[35]. In patients with chronic kidney disease (CKD), the high burden of neurocognitive impairment is well-described, and affects the domains of attention, memory, and executive function[263]. We also recently demonstrated that robotic technology can precisely quantify impairments in visuomotor function in patients with CKD[264]. In contrast, there is no prospective data on adult neurocognitive impairment after AKI.

The objective of this prospective observational study was to use robotic technology (Kinarm) to quantify neurocognitive impairment in patients who recently experienced an episode of AKI. In this study, neurocognitive performance was compared to both healthy controls, as well as an active control group: patients matched for cardiovascular risk factors (but without any history of kidney disease). We hypothesize that Kinarm will be able to identify impairments in patients with AKI that are not detected using a traditional clinical assessment tool, and that patients with AKI will perform worse than patients without kidney disease.

4.3 Material and Methods

Study Design, Location, Participants, and Data Acquisition

This prospective observational study was performed at a tertiary academic teaching hospital, where eligible patients were recruited from a specialized AKI Follow-up Clinic[265]. Adult (>17 years) patients were eligible if their AKI event occurred recently (< 1 year), and had KDIGO stage 2-3 AKI. Patients who were diagnosed as KDIGO stage 1 AKI, were eligible for the AKI Follow-up Clinic if they had KDIGO stage 1 AKI with pre-existing CKD and/or incomplete kidney recovery at hospital discharge (serum creatinine (Cr) ≥ 25% of pre-AKI baseline). Patients were excluded if they had any documented history of stroke, neurodegenerative disease, neurocognitive impairment, psychiatric diagnosis (e.g. schizophrenia), vison loss that was not corrected, were kidney transplant recipients, or had a baseline estimated *glomerular filtration rate* (eGFR) <15mL/min/1.73m^2. Informed consent was provided before any neuropsychological assessments were performed or clinical data was abstracted. The cause of AKI (nephrologist-adjudicated), co-morbidities, baseline Cr (defined as the closest value that was 7-365 days prior to the episode of AKI[266]), highest hospital Cr, serum Cr, and eGFR values at both neurocognitive test times, along with the AKI KDIGO stages were abstracted from the clinic reports. Demographic variables such as ethnicity, handedness, and highest education were collected at the first neuropsychological assessment. The study was approved by the Queen's University and Affiliated Hospitals Health Sciences Research Ethics Board and was performed in accordance with the Declaration of Helsinki.

Healthy Control and Active Control Groups

For this study, patients recovering from AKI were compared to both a healthy control population (RBANS normalizes scores to age, and Kinarm normalizes scores to age, sex, and handedness), as well as an active control group that was matched for cardiovascular risk factors, such as hypertension and diabetes mellitus which may independently affect neurocognitive performance not captured by healthy controls. This active cohort was selected from a convenience sample of patients awaiting cardiac surgery[248,267]. These patients were selected on the basis of normal pre-operative kidney function and lack of documented neurocognitive impairment and neurocognitive disease. By having a clinical control group that was matched for these cardiovascular risk factors, it allowed for greater certainty that impairment detected was due to the episode of AKI, and not these co-morbidities. Although the mean age of the active control group was younger than the cohort of patients with AKI (Table 14), the Kinarm and RBANS assessments are normalized to age allowing direct comparisons between groups. We only used the pre-operative scores as post-operative neurocognitive impairment may be caused by cardiac surgery[268].

Neurocognitive Assessment

The neurocognitive assessment was performed two times during the study. The first assessment was performed either on the day of consent, or the next clinic appointment. The second assessment was then completed on the patient's next clinic appointment following their previous assessment. The mean time between the AKI event and assessments is shown in Table 14. The neurocognitive assessment consisted of a standardized clinical assessment for measuring cognitive decline or improvement[52]: The Repeatable Battery for the

Assessment of Neuropsychological Status (RBANS), and a robotic assessment that quantifies sensory, motor, and cognitive performance[53]: Kinarm Endpoint Lab (Kinarm)[54]. The assessment took on average one hour and twenty minutes to complete, and was administered by trained research staff. We recently demonstrated the feasibility of this assessment battery on patients with CKD[264].

The RBANS domains and components, Kinarm task descriptions, and affiliated neurocognitive domains are shown in Table 15. Specifically, the RBANS measures 5 domains: immediate memory, delayed memory, attention, visuospatial, and language. These 5 domains are summarized by a composite score, the Total Scale Score. The final scores of the RBANS were standardized by age. A score that is < 75.25 (1.65 standard deviations (SD) below the mean of 100) was considered impaired[264]. The mean and standard deviation for the RBANS normative population is derived from healthy, age-matched control individuals[16].

In comparison, Kinarm quantifies performance in the sensory, motor, and cognitive domains to produce a summarized performance score known as the task score. This task score is based on task parameters, along with spatial and temporal aspects of movement[58,269]. Additionally, the task score is a normalized measure of performance that is generated from a large cohort of healthy individuals (range = 94 to 494, depending on the task). This healthy cohort provides the values for each task parameter that are used to create a Box-Cox transformations, which converts this data into a standard normal distribution (mean = 0, standard deviation = 1, distribution symmetric) including regression models to factor out the influence of age, sex, and handedness on performance. These normalized parameters are then aggregated together and transformed into z-task scores

(standard normal distribution) before a final transformation to a positive value such that task scores near 0 reflect best performance and values of 1 and 1.96 reflect performance at the 68th and 95th percentile respectively, for the healthy cohort. These equations are implemented in the software used to run the Kinarm tasks (Dexterit-E, version 3.9) generating a normalized measure of performance for each participant in the present study. Impairments were defined as a task score >1.96, which corresponds to performance below the 95th percentile of the healthy cohort.

To minimize learning effects on the subsequent assessment, different RBANS versions were used for each assessment. For Kinarm, previous research has found that there was good retest reliability along with minimal practice effects for most tasks in both adults[55] and children[56], although there is some learning effect for the reverse visual guided reaching task[269]. The Kinarm also uses different variations of the tasks for trails making test forms A and B, along with different targets for the task of object hit and avoid.

Data Analysis

Descriptive statistics were used to describe the patients' neurocognitive performance. To determine whether there were any significant clinical or demographic differences between the AKI cohort and the active controls, a T-test or Fisher's exact test was performed as appropriate, with a p-value <0.05 being deemed significant. Z-task scores were used for statistical comparisons between groups regrading Kinarm data. An analysis of variance (ANOVA) followed by a Tukey's HSD post hoc test was used to determine if there were any significant differences in performance between the two cohorts at either testing time, while accounting for multiple comparisons when investigating if AKI severity impacted performance. All graphs and analyses were preformed using R software[255].

4.4 Results

Enrollment

Participants with AKI were enrolled from May 2018 through March 2020 (Figure 11). During this time, 94 patients were screened, 64 were considered eligible, and 43 consented. Most ineligible patients were discharged from the clinic or were deemed unsuitable by the physician due to a psychiatric diagnosis. Of the eligible patients, 11 were not interested and 10 were undecided at the time they were approached. Of the 43 patients that consented, 15 were not able to undergo any testing due to COVID-19 pandemic restrictions, 5 underwent 1 assessment only, 4 withdrew consent, and 3 no longer wished to return to clinic. Thus, 16 participants underwent both assessments. The active control group was obtained from patients participating in a separate study examining the neurocognitive consequences of cardiac surgery. Patients in this group were enrolled between April 2014 and December 2019 (Figure 11). During this time, there were 272 eligible patients of which 91 consented to take part in the study. Of those that consented to the study, 88 performed their assessment prior to their cardiac surgery. From this cohort, a convenience sample of 21 patients was selected based on their lack of pre-existing kidney disease.

Patient Characteristics

Clinical and demographic variables for the AKI cohort and the active controls are summarized in Table 14. When comparing these groups, demographics such as ethnicity, handedness, co-morbidities of diabetes and hypertension, and highest reported education were not significantly different (Table 14). Since our active control group was selected on the basis of absent pre-existing kidney disease, unsurprisingly there was significant

differences with regards to creatinine and eGFR at the time of the first assessment (Table 14). The active control group was also younger than the AKI cohort. However, both RBANS and Kinarm assessments are normalized to age facilitating direct comparison between the two groups.

Demographics specific to the patients with AKI are as follows: 6 (29%) had pre-existing kidney disease, with an average baseline Cr of 104 umol/L (standard deviation (SD) 31 umol/L). During their episode of AKI, 12 patients (57%) required dialysis and had a mean highest Cr of 716 umol/L (SD 438 umol/L). 86% (18/21) had KIDGO stage 3 AKI, with the remaining 3 patients having either Stage 2 (2/21, 10%) or Stage 1 (1/21, 5%). The primary cause of AKI consisted of: sepsis (4/21, 19%), rhabdomyolysis (4/21, 19%), cardiovascular related (4/21, 19%), pneumonia (4/21, 19%), and obstruction (3/21, 14%). By the first assessment, 9 patients (43%) had recovered to ≤25% of their baseline serum Cr. During the first assessment, the mean Cr and eGFR was 139 umol/L (SD 60 umol/L) and 48.3 mL/min/1.73 m² (SD 19 mL/min/1.73 m²) respectively. For the second assessment the average Cr and eGFR was 152 umol/L (SD 58 umol/L) and 41 mL/min/1.73 m² (SD 18 mL/min/1.73 m²).

Kinarm Quantifies More Impairment Than RBANS In Patients With AKI

The mean time in between the episode of AKI and first assessment was 6.8 months, and the mean time between the first and second assessments was 4.6 months (Table 14). Regarding the neuropsychological battery, little impairment was detected using the standardized clinical assessment (RBANS) at both assessments for the patients with AKI when compared to healthy control data (Table 15, Figure 12A). At the first assessment, one AKI participant was defined as having global impairment using the composite Total Scale

Score. At the second assessment, no participants were defined as impaired on the Total Scale Score. With regards to the individual domains, participant performance is summarized in Table 15. Specifically, at the first assessment few participants were defined as impaired in the domains of: visuospatial (3/20), delayed memory (3/20), attention (2/20), and immediate memory (1/20). At the second assessment, impaired performance was detected in the domains of visuospatial (2/16) and delayed memory (1/16) only (Table 15).

When comparing patients with AKI to our active control group, there was no difference in mean scores for the Total Scale Score (Figure 12A). The only difference noted in RBANS performance was in the domain of immediate memory (p-value <0.05), where the performance on the second assessment by the AKI cohort was significantly better than their performance at baseline (Figure 12A).

In comparison to the RBANS, the Kinarm categorized a higher proportion of patients with AKI as impaired at both assessments using aged matched healthy controls (Table 15, Figure 12B). At the first assessment, reverse visually guided reaching (11/21), visually guided reaching (10/21), and trails making test form A (10/20) categorized the highest proportion of patients with AKI as impaired (scores >1.96) (Table 15). These tasks specifically measure attention, visuomotor, and executive function (Table 15). The other Kinarm tasks: trails making test form B (5/20, attention, visuomotor and executive function), object hit (4/16, attention and visuomotor), object hit and avoid (4/17, attention, visuomotor and executive function), ball on bar (3/13, visuomotor and motor range and coordination), arm position matching (1/18, proprioception), and spatial span (1/15, working memory) demonstrated varying degrees of impairment at the first assessment (Table 15). The number of patients that were classified as impaired decreased at the second

assessment, however impairments were still detected on 8/9 tasks when compared to the healthy age-matched controls. These tasks included: reverse visually guided reaching (8/16), trails making test forms A+B (6/15), visually guided reaching (5/16), object hit (4/13), object hit and avoid (3/12), ball on bar (2/12), and arm position matching (1/13) (Table 15). Spatial span was the only task that did not categorize any patients with AKI as impaired on the second assessment (Table 15).

When comparing Kinarm performance between the patients with AKI and the active control group, significant performance differences were also detected on 4/9 tasks (Figure 12B). Performance differences between the two groups at the first assessment were seen on the tasks of: arm position matching (p-value <0.05), reverse visually guided reaching (p-value <0.05), visually guided reaching (p-value <0.01), and trails making test form A (p-value <0.001) (Figure 12B). During the second assessment, only one task (object hit) was significantly different (p-value <0.05) between the active control group and the patients with AKI (Figure 12B).

Neurocognitive Performance Mirrors Severity of AKI in Kinarm Tasks Measuring Visuomotor and Attention

The above data suggests that, at least for some Kinarm tasks, patients with AKI are more impaired at their first assessment but recover some neurocognitive function upon repeat testing. To determine whether or not neurocognitive performance mirrored the recovery of renal function, the cohort was subdivided on the basis of whether or not they recovered to $\leq$25% of their baseline serum Cr by the time of their first assessment. When compared to the active control group, there were no differences in RBANS scores (either Total Score or any of the subdomains) for patients that either recovered or did not recover

kidney function at either assessment time point (Figure 13A). In contrast, performance on the Kinarm tasks of visually guided reaching (visuomotor) and trails making test form A (visuomotor, attention) were significantly worse for patients with AKI who had not recovered kidney function, compared to active controls (Figure 13B). This significant difference was seen at the first assessment only (Figure 13B). For patients that had recovered their kidney function, performance on the Kinarm tasks were similar to the active control group, with the exception of trails making test form A where they performed significantly worse than the active controls, but again at the first assessment only (Figure 13B).

The need for dialysis was also used as an indicator for the severity of AKI. There was no significant difference in performance between the active control participants and the participants with AKI regardless of the need for dialysis on any of the sections of the RBANS (Figure 14A). When comparing performance on the Kinarm assessment, only the task of trails making test form A demonstrated significant differences between the groups (Figure 14B). Patients with AKI performed worse than the active control patients at the first assessment, regardless of the need for dialysis (Figure 14B). This difference did not persist at the second assessment.

4.5 Discussion

Although neurocognitive impairment is highly prevalent in patients with chronic kidney disease[235], the impacts of AKI on the brain are largely unknown. This is the first prospective study to quantify neurocognitive functioning in patients who experience a single episode of AKI. We demonstrated that robotic technology was able to quantify subtle impairments in patients who experience an episode of AKI, which were not detected by a traditional assessment (RBANS). Particularly, impairment were seen in the domains of attention, visuomotor, and executive function when compared to healthy controls. When compared to a control group matched for cardiovascular risk factors (but with no history of kidney disease), patients with AKI on average performed worse and had significantly different scores in the domains of attention, visuomotor, and executive function. In addition, performance on tasks was generally not affected by whether or not renal recovery had occurred or if dialysis was required, although the numbers for subgroup analyses were low, thus limiting our ability to draw causal inferences about the association between AKI and neurocognitive performance.

For the majority of our cohort of patients with AKI, no impairment was detected using a common neuropsychological screening battery for neurocognitive impairment. Robotic technology however, was able to quantify robust and often profound impairments in several neurocognitive domains (5-52% impairment, Kinarm task dependent). This is similar to what we have demonstrated in patients with CKD[264], although the impairments in patients with AKI were not as severe. These impairments were detected in approximately 25% of the AKI cohort who were impaired at both initial and follow up assessments, when compared to healthy aged, sex matched controls. Subtle impairments in attention, executive

function, and visuomotor abilities may lead patients to have a lower quality of life, and experience difficulties in everyday tasks. Presently however, follow-up data regarding maintenance and quality of life for patients with AKI post-hospitalization is limited[270], and will need to be addressed in future research.

Interestingly, patients who experience an episode of AKI on average performed worse when compared to an active control group on tasks that measured attention, visuomotor, and executive function. Also notable, worse performance was detected on a task that measured attention and visuomotor capabilities regardless of the severity of AKI. The mechanisms underlying this impairment are not clear. However, an animal model of acute kidney injury demonstrated that mice developed acute locomotor dysfunction, presumably related to high levels of circulating inflammatory cytokines in addition to astrocyte and microglial activation[271]. Future studies should aim to characterize the relationship between neurocognitive, kidney recovery, systemic inflammatory markers, and imaging evidence brain pathology. Additionally, further investigation and stratification via cause of AKI may prove insightful.

This is the first prospective observational study to demonstrate quantitative deficits in neurocognitive function in individuals after a single episode of AKI. However, our study has several limitations. First, the follow-up rate was lower than anticipated. The main reason for this was the COVID-19 pandemic, as many of the patients that were recruited were done so in the months immediately preceding the pandemic. Our hospital also transitioned primarily to virtual visits, which precluded neurocognitive follow-up for a large proportion of our cohort. Secondly, our single-centre design limits external generalizability, as our study only included Caucasian individuals, which reflects our local

demographics (only 5% of our region identified as a visible minority)[272]. This however this is not reflective of the general AKI population[13]. Thirdly, we compared Kinarm to RBANS, which although comprehensive, is not a substitute for a full neuropsychological battery administered by a trained neuropsychologist. Finally, to discern if AKI is the sole cause of the neurocognitive impairment, a larger cohort is needed to untangle the independent effects of AKI from other important covariates, such as underlying precipitant, severity of disease, and co-morbid illnesses.

Despite these limitations, this study has the following strengths. Importantly, this study has a well-defined AKI survivor population that was collected from a specialized AKI referral clinic within a year of the event. Secondly, we used novel robotic technology that provides robust, objective, and quantifiable data on neurocognitive performance, allowing for detection of subtle impairments. Thirdly, we used both healthy control data that was matched to age and sex, along with a matched active control group to quantify the neurocognitive impairment experienced in patients with AKI. Lastly, we are the first investigators to longitudinally investigate the neurocognitive performance after an episode of AKI, demonstrating that impairments are common (and can be severe), which emphasises the need to perform neurocognitive assessments (or at least screening) early in the care of these patients. This study will help guide future research regarding the quantification of neurocognitive impairments experienced by those that survive an episode of AKI.

In summary, this is the first study to quantify impairment in individuals after a recent episode of AKI. By using robotic technology we were able to quantify subtle impairments in attention, executive function, and visuomotor function that were not detected by a routine clinical assessment. Patients with AKI performed worse than individuals matched for age, sex, and handedness, as well patients matched for cardiovascular risk factors. Further studies are needed to discern the true extent of this impairment and how it affects the patients' quality of life, including implications for how the cognitive health of survivors of should be assessed and managed.

4.6 Tables

Table 14: Patient Characteristics: Acute Kidney Injury and Cardiac

Patient Characteristic	**AKI (N= 21)**	**Active Control (N=21)**	**P value**
Age (Mean, Range)	71.4 (57-84)	63.9 (53-79)	**<0.01**
Sex (N, %)			
Male	16 (76.2%)	19 (90.5%)	>0.05
Handedness (N, %)			
Right	20 (95.2%)	20 (95.2%)	>0.05
Ethnicity (N, %)			
Caucasian	21 (100%)	21 (100%)	>0.05
Highest Reported Education (N, %)			
High School College or University Masters Unknown	7 (33.3%) 13 (61.9%) 1 (4.8%) 0 (0%)	9 (42.9%) 8 (38.1%) 3 (14.3%) 1 (4.8%)	>0.05
Co-morbidities (N)			
Diabetes Hypertension Cardiovascular [a] Cancer [b,c] Other [d,e]	9 8 21 7 26	5 12 21 2 22	>0.05 >0.05
Cause of AKI (N, % of Total N)			
Cardiovascular [f] Infection [g] ATN Rhabdomyolysis Obstruction [h] Other [i]	4 (19.0%) 6 (28.6%) 3 (14.3%) 4 (19.0%) 3 (14.3%) 8 (38.1%)		
KDIGO AKI Stage (N, %)			
Stage 1 Stage 2 Stage 3	1 (4.8%) 2 (9.5%) 18 (85.7%)		
Recovered ≤25% of Kidney Function (N, %)			
Yes No	9 (42.9%) 12 (57.1%)		
Baseline Parameters Before Incident AKI			
Baseline Creatinine (Mean, Range) umol/L*	104.1 (67-198)		
Existing Renal Disease (N, %) Yes No Unknown	 6 (28.6%) 14 (66.6%) 1 (4.8%)	 0 (0%) 21 (100%) 0 (0%)	**<0.01**
Hospital AKI Data			
Highest Hospital Creatinine (Mean, Range) umol/L	715.5 (271-1762)		
Required Dialysis Yes No	 12 (57.1%) 9 (42.9%)		
First cognitive testing (N=21)			
Months Between AKI incident and Test 1 (Mean, Range)	6.8 (2-15)		
Creatinine (Mean, Range) umol/L	139.2 (68-361)	81.3 (65-111)	**<0.001**
eGFR (Mean, Range) mL/min/1.73 m²	47.7 (10-98)	84.9 (59-104)	**<0.0001**
Second cognitive testing (N=16)			
Months Between Test 1 and Test 2 (Mean, Range)*	4.6 (4-14)		
Creatinine (Mean, Range) umol/L*	151.5 (76-338)		
eGFR (Mean, Range) mL/min/1.73 m²*	41.4 (11-93)		

Table 14: Summary of baseline characteristics for the AKI and Cardiac Cohorts. Abbreviations: AKI - Acute Kidney Injury, ATN - Acute Tubular Necrosis, eGFR - estimated glomerular filtration rate, KDIGO - Kidney Disease Improving Global Outcomes. * Indicates excluded values that were unknown or not available at the time of assessment, as one patient's pre-AKI creatinine was unknown at the time of the AKI incident and 5 patients did not complete their second assessment. Significant differences between the AKI and cardiac cohort are bolded.

Note: the cause of AKI and patient co-morbidities were multifactorial for the majority of patients. Therefore if AKI was caused by more than one attribute (ex. infection and obstruction), or the patient had more than one co-morbidity in each section (ex. dyslipidemia and gout) it was accounted for in both sections or in the same section depending on the classification.

[a] AKI cardiovascular co-morbidities: coronary artery disease (N=7), atrial fibrillation (N=4), peripheral vascular disease (N=3), pacemaker (N=2), heart failure (N=2), deep vein thrombosis (N=1), transcatheter aortic valve implantation (N=1), and aortic valve replacement (N=1).

[b] AKI cancer co-morbidities: ovarian (N=2), prostate (N=2), colon (N=2), gastric (N=1), and lung (N=1).

[c] Cardiac cancer: ovarian (N=1), and prostate (N=1).

[d]AKI other co-morbidities: sleep apnea (N=6), dyslipidemia (N=4), chronic obstructive lung disease (N=4), gout (N=3), hypothyroidism (N=3), osteoarthritis (N=3), gastroesophageal reflux disease (N=2), and achondroplasia (N=1).

[e]Cardiac other: dyslipidemia (N=7), hypothyroidism (N=3), sleep apnea (N=3),

osteoarthritis (N=3), gastroesophageal reflux disease (N=2), chronic obstructive pulmonary disease (N=2), kidney stones (N=1), and Gilbert Syndrome (N=1).

[f] Cardiovascular causes of AKI: cardiac surgery (N=3), and heart failure (N=1).

[g] Infection causes of AKI: sepsis (N=4), viral gastritis (N=1), and infection unspecified (N=1).

[h]Obstruction cause of AKI: obstructive neuropathy (N=1), bladder obstruction (N=1), and obstruction unspecified (N=1).

[i]Other cause of AKI: pneumonia (N=4), contracted induced (N=2), hepatorenal (N=1), and hyperkalemia (N=1).

Table 15: Neurocognitive Battery Tasks, Task Components and Descriptions, Domains Assessed, and Test Performance For Acute Kidney Injury and Cardiac Patients

Neurocognitive Test	Task/Domain	Task Components/ Task Description	Domain Assessed	AKI Test 1 (N impaired, %)	AKI N Completed Test 1 (Max N=21)	AKI Test 2 (N impaired, %)	AKI N Completed Test 2 (Max N=16)	Active Control (N impaired, %)
RBANS	Attention	Digit Span, Symbol Coding	Attention	2 (10.0%)	20	0 (0%)	16	0 (0%)
	Immediate Memory	List Learning, Story Memory	Memory	1 (4.8%)	21	0 (0%)	16	1 (4.8%)
	Delayed Memory	List Recall, List Recognition, Story Recall, Figure Recall	Memory	2 (10.0%)	20	1 (6.3%)	16	1 (4.8%)
	Visuospatial	Figure Copy, Line Orientation	Visuospatial	3 (15.0%)	20	2 (12.5%)	16	2 (9.5%)
	Language	Picture Naming, Semantic Fluency	Language	0 (0%)	20	0 (0%)	16	0 (0%)
	Total Scale Score	A summary score based on the performance on all the RBANS domains, representative of global performance on the RBANS.	Composite Performance Score	1 (5.0%)	20	0 (0%)	16	0 (0%)
Kinarm	Arm Position Matching	Patients are asked to mirror match the arm position the robot has moved one arm to with their other arm.	Proprioception, Somatosensory	1 (5.6%)	18	1 (7.7%)	13	1 (4.8%)
	Ball on Bar	A bar connects the patients 2 arms with a ball on top of it. Patients are then instructed to place this ball in various targets on the screen. As the task progresses, the ball becomes less fixed to the bar increasing the tasks difficulty.	Visuomotor skill, Motor Range and Coordination	3 (13.0%)	13	2 (16.7%)	12	2 (10%) *
	Object Hit	The patient's hands become paddles and they are instructed to hit as many falling balls away from them as possible. As the task progresses the quantity and speed at which the balls fall increases.	Attention, Visuomotor	4 (25.0%)	16	4 (30.8%)	13	1 (4.8%)
	Object Hit and Avoid	Similar to OH, but this time the patients must only hit 2 specific shapes while avoiding all other shapes. As the task progresses the quantity and speed at which the targets fall increases as in the OH task.	Attention, Visuomotor and Executive Function	4 (23.5%)	17	3 (25.0%)	12	1 (4.8%)
	Visually Guided Reaching	The patients hand is represented by a dot. They are then instructed to move this dot as quickly and accurately as possible into various targets on the screen.	Visuomotor	10 (47.6%)	21	5 (31.3%)	16	2 (9.5%)
	Reverse Visually Guided Reaching	Similar to VGR, but the light representing the hand now moves in the opposite direction of the arm movement.	Visuomotor, Executive Function	11 (52.4%)	21	8 (50.0%)	16	5 (23.8%)
	Spatial Span	Patients are shown a sequence in a 3x4 box matrix and asked to replicate it. The length of the sequence depends on if previous response was correct or not.	Working Memory	1 (6.7%)	15	0 (0%)	12	1 (4.8%)
	Trail Making Test A	The patient is asked to connect the numbers 1-25 in order as quickly as possible.	Attention, Visuomotor	10 (50.0%)	20	6 (40.0%)	15	2 (9.5%)
	Trail Making Test B	Similar to TMT-A, but the patient is now asked to alternate between number and letters (1-A-2-B-3) as quickly as possible.	Attention, Visuomotor, Executive Function	5 (25.0%)	20	6 (40.0%)	15	1 (4.8%)

Table 15: The neurocognitive battery performed by patients. The battery is comprised of: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Kinarm. The table also depicts the domains assessed and tasks that make up these domains for the RBANS, and the Kinarm's task descriptions. Test performance and number of patients who completed the task at each time point are also included, along with the active control group. Patients with AKI did not complete tasks mainly due to time constraints. The number of impaired was determined by a score outside the 95% cut off (RBANS: <75.25, Kinarm: >1.96). * One patient did not complete the ball on bar task in the active control group, making the N value for that task 20. All other tasks for the active control group had an N value of 21.

4.7 Figures

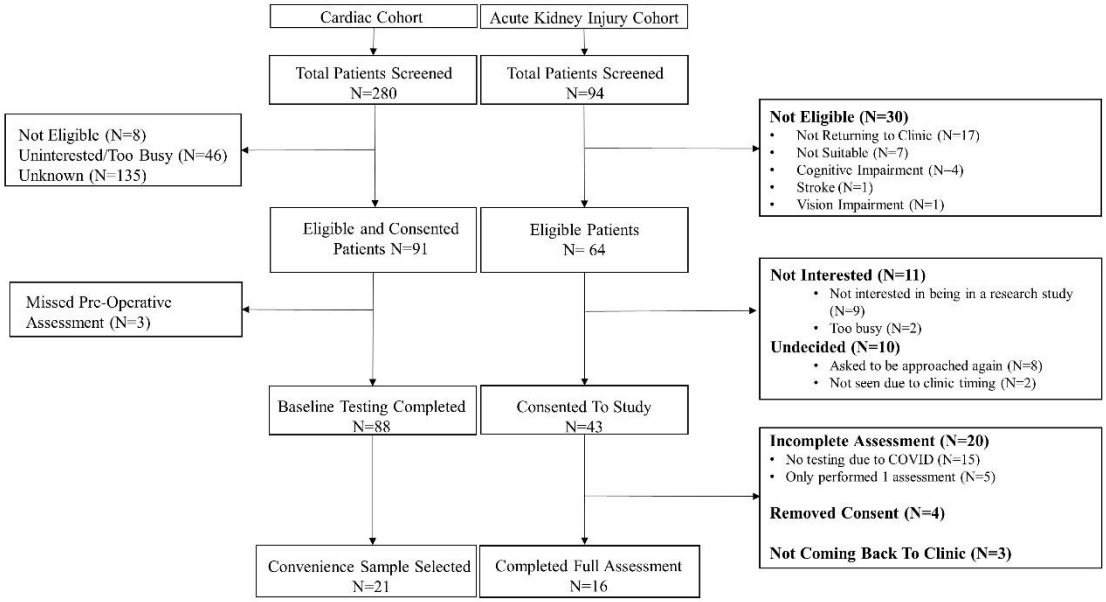
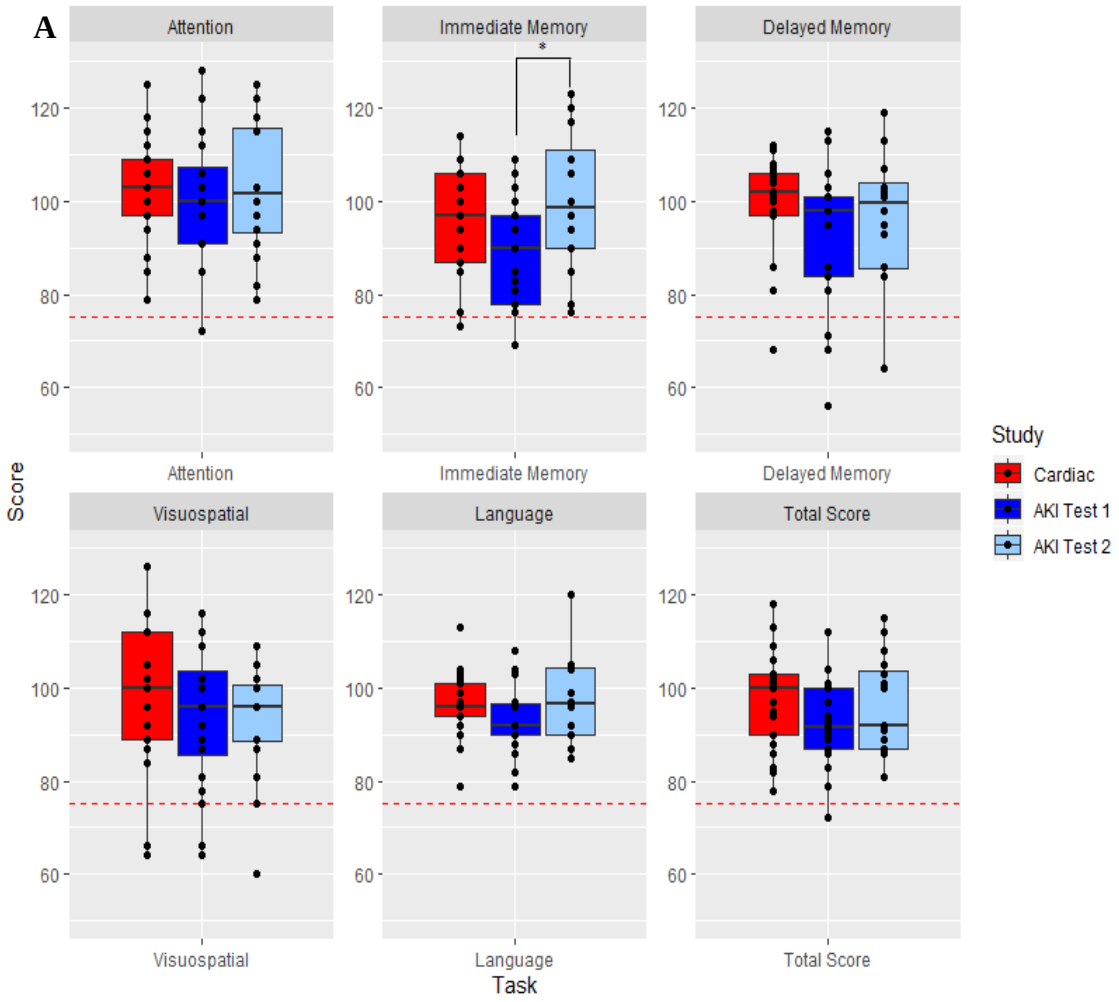


Figure 11: Consort diagrams for AKI and Cardiac Cohorts. AKI recruitment was from May 2018 to March 2020. Note: for the patients with AKI that were deemed unsuitable, this was determined by the physician due their psychiatric diagnosis. The cardiac patients were selected from a group of patients who were awaiting cardiac surgery between April 2014 and December 2019.


A
Attention
Immediate Memory
Delayed Memory
Visuospatial
Language
Total Score
Score
Task
Study
Cardiac
AKI Test 1
AKI Test 2
120
100
80
60
*

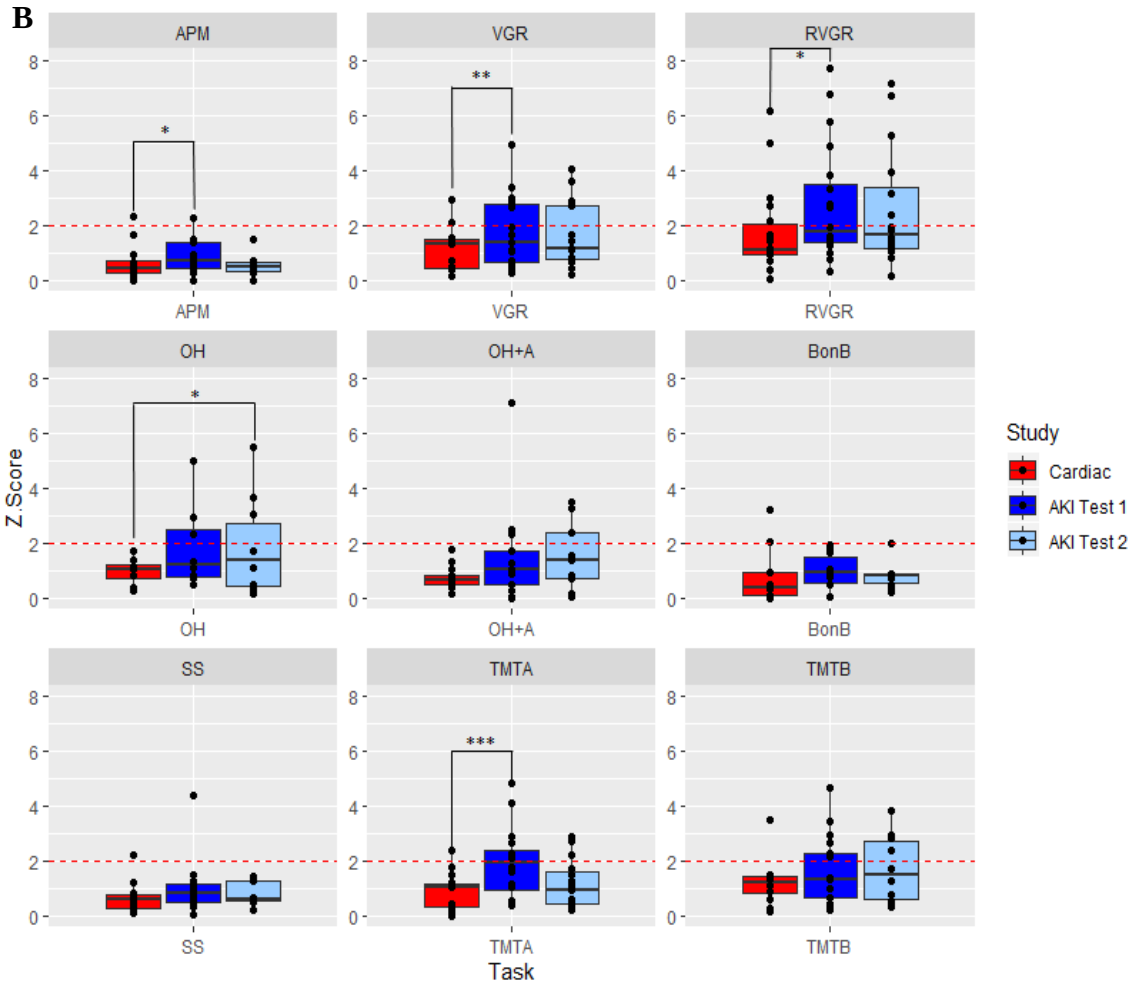
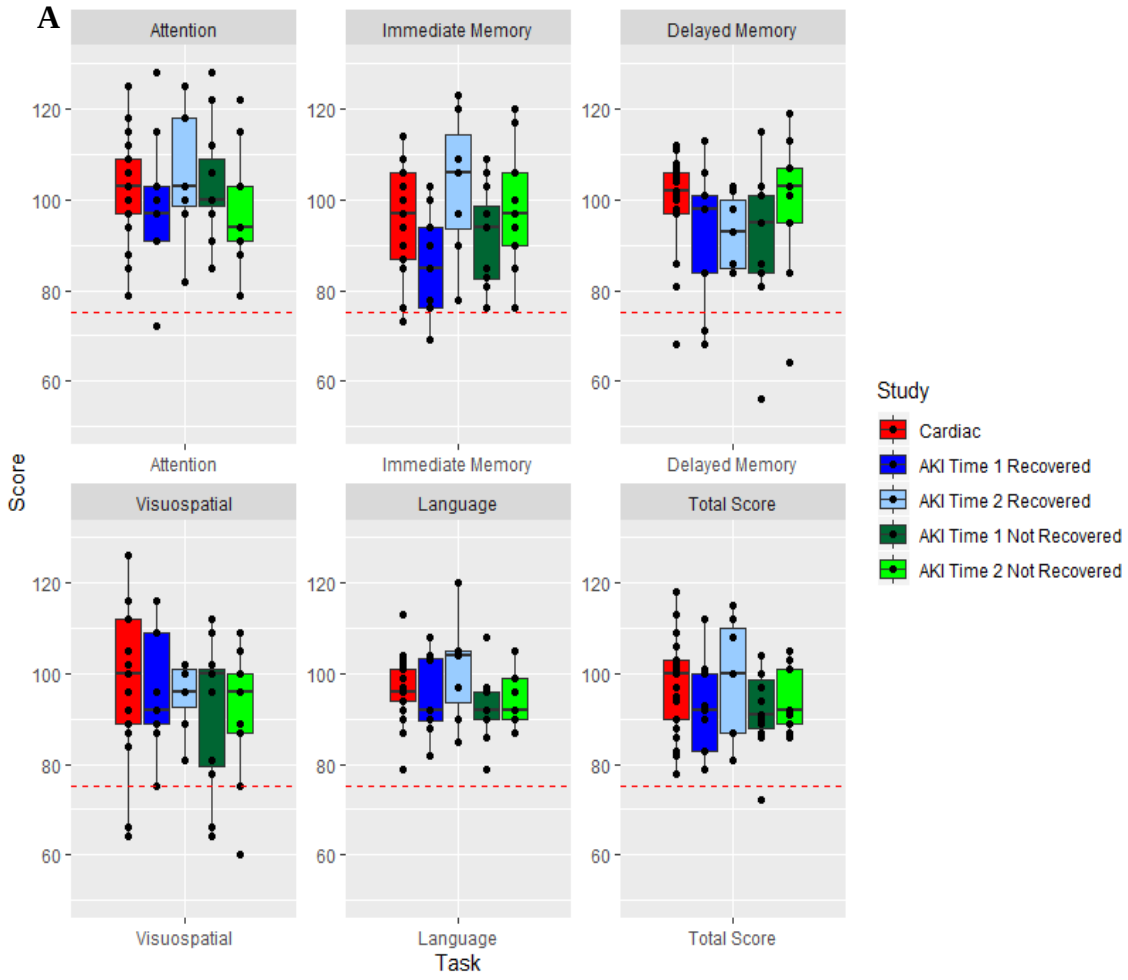


Figure 12: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Kinarm assessments for both cohorts. Figure 12A: depicts the performance on the RBANS. Figure 12B: depicts performance on the Kinarm using Z-scores. In both graphs the dashed red line represents the 95th percentile cut off for normative performance (RBANS: <75.25, Kinarm: >1.96). In Figure 12A performance below the red line indicates impairment, whereas in Figure 12B anything above the line indicated impairment. * indicates performance was significantly different by <0.05, ** indicates significantly different by <0.01, and *** indicates significance <0.001.


A
Attention
Immediate Memory
Delayed Memory
Visuospatial
Language
Total Score
Score
120
100
80
60
Task
Study
Cardiac
AKI Time 1 Recovered
AKI Time 2 Recovered
AKI Time 1 Not Recovered
AKI Time 2 Not Recovered

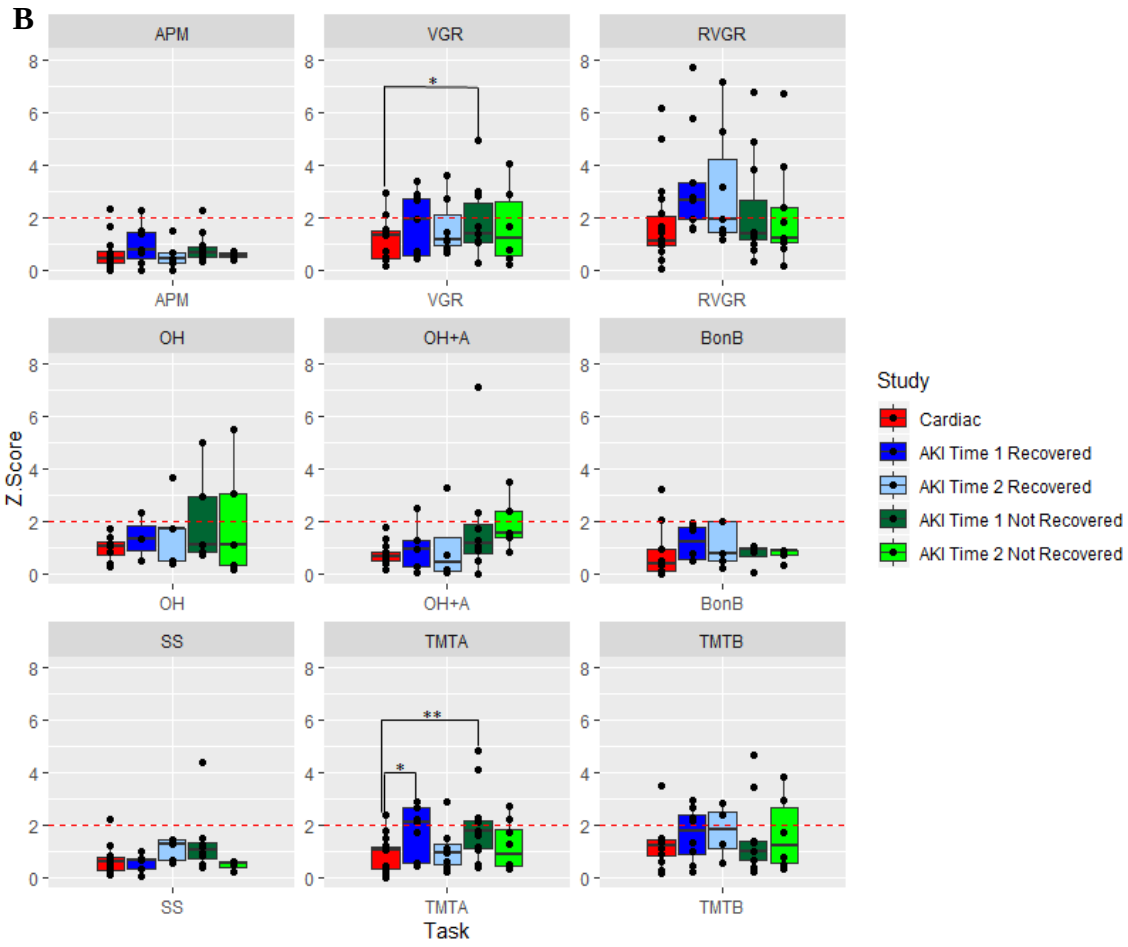
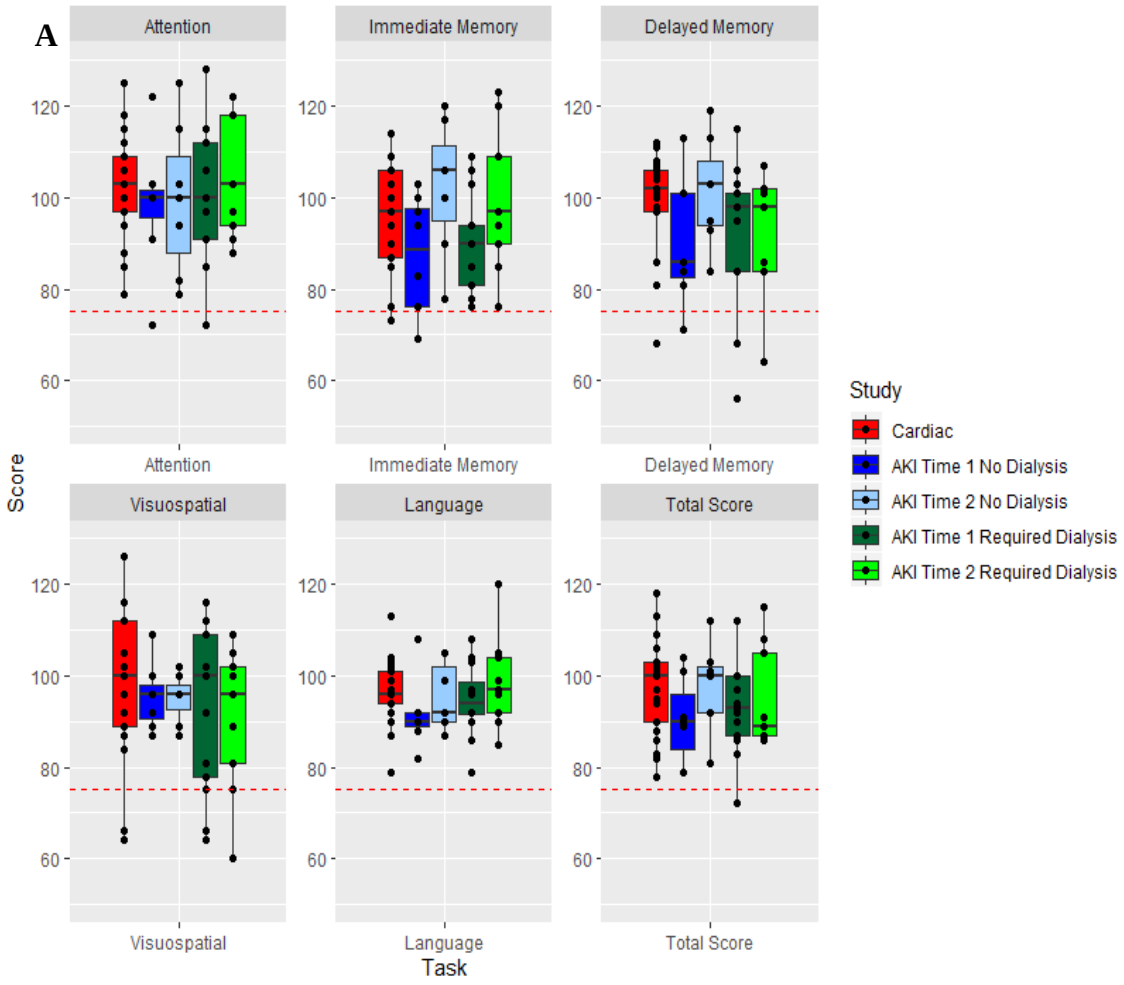


Figure 13: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Kinarm assessments for both cohorts with regards to if the patients with AKI recovered ≤25% of their kidney function or not by their first assessment. Figure 13A: Performance on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Note: the red dashed line at 75.25 represents the 95th percentile cut off and anything below the line indicates impaired neurocognitive performance. Figure 13B: Performance on the Kinarm. Note: the red dashed line at 1.96 represents the 95th percentile cut off and anything above this line indicates impaired neurocognitive performance. * denotes a significant difference in score with a p-value<0.05, ** indicates a p-value <0.01.


A
Attention
Immediate Memory
Delayed Memory
Visuospatial
Language
Total Score
Score
120
100
80
60
Task
Study
Cardiac
AKI Time 1 No Dialysis
AKI Time 2 No Dialysis
AKI Time 1 Required Dialysis
AKI Time 2 Required Dialysis

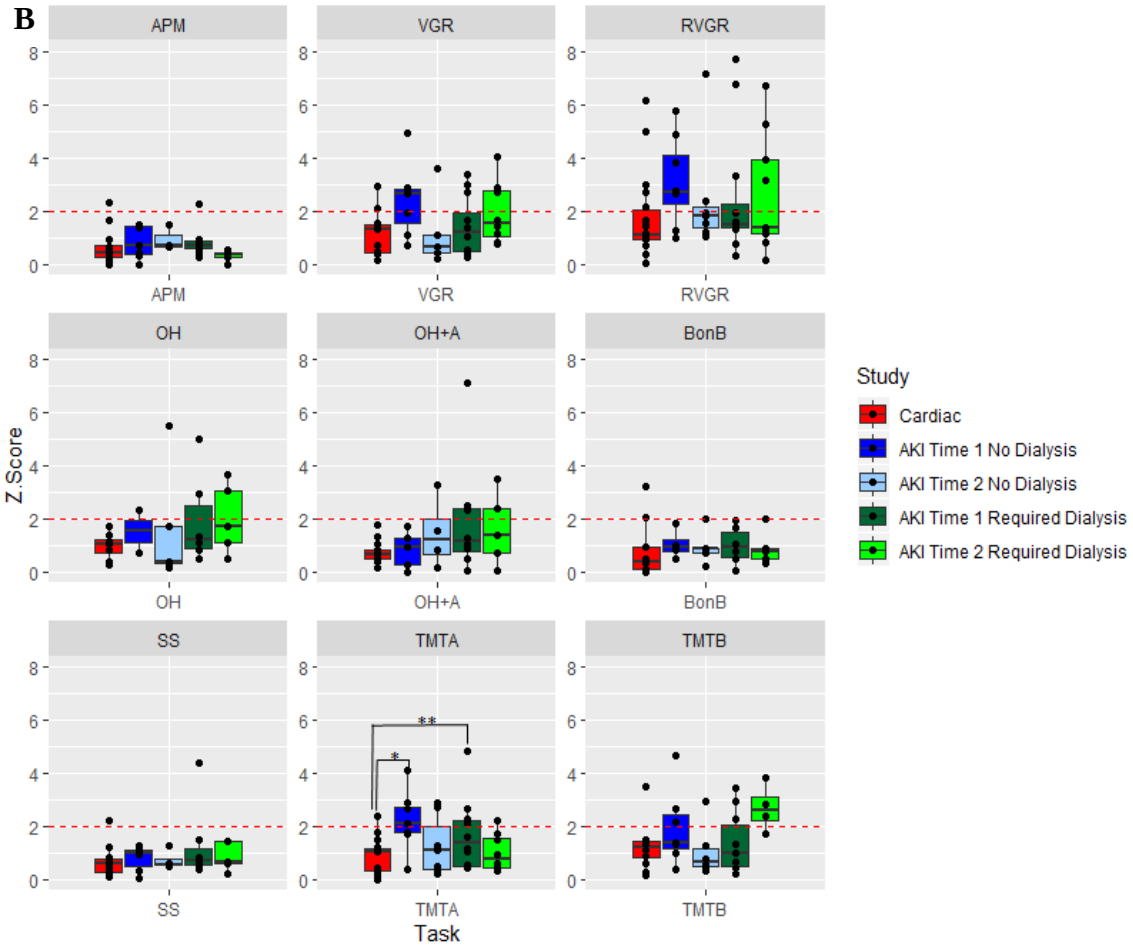


Figure 14: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Kinarm assessments for both cohorts with regards to if the patients with AKI required dialysis or not during their hospitalization. Figure 14A: Performance on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Note: the red dashed line at 75.25 represents the 95th percentile cut off and anything below the line indicates impaired neurocognitive performance. Figure 14B: Performance on the Kinarm. Note: the red dashed line at 1.96 represents the 95th percentile cut off and anything above this line indicates impaired neurocognitive performance. * denotes a significant difference in score with a p-value<0.05, ** indicates a p-value <0.01.

Chapter 5

Cerebral Oxygenation In Hemodialysis Patients - A Feasibility Study

5.1 Abstract

Background: Patients on hemodialysis (HD) are known to exhibit low values of regional cerebral oxygenation (rSO2) and impaired neurocognitive functioning. The etiology of both is currently unknown.

Objective: To determine the feasibility of serially monitoring rSO2 in patients initiating HD. Additionally, we sought to investigate how rSO2 is related to hemodynamic and dialysis parameters.

Design: Prospective observational study.

Setting: Single-centre tertiary academic teaching hospital in Ontario, Canada.

Participants: Six patients initiating HD were enrolled in the study.

Methods: Feasibility was defined as successful study enrollment (>1 patient/month), successful consent rate (>70%), high data capture rates (>90%), and assessment tolerability. rSO2 monitoring was performed 1 time/week for the first year of dialysis. A neuropsychological battery was performed three times during the study: before dialysis initiation, 3 months, and 1 year post dialysis initiation. The neuropsychological battery included a traditional screening tool: The Repeatable Battery for the Assessment of Neuropsychological Status, and a robot-based assessment: Kinarm.

Results: Our overall consent rate was 33% and our enrollment rate was 0.4 patients/month. In total 243 rSO2 sessions were recorded, with a data capture rate of 91.4% (222/243) across the 6 patients. Throughout the study no adverse interactions were reported. Correlations between rSO2 with hemodynamic and dialysis parameters showed individual patient variability. However at the individual level, all patients demonstrated positive correlations between mean arterial pressure and rSO2. Patients that had more than

3 liters of fluid showed significant negative correlations with rSO2. Less neurocognitive impairment was detected after initiating dialysis.

Limitation: This small cohort limits conclusions that can be made between rSO2 and hemodynamic and dialysis parameters.

Conclusions: Prospectively monitoring rSO2 in patients was unfeasible in a single dialysis unit, due to low consent and enrollment rates. However, rSO2 monitoring may provide unique insights into the effects of HD on cerebral oxygenation that should be further investigated.

Trial Registration: Due to the feasibility nature of this study, no trial registration was performed.

5.2 Introduction

Patients with end stage kidney disease undergoing hemodialysis (HD) are known to have moderate to severe neurocognitive impairments, which may go undiagnosed unless formal testing is performed[273]. When examined, patients demonstrate global neurocognitive impairment[273–275], with particular deficits in the domains of executive function[274,276], memory[276], and attention[276]. Despite the high prevalence of neurocognitive impairment in patients undergoing HD, the underlying cause is unknown.

Although the causes of neurocognitive impairment are multi-factorial, it is possible that the process of HD causes detrimental effects to the brain. Particularly, HD may increase the incidence of stroke[277], cause systemic circulatory stress by affecting vulnerable perfusion-dependent vascular beds[278], and produce significant shifts in acid/base balance[279]. Decreases in white matter integrity[204], along with an increased incidence of silent infarcts[280] have also been documented. Prospective serial monitoring of cerebral perfusion has not been performed in patients initiating HD.

Regional cerebral oxygenation (rSO2) is a surrogate marker for cerebral perfusion, and may provide insight into the deleterious cerebral effects of HD. rSO2 can be measured using near-infrared spectroscopy (NIRS), which has been extensively used in cardiac surgery[43], and has been shown to linearly correlate with CT perfusion[281,42]. NIRS was selected for this study as it relatively inexpensive in comparison to magnetic resonance imaging, is portable and requires little training in order to setup, is non-invasive, and allows for continuous monitoring while producing a real-time assessment of the oxygenation status of hemoglobin[41,282]. Studies comparing rSO2 before dialysis initiation to control subjects demonstrated that dialysis patients had lower rSO2 levels than controls, with

values being 40-55% and 70% respectively[41,44–46]. In addition, lower rSO2 levels have been measured in the frontal lobe and extremities during HD, suggesting that tissue ischemia may be occurring[46]. Finally, rSO2 levels have also been negatively correlated with blood pH, diabetes, and the duration of time the patient has been on HD[283]. In addition to NIRS, studies using other imaging modalities have investigated the impact of dialysis on the brain. In particular, a study using diffuser tensor imaging was able to investigate the structural integrity of patients receiving HD and determined that neurocognitive deficits were correlated with white matter damage[49]. Additionally, positron emission tomography–computed tomography determined that global cerebral blood flow decreased by 10+/-15% by the end of a dialysis session[284], and Doppler studies have confirmed this decline and further added that cerebral blood flow declines were related to intradialytic neurocognitive impairment[50].

Our overall hypothesis is that repetitive cerebral hypoperfusion during HD contributes to the neurocognitive impairment reported in patients undergoing HD. However, the feasibility of prospectively monitoring rSO2 in patients initiating HD however is unknown. Therefore, the primary objective of the study was to assess the feasibility of serially monitoring rSO2 weekly for one year after HD initiation. Secondly, relationships between rSO2 with hemodynamic and dialysis parameters were examined, along with changes in patient neurocognitive performance after the initiation of dialysis.

5.3 Material and Methods

Study Design, Location, Participants, and Data Acquisition

This prospective observational study was performed at an academic teaching hospital. Eligible patients were recruited from a multidisciplinary chronic kidney disease (CKD) clinic if they were >17 years old and had chosen in-centre HD as their kidney replacement therapy. Patients were excluded if they had any documented history of stroke or neurodegenerative disease. Patients who also chose home based kidney replacement therapy (home HD or peritoneal dialysis (PD)) were also excluded. All patients provided informed consent before any monitoring or neuropsychological testing was performed. The cause of CKD and co-morbidities were abstracted from clinic reports. Ethnicity, primary language, handedness, and highest education were collected at the first neurocognitive assessment. All hemodynamic and dialysis parameters were collected by Cordiax 5008 dialysis machine in 15 minute intervals during the dialysis sessions. These parameters included: heart rate, blood pressure, total fluid removed, ultrafiltration rate, dialysate temperature, and pre and post dialysis weight. The study was approved by Queen's University and Affiliated Hospitals Health Sciences Research Ethics Board.

Feasibility Definition

Feasibility was defined as: 1) successful patient enrollment (defined as >1 patient/month), 2) successful informed consent (defined as >70%), 3) high rSO2 data capture rates (>90%), and 4) rSO2 sensor monitoring tolerability.

rSO2 Monitoring

The CASMED Foresight cerebral oximeter was used to capture rSO2 during HD. rSO2 monitoring occurred on the first dialysis day of the week (Monday or Tuesday dialysis schedule dependant) for the patients' first year of dialysis. The CASMED oximeter captures and displays the patient's rSO2 level every 2 seconds for the 4 hours they receive their dialysis treatment. Each sensor is 5 centimeters (cm) in length and is placed directly on the forehead, allowing near-infrared light to penetrate roughly 2.5 cm into the frontal cortex [285].

Neurocognitive Assessment

Neurocognitive assessments were performed at three time points: prior to initiation of HD, 3 months, and 1 year after HD initiation. The assessment included the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and a robotic assessment using the Kinarm Endpoint Lab[54] (Kinarm). This battery has recently been proven feasible in quantifying neurocognitive impairment in those with CKD[264], and took approximately one hour and twenty minutes to complete.

The RBANS and Kinarm task components and descriptions are itemized in Table 16. The RBANS tests 5 domains: immediate memory, delayed memory, attention, visuospatial, and language, and is summarized with a composite score (Total Scale Score). Kinarm Standard Tests were used to quantify sensory, motor, and cognitive functions associated with the upper limbs[53]. This robotic assessment provides objective and quantitative measures of neurocognitive performance, and has been shown to detect more impairment in patients with CKD, compared to traditional testing[264]. Kinarm Task Scores are a composite summary score characterizing patient performance by incorporating a

number of spatial and temporal parameters. These Task Scores are corrected for age, sex, and handedness, that is then transformed into a positive score, where 0 denotes best performance possible and 1.96 denotes the 95th percentile for neurologically healthy performance. RBANS scores are normalized by age only. We defined impairment as scores beyond the 95th percentile, as it allows for greater certainty of true impairment. Therefore, a score of <75.25 (1.65 standard deviation (SD)) on the RBANS, and a score >1.96 on Kinarm were considered impaired.

Data Analysis

We used descriptive statistics to describe neurocognitive performance. Additionally, significant change in performance on Kinarm were calculated using significant change thresholds and confidence intervals, which is described in Simmatis, et al. 2020[269]. To determine if hemodynamic and dialysis parameters were related to rSO2, Pearson correlation plots were created using the p-values with a 95% confidence level. We acknowledge that due to the vast amount of data available to analyze for each individual patient, spurious associations may be identified. Therefore we will characterize the associations based on Cohen's work[286] as either small association (questionable clinical significance; r<0.2), moderate association (r=0.3-0.4), and strong association (r>0.5). All analyses were performed using R Studio[255]. For completeness, both the Pearson correlation coefficients (r-value) and p-values are included for both the cohort as a whole and per individual patient (Table 17).

5.4 Results

Feasibility

Participants were enrolled from June 2015 till March 2019. During that time 255 patients were assessed, and 58 were considered eligible (Figure 15). The majority of patients were not eligible due to their renal replacement therapy of choice being PD (Figure 15). Of the 58 patients: 21 were not interested, 12 asked to be approached again, 6 had not decided on their dialysis modality when approached, and 19 (33%) consented (Figure 15). Of those 19, 9 withdrew from the study, 3 required unexpected emergency dialysis before completing their neuropsychological assessment, and 1 switched to home HD (Figure 15). Thus, 6 patients completed the study in its entirety (Figure 15). Therefore, roughly 1/3 of the eligible population was enrolled (19/58), and of those enrolled roughly 1/3 completed the study (6/19). The overall recruitment rate was 0.40 patients/month.

When examining the data capture rates of rSO2 between the six patients there was a total of 243 rSO2 data sessions recorded. Five patients completed a year of rSO2 monitoring, while one had 8 months of monitoring due to the need to transfer to a satellite dialysis clinic. Of the 243 sessions, it was determined that 91.4% (222/243) were successful. A successful data capture session was defined as any session that had less than 5 minutes of rSO2 data missing, equating to approximately 2% of the data session missing. The main reason for missing data was due to the sensor lifting from the forehead causing ambient light to interfere with the rSO2 reading. Lastly, during each dialysis session the patient was monitored to ensure that there were no adverse reactions from the sensors adhesive. Throughout the study no reactions were detected.

Patient Characteristics

Patient demographics are located in Table 18. The mean age of the participants was 68.5, all spoke primarily English, and were right hand dominant (Table 18). Five out of the six patients were male and had a highest education of grade 12 and above (Table 18). Diabetic nephropathy was the primary cause of CKD (5/6), along with hypertension (1/6), and focal segmental glomerulosclerosis (1/6) (Table 18). Diabetes (5/6), hypertension (5/6), and cardiovascular disease (4/6) were all common co-morbidities in the cohort (Table 18). This cohort's baseline characteristics were comparable with regards to age, education level, history of diabetes or hypertension when compared to our published data of patients with stage 5 CKD from the same centre[264].

All Patients Showed Consistent Positive Correlations Between rSO2 and Mean Arterial Pressure.

The relationship between the hemodynamic parameters of mean arterial pressure (MAP) and heart rate with rSO2 were investigated. rSO2 and MAP were positively correlated for all study patients (r range= 0.19 to 0.45) (Figure 16A). Although there were individual patient variability regarding heart rate (pulse) and rSO2, all six patients showed a significant correlations (both positive and negative, r range= -0.28 to 0.44) (Figure 16B). All individual and group correlation r and p-values are summarized in Table 17 along with a summary figure of the combined groups' performance (Figure 17).

Total Fluid Removed Showed a Moderate Correlation With rSO2

The dialysis parameters of total fluid removed, dialysate temperature, and ultrafiltration rate were investigated with relation to rSO2. Negative associations were found between total fluid removed and rSO2. These correlations were only present in the

four patients who on average, had more than 3L of fluid removed (r range= -0.43 to -0.29) (Figure 18A). Both dialysate temperature and ultrafiltration rate showed few correlations with and rSO2 at the patient level. Regarding ultrafiltration rate, only 2 patients exhibited moderate negative correlations (r= -.43, -0.33) the rest showed no association (Figure 18B). Dialysate temperature was not associated with rSO2 in 5/6 patients in our cohort (Figure 18C).

Dialysis Vintage Was Strongly Correlated With rSO2

The effects of dialysis vintage on rSO2 was also assessed. Although there was individual patient variability, all 6 patients demonstrated strong correlations (r range= -0.68 to 0.89) (Figure 19).

Neurocognitive Outcomes

All patients completed the RBANS (standardized assessment) and Kinarm (robotic assessment) at the baseline (stage 5 CKD) and 3 month assessment intervals. However, two patients did not complete the 1 year follow up assessment, as one patient transferred to a satellite clinic and the other expired. No impairment was detected for any patient at any of the time intervals for the total scale score on the RBANS, which is indicative of global performance (Figure 20A). Regarding the attention domain two patients were impaired at baseline. The domains of visuospatial, immediate memory, and delayed memory demonstrated 1 patient as impaired at baseline (Figure 20A). After 3 months of dialysis, performance was almost identical with the exception of the immediate memory domain, in which no patient was impaired on (Figure 20A). At the one year follow up, only the domains of attention and immediate memory had 1 patient as impaired (Figure 20A).

The Kinarm assessment identified more impairment at baseline, with 8/9 tasks categorizing at least one patient as impaired (Figure 20B). The task of visually guided reaching which measures visuomotor capabilities showed the most impairment at baseline with 4/6 patients scoring outside the normative range (Figure 20B). Tasks measuring proprioception, visuomotor, attention, memory, and/or executive function showed 1 to 3 out of the 6 patients as impaired (Figure 20B). Once dialysis was initiated, improvement was seen on all but 3 tasks (arm position matching (1/6), object hit and avoid (1/6), and Trails Making Test B (3/6)) (Figure 20B). One task (ball on bar) which measures motor range and visuomotor capabilities was impaired at 3 months for one patient but not at baseline (Figure 20B). All tasks except reverse visually guided reaching (1/4) demonstrated no clinical impairment in the four individuals who completed the 1-year testing (Figure 20B). When investigating individual significant change in performance across the time intervals for the Kinarm, it was determined that the tasks of: visually guided reaching (3/6 at 3 months, 2/6 at 1 year), and trails making test A (2/6 at 3 months, 1/6 at 1 year) and B (3/6 at 3 months, 2/6 at 1 year) demonstrated the most improvement after dialysis initiation. Arm position matching also demonstrated that 2/6 patient's performance significant improved, along with 1/6 patients on object hit and object hit and avoid after 3 months of dialysis (Figure 20B).

5.5 Discussion

The mechanisms that contribute to the neurocognitive impairment in patients undergoing HD are poorly understood. This study investigated whether repetitive cerebral hypoperfusion contributed to neurocognitive impairment in patients initiating HD, by determining the feasibility of serially monitoring rSO2 for a patients' first year of HD. Although our data capture rate was 91.4%, the low enrollment and consent rates at a single-centre were identified as the main impediments to the feasibility of this study. Individual patient variability was present throughout the study with regards to neurocognitive performance, hemodynamic and dialysis parameters, and rSO2.

This study was ultimately unfeasible due to the low consent (33%) and recruitment (0.4 patients/month) rates at a single-centre level. Notably however, of 255 eligible patients, 197 were ineligible due to a previous neurological disease or selection of at home HD or PD, which drastically limited our potential study pool. Interestingly however, poor patient enrollment has already been highlighted as a factor that limits the extent of clinical and transitional research in nephrology[287]. A survey on medical research participation in individuals without CKD determined that although the majority of participants reported they were willing to participate in research (59-86%), only 11% participated[288].

The average consent and enrollment rates for patients undergoing HD to participate in research is scarce, but would be important to identify, as it would provide benchmarks for future feasibility studies. To understand our feasibility metrics, we have identified a convenience sample of 12 feasibility studies regarding patients undergoing HD[214,289–299] that contextualize our findings. Of the studies that provided study durations, the calculated enrollment rates ranged from 2.4 to 40 patients/month[290,291,295–299]. Consent rates ranged

from 29 to 72%, with a study completion rate range from 70 to 100%[214,290,291,293,296–299]. Therefore, our enrollment rate was lower than these studies at 0.4 patients/month, but our consent (33%) rate was comparable.

Since low enrollment and consent rates were the major factors affecting the feasibility of our study, strategies to improve these metrics are important to identify. Firstly, 10 patients were considered ineligible because they had selected home HD. Home rSO2 monitoring could be considered to account for patients who choose to dialyze at home, which could increase the enrollment rate and generalizability, as both HD and PD patients could be enrolled. Secondly, 3 consented participants were considered ineligible because they required emergent HD prior to completing baseline neurocognitive assessment. Determining when a patient will require dialysis is difficult due to the complexity of the disease[300]. Therefore, a strategy to improve enrollment of these individuals could be to implement screening measures such as the mini-mental state exam (MMSE) at the time of consent. However, a caveat with screening tools such as the MMSE, is they may not be sensitive enough to detect subtle cognitive deficits[239]. For instance, the RBANS did not detect any global impairment in our cohort, whereas the majority of patients demonstrated objective and quantifiable impairment with the robotic testing. Another way to include patients who require emergency dialysis, would be to recruit patients who have been on dialysis for less than a month. However the challenge with this, is that it has been determined that a single episode of dialysis may impact cognitive performance[214]. Lastly, challenges regarding recruitment may be in part remedied by the patient's radius to the dialysis unit and centre. Our centre receives patients from a vast geographic area and includes multiple satellite units. More urban centres may have more

eligible patients available to them as patients are closer to the treatment centre, and these dialysis units may have a larger capacity.

Our study focused on individual data versus group data with regards to determining the associations between rSO2 and related variables. We have previously demonstrated significant inter-individual variability in the association between rSO2 and the hemodynamic variables of MAP and HR in critically ill patients, which may be lost when group data is pooled[301]. The present study would suggest that patients undergoing HD have similar inter-individual variability. Should cerebral hypoperfusion be identified as a risk factor for neurocognitive impairment in individuals undergoing HD, the high inter-individual variability would limit any "one-size fits all" approach to optimizing cerebral perfusion during dialysis.

Surprisingly, the quantitative deficits identified with Kinarm improved after the initiation of dialysis in our cohort. This is not consistent with prior studies[60,302]. However, the impairments that were detected (visuomotor, attention, and executive function) were similar to what we discovered in our CKD population using the same neurocognitive battery[264]. Given the small sample size of our study, it is difficult to speculate as to why our data differs, or if this trend would remain with a larger sample. Neurocognitive improvement in this cohort may be due in part to the fact that this robotic tool is assessing neurocognitive domains not previously studied extensively in patients with CKD receiving HD. Additionally, it has been postulated that the complex nature of the Kinarm tasks measure both cortical and subcortical brain areas through the use of the sensorimotor circuits which involve subcortical structures such as the basal ganglia and cerebellum, along with cortical areas such as the frontalparital cortex known to be involved in skilled

goal directed motormovements[303]. However, imagining would be needed in order to determine the precise cortical areas of activation per Kinarm task.

In addition to the small sample size, this study has several limitations. First, a major limitation of using NIRS is that the sensor only penetrates 2.5 cm[285] through the skull into the frontal lobe. While this technology can determine the oxygenation status of cortical tissue and its immediately adjacent subcortical white matter, it likely does not assess the deeper subcortical tissues known to be affected in patients with kidney disease[304,305]. Secondly, we did not screen our patients for mood disorders, such as depression, which is known to be confounding variable for neurocognitive performance[189], and such information would be important to obtain in future work.

In summary, serially capturing rSO2 data during a patients' first year of dialysis was unfeasible in a single dialysis unit given the low consent and enrollment rates. However, data capture rates were >90% and interesting associations with respect to MAP, total fluid removed, and dialysis vintage with rSO2 were identified at the individual patient level. Future studies are needed to determine the true extent of impairments caused by HD, and how this process affects the patient's rSO2 levels, cognition, quality of life, and mortality.

Tables

Table 16: Neurocognitive Battery Tests with Task Components and Descriptions: Feasibility

Neurocognitive Test	Domain/Task	Task Components and Description
RBANS	Attention	Digit Span, Symbol Coding
	Immediate Memory	List Learning, Story Memory
	Delayed Memory	List Recall, List Recognition, Story Recall, Figure Recall
	Visuospatial	Figure Copy, Line Orientation
	Language	Picture Naming, Semantic Fluency
	Total Scale Score	A summary score based on the performance on all the RBANS domains. It is a represents the global performance on the RBANS assessment.
Kinarm	Arm Position Matching	The robot moves one of the patient's arms. Patients are then asked to mirror match this position with the other arm. This task measures proprioception and somatosensory.
	Ball on Bar	A bar appears between the patients 2 hands with a ball on top of it. The patient is then asked to move the ball into targets that appear on the screen. There are three levels with increasing difficulty, where the ball goes from being fixed in position to being able to freely move and fall off the bar (depending on how level the patient keeps the bar). This measurers visuomotor skill, motor range, and coordination.
	Object Hit	Paddles appear at the patients hands and they are instructed to hit as many balls (which fall from the top of the screen) away as possible. As the task progresses the quantity and speed at which the balls fall increases. Measures attention and visuomotor capabilities.
	Object Hit and Avoid	Similar to object hit, but this time 2 shapes are shown to the patient which they are instructed to hit while avoiding all the other distractor targets. Again, as the task progresses the quantity and speed at which the targets fall increases. Measures attention, visuomotor, and executive function.
	Visually Guided Reaching	A target appears on the screen and the patient is asked to move the dot that represents their hand into the target as quickly and accurately as possible. A measure of visuomotor capabilities.
	Reverse Visually Guided Reaching	Similar to visually guided reaching, but the light representing their hand now moves in the opposite direction of the arm movement. Measures visuomotor capabilities and executive function.
	Spatial Span	The patient is shown a sequence and is then asked to replicate it. The length of the sequence depends on if the patient got the previous sequence correct or not. A measure of working memory.
	Trail Making Test A	The patient is asked to connect the numbers 1 to 25 in order as quickly as possible. The number arrangement is predetermined and no connecting lines may overlap. Measures visuomotor and attention.

	Trail Making Test B	Similar to TMT-A, but the patient is now asked to alternate between number and letters (1-A-2-B-3) as quickly as possible. Like TMT-A the arrangement is predetermined and no connecting lines may overlap. A measure of visuomotor, attention, and executive function.

Table 16: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Kinarm domains and tasks assessed, with task components, and descriptions.

Table 17: Correlations Between rSO2 and Dialysis Parameters

Patient	Whole Cohort		1		2		3		4		5		6	
	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value
Mean Arterial Pressure (mmHg)	0.16	<0.001	0.45	<0.001	0.19	<0.001	0.20	<0.001	0.20	<0.001	0.29	<0.001	0.25	<0.001
Pulse (BPM)	-0.42	<0.001	0.23	<0.001	-0.28	<0.001	0.44	<0.001	-0.12	<0.01	0.21	<0.001	-0.27	<0.001
Total Fluid Removed (L)	-0.052	<0.01	-0.43	<0.001	0.091	<0.05	0.063	NS	-0.46	<0.001	-0.29	<0.001	-0.38	<0.001
Temperature (C)	-0.023	NS	-0.0014	NS	-0.076	NS	0.062	NS	-0.050	NS	-0.12	<0.001	-0.010	NS
Ultrafiltration Rate (mL/Hr/Kg)	-0.0007	NS	-0.43	<0.05	0.25	NS	0.08	NS	-0.33	<0.05	-0.11	NS	-0.08	NS
Average rSO2/Week	0.22	<0.001	-0.68	<0.001	0.89	<0.001	-0.61	<0.001	-0.35	<0.05	0.79	<0.001	0.74	<0.001

Table 17: Cohort and individual patient correlations between regional cerebral oxygenation saturation (rSO2), hemodyanmaic, and dialysis paramerters. Abbreviations: mmHg= millimetre of mercury, BPM= beats per minute, C= celcius, L= litre, mL= millalitre, Hr= hour, Kg= kilogram, and NS= not significant.

Table 18: Patient Characteristics: Feasibility

Patient Characteristic	**Total Cohort N= 6**
Age (Mean, Range)	68.5 (51-88)
Sex (N, %)	
Male Female	5 (83.33) 1 (16.67)
Handedness (N, %)	
Right	6 (100)
English As A Second Language (N, %)	
No	6 (100)
Ethnicity (N, %)	
Caucasian	6 (100)
Highest Reported Education (N, %)	
Grade 8-11	1 (16.67)
Grade 12	3 (16.67)
University	1 (16.67)
Masters	1 (16.67)
Cause Of CKD (N, % of Total N)	
Diabetic Nephropathy	5 (83.33)
Hypertension	1 (16.67)
Focal Segmental Glomerulosclerosis (FSG)	1 (16.67)
Co-morbidities (N, % of Total N)	
Diabetes	5 (83.33)
Hypertension	5 (83.33)
Cardiovascular [a]	4 (66.67)
Sleep Apnea	3 (50)
Other [b]	8

Table 18: Summary of patient clinical and demographic variables. Note: cause of CKD was multifactorial for the majority of patients, therefore if the cause of CKD was determined to be both diabetes and hypertension it was accounted for in both sections.

[a]Cardiovascular co-morbidities: coronary heart disease (N=3), peripheral vascular disease (N=1).

[b]Other co-morbidities: dyslipidemia (N=2), hyperthyroidism (N=2), hyperlipidemia (N=1), proteinuria (N=1), albuminuria (N=1), left nephrectomy (N=1).

5.6 Figures

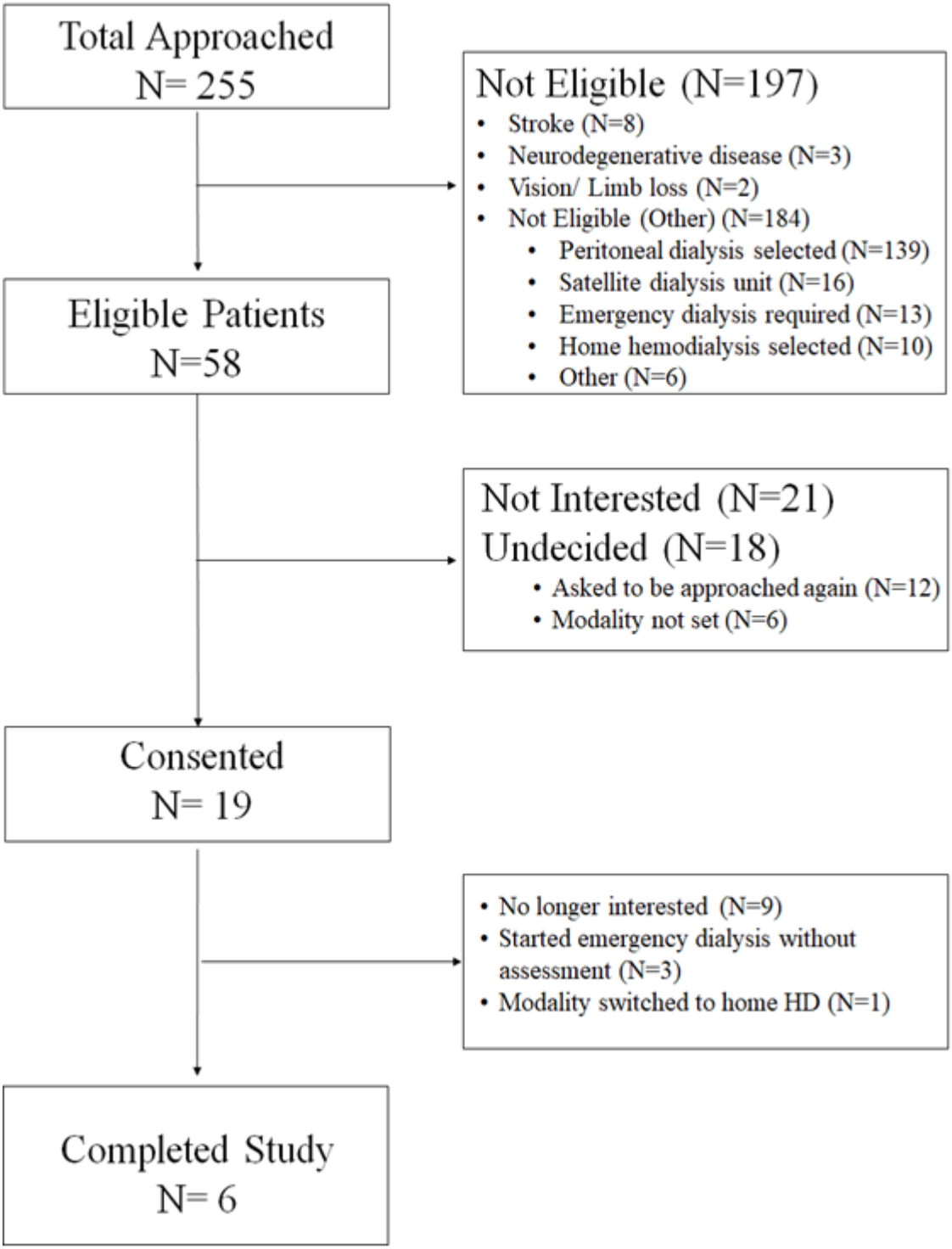


Figure 15: Feasibility consort diagram, from June 2015 till March 2019.

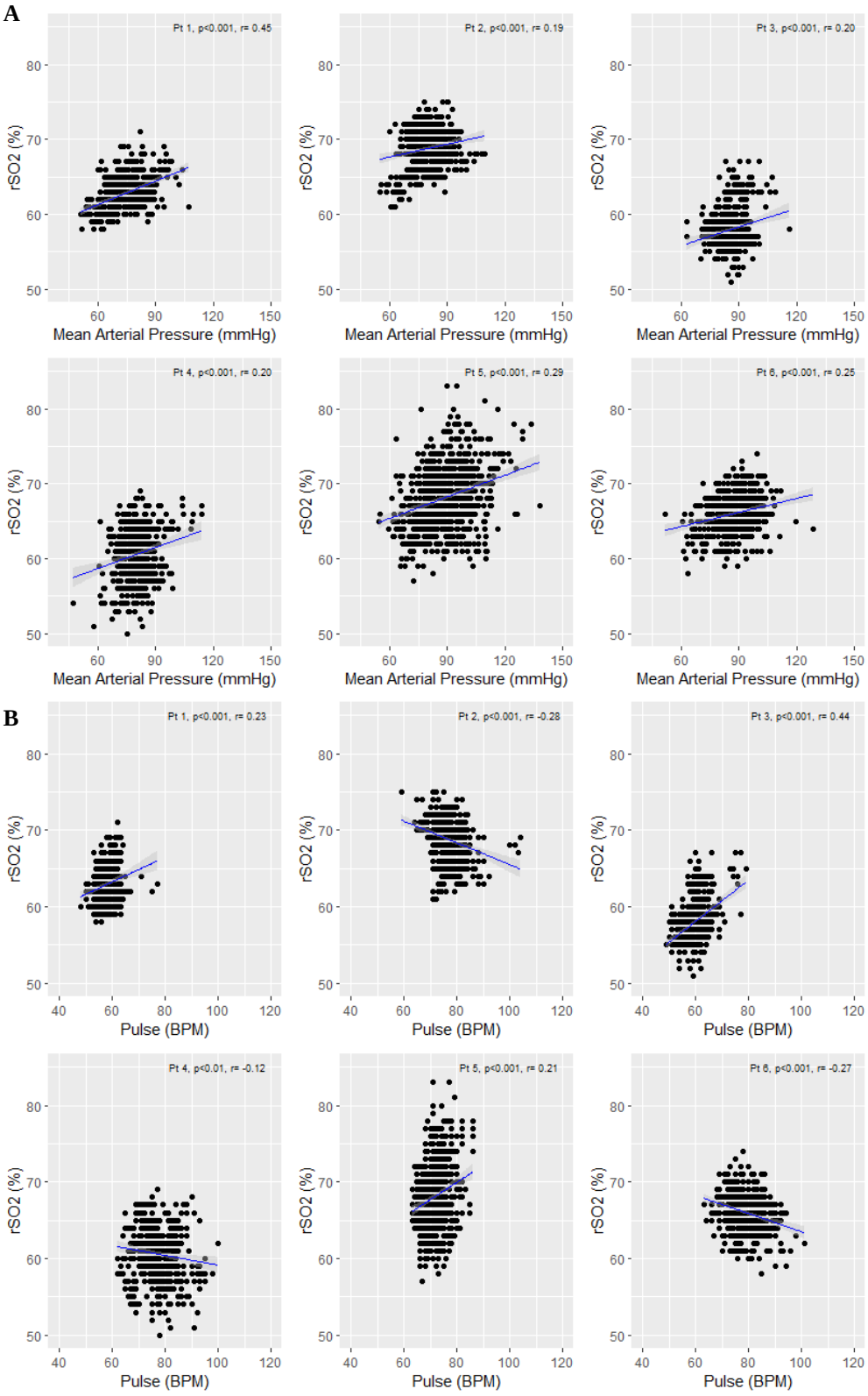

A
Pt 1, p<0.001, r= 0.45
Pt 2, p<0.001, r= 0.19
Pt 3, p<0.001, r= 0.20
Pt 4, p<0.001, r= 0.20
Pt 5, p<0.001, r= 0.29
Pt 6, p<0.001, r= 0.25
rSO2 (%)
Mean Arterial Pressure (mmHg)
B
Pt 1, p<0.001, r= 0.23
Pt 2, p<0.001, r= -0.28
Pt 3, p<0.001, r= 0.44
Pt 4, p<0.01, r= -0.12
Pt 5, p<0.001, r= 0.21
Pt 6, p<0.001, r= -0.27
Pulse (BPM)

Figure 16: Correlations between regional cerebral oxygenation saturation (rSO2) and hemodynamic parameters for all patients. Figure 16A: depicts the correlations between rSO2 and mean arterial pressure (MAP). MAP was calculated by: 1/3 systolic blood pressure + 2/3 diastolic blood pressure. Figure 16B: depicts the correlations between rSO2 and pulse. On all graphs the blue line represents the line of best fit, with the grey shaded area depicting the 95% confidence interval. Abbreviations: pt= patient, rSO2= reginal cerebral oxygen saturation, MAP= mean arterial pressure. BPM: beats per minute, and mmHg: millimeter of mercury.

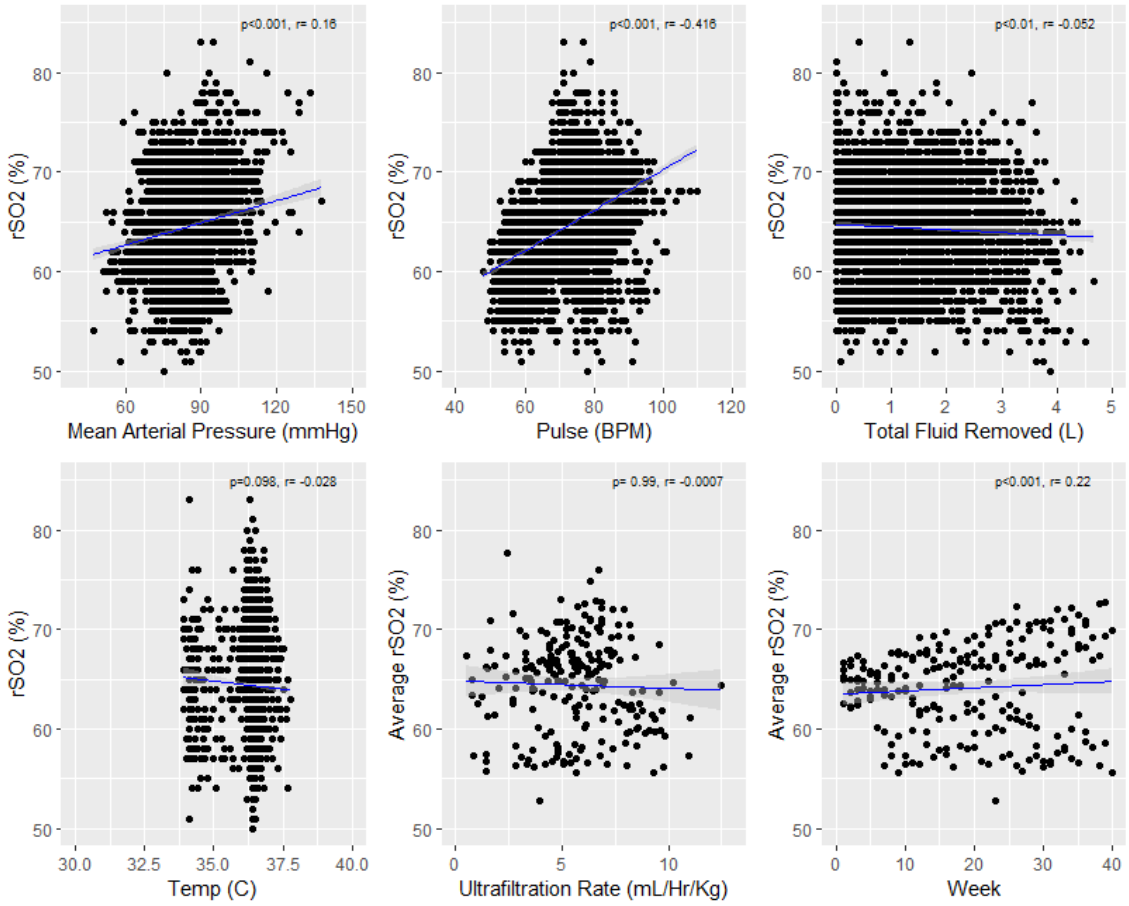
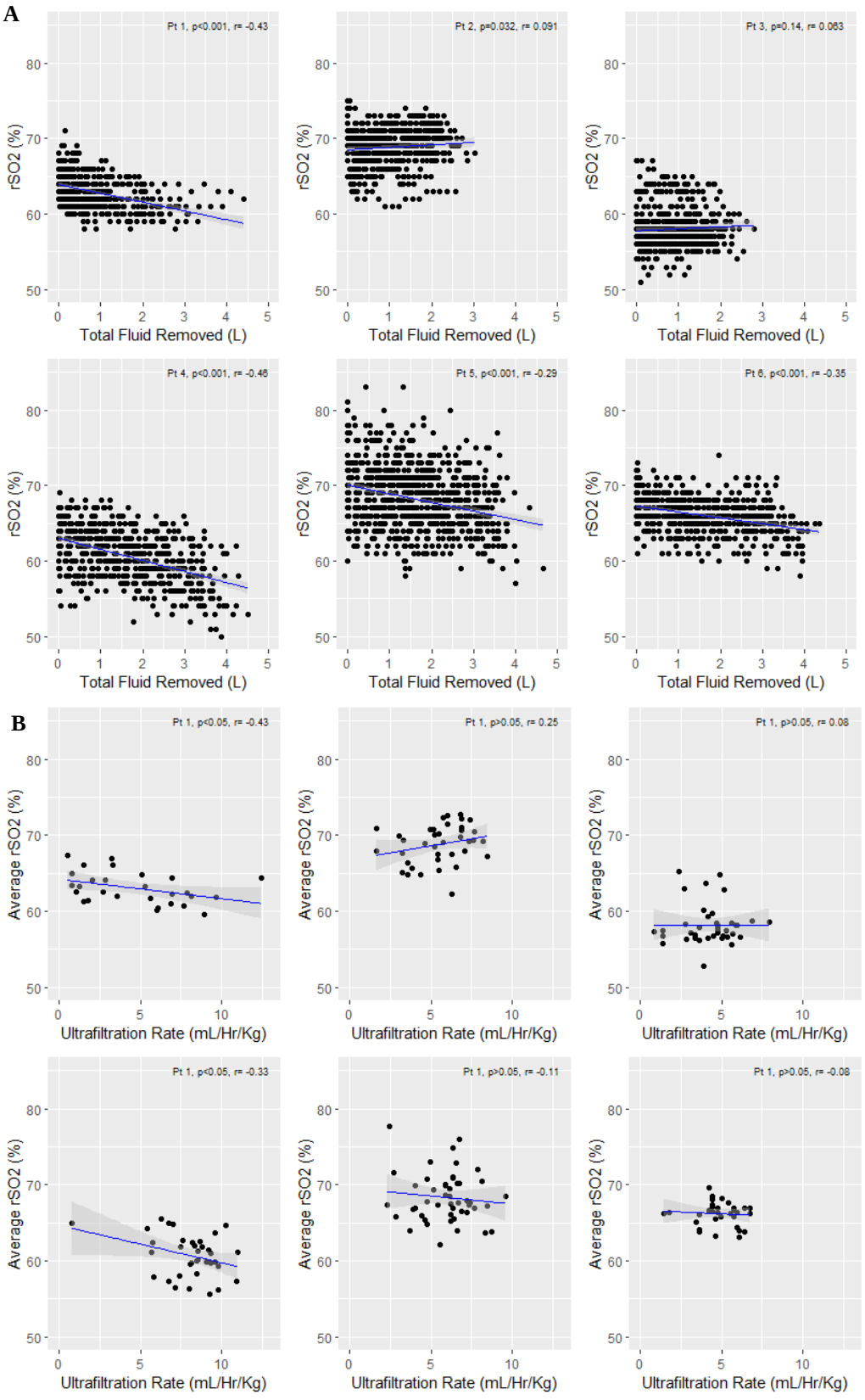


Figure 17: Correlations between rSO2, hemodynamic, and dialysis parameters of the entire cohort. Abbreviations: mmHg= millimetre of mercury, BPM= beats per minute, C= celcius, L= litre, mL= millalitre, Hr= hour, and Kg= kilogram.


A
Pt 1, p<0.001, r= -0.43
Pt 2, p=0.032, r= 0.091
Pt 3, p=0.14, r= 0.063
Pt 4, p<0.001, r= -0.46
Pt 5, p<0.001, r= -0.29
Pt 6, p<0.001, r= -0.35
rSO2 (%)
Total Fluid Removed (L)
B
Pt 1, p<0.05, r= -0.43
Pt 1, p>0.05, r= 0.25
Pt 1, p>0.05, r= 0.08
Pt 1, p<0.05, r= -0.33
Pt 1, p>0.05, r= -0.11
Pt 1, p>0.05, r= -0.08
Average rSO2 (%)
Ultrafiltration Rate (mL/Hr/Kg)

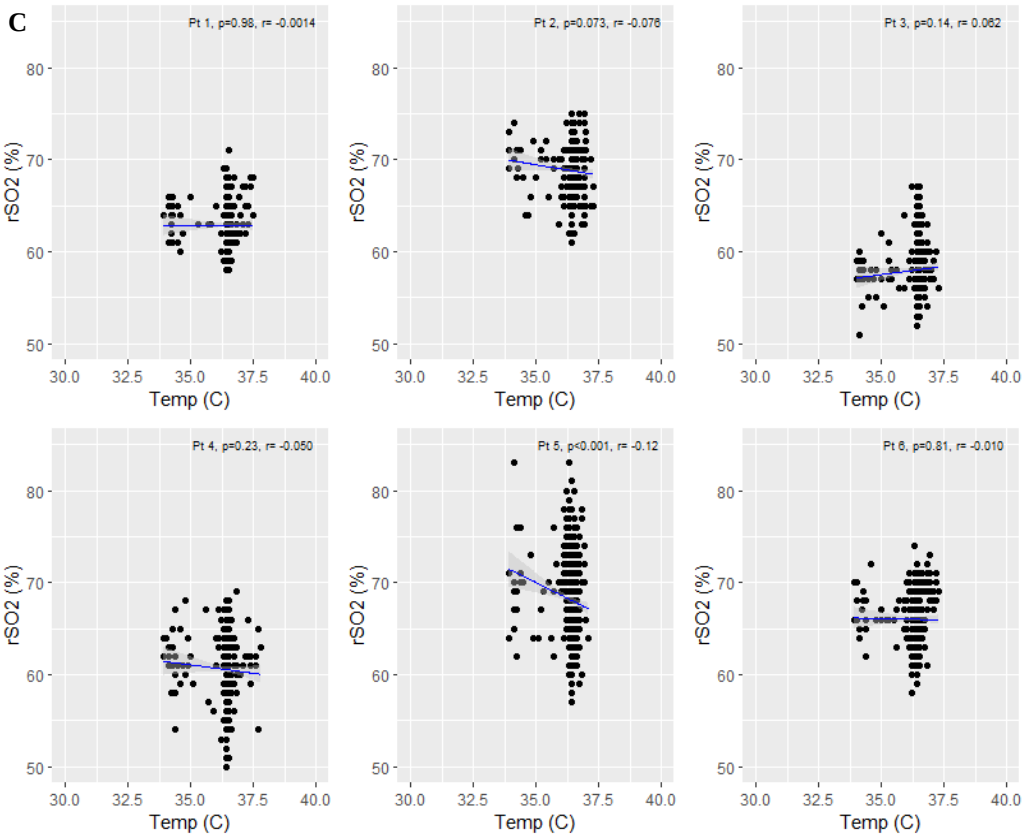


Figure 18: Correlations between regional cerebral oxygenation saturation (rSO2) and dialysis parameters. Figure 18A: depicts the relationship between rSO2 and the total fluid removed, whereas Figure 18B shows the correlations between rSO2 and the ultrafiltration rate taking into account the patient's body weight (mL/Hr/Kg). Finally, Figure 18C: depicts the correlations between rSo2 and dialysate temperature. The blue line represents the line of best fit, with the grey shaded area depicting the 95% confidence interval. Abbreviations: pt= patient, rSO2= reginal cerebral oxygen saturation, L= litre, mL= millilitre, Hr= hour, Kg=kilograms, Temp= Dialysate Temperature, and C=degrees Celsius.

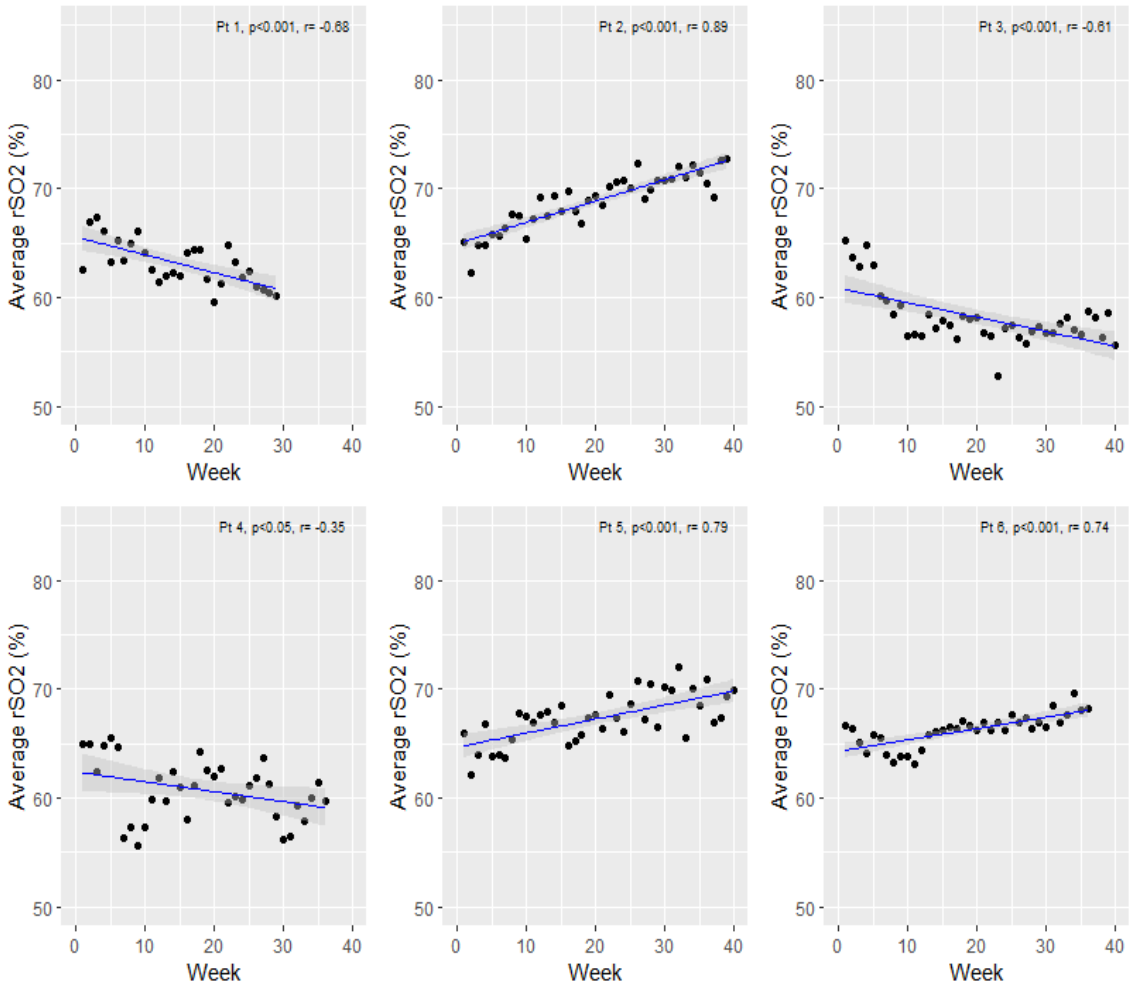
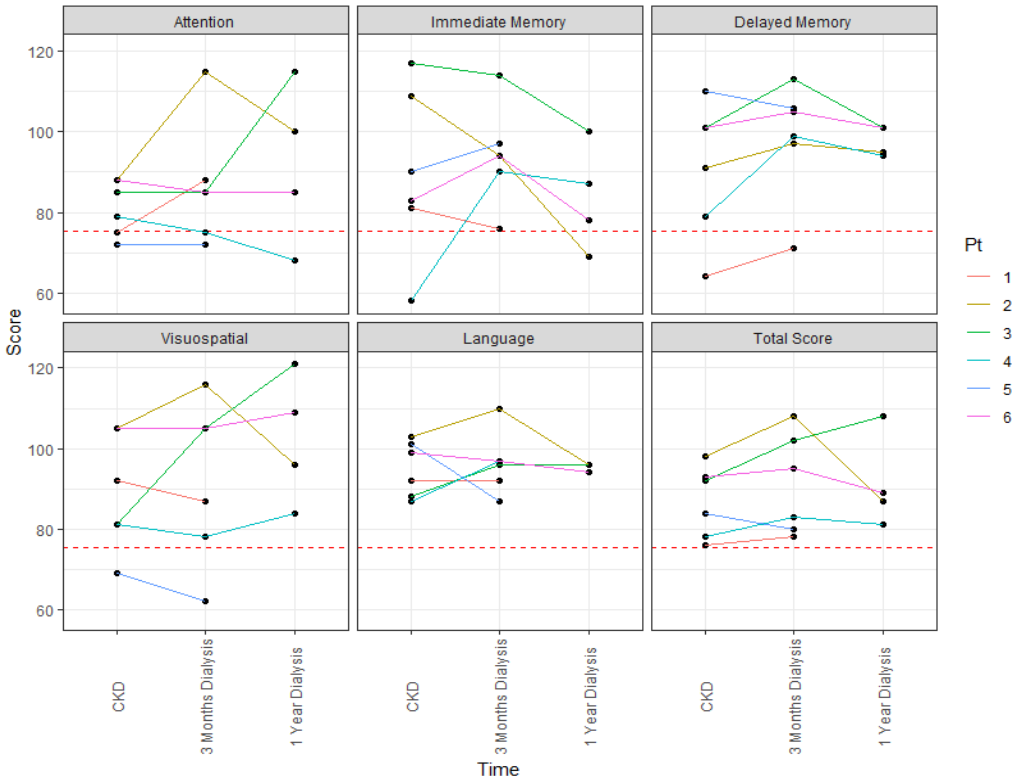


Figure 19: Correlations between the average weekly regional cerebral oxygenation saturation (rSO2) and dialysis vintage. Note: that patient 1 only received roughly 8 months on rSo2 monitoring before switching to a satellite dialysis clinic. Abbreviations: pt= patient and rSO2= reginal cerebral oxygen saturation.

A


Attention
Immediate Memory
Delayed Memory
Visuospatial
Language
Total Score
Score
120
100
80
60
CKD
3 Months Dialysis
1 Year Dialysis
Time
Pt
1
2
3
4
5
6

B

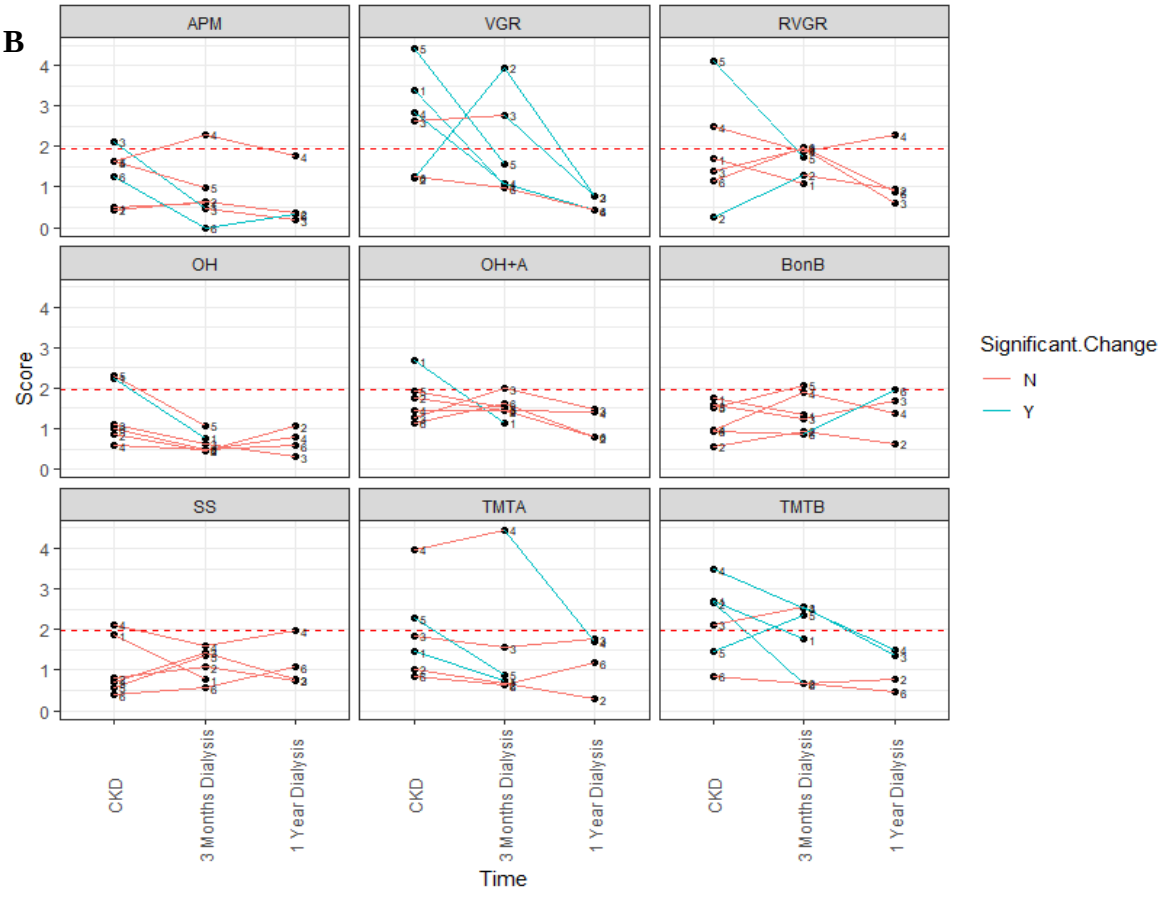

APM
VGR
RVGR
OH
OH+A
BonB
SS
TMTA
TMTB
Score
4
3
2
1
0
CKD
3 Months Dialysis
1 Year Dialysis
Time
Significant.Change
N
Y

Figure 20: Neuropsychological assessment: feasibility. Each line represents a patient's performance across the testing time points: before dialysis (stage 5 chronic kidney disease (CKD)), 3 months, and 1 year post dialysis initiation. Note: patient 1 and 5 did not complete their 1 year assessments, as one patient transferred to a satellite dialysis clinic, and the other expired before the assessment could be completed. Figure 20A: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Scores. The dashed red line represents the 1.65 SD cut-off. Anything below the red dotted line (a score of 75.25) indicates impairment. Each patient's performance is denoted by a different color. Figure 20B: robotic Kinarm assessment. The dashed red line represents the impairment cut off of 1.96 (the 95^{th} percentile of healthy performance cut-off). Anything above the dashed red line indicates impairment. Each patient's performance is labelled by their patient number. Significant difference in performance is denoted by the blue line between test points. A red line indicated no significant change in performance.

Chapter 6

General Discussion, Chapter Overviews, and Conclusions

6.1 General Discussion

Currently, it is estimated that 4 million Canadians[3], and 1 billion individuals worldwide[1] are living with CKD[3]. Due to high prevalence rates, it is becoming increasingly recognized that patients with CKD may have neurocognitive impairments[24,235,306]. Understanding the neurocognitive consequences of CKD has become a research priority for nephrologists, neurologists, and neuroscientists. This thesis had three main objectives:

1. To summarize the reported neurocognitive impairment across the spectrum of kidney disease by performing a comprehensive systematic review and meta-analysis. The objective of the systematic review was to determine which neuropsychological assessments are typically used to quantify neurocognitive impairments in those who were CKD non-dialysis dependent, CKD dialysis dependent, kidney transplant recipients, and non-CKD controls. The objective of the meta-analysis was to determine if there were significant differences regarding performance between the kidney disease populations and non-CKD controls on the neurocognitive assessments.
2. To use novel objective robotic technology (Kinarm) to quantify neurocognitive impairment in those with kidney disease. In particular, patient cohorts of interest were: CKD non-dialysis dependent, CKD dialysis dependent, and those who had recently survived an episode of AKI. This technology was used concurrently with a standardized traditional screening tool (RBANS) to compare neurocognitive outcomes.

3. To investigate the feasibility of serially monitoring rSO2 weekly during the patients first year of HD. This objective would provide insight into a potential mechanism of neurocognitive impairment, since the literature demonstrates that there is a particularly high prevalence of neurocognitive impairment in individuals undergoing HD[18].

6.2 Systematic Review and Meta-Analysis Demonstrates That Better Tools Are Needed To Quantify Subtle Neurocognitive Impairments in Patients with Kidney Disease

In order to contextualize the impairments typically seen in those with CKD, a systematic review and meta-analysis was performed. This review demonstrated that the majority of neurocognitive impairment described in the literature used traditional screening measures such as the MMSE[24]. Although the MMSE is quick, it lacks the sensitivity to detect mild neurocognitive impairment[239]. Despite the common use of screening tools in research studies, they are not designed to assess mild neurocognitive impairment alone[241]. Thus, screening tools used to quantify impairment in this population may miss subtle neurocognitive impairments. For example, this review demonstrated that patients who were dialysis-dependent and pre-dialysis CKD scored significantly worse on the MMSE compared to non-CKD controls. However, the mean values for the patients with CKD (dialysis and non-dialysis) were still above the traditional cut-off for dementia, suggesting subtle neurocognitive impairment may be present.

This systematic review and meta-analysis highlights the fact that over-reliance on dementia screening tools may underestimate the magnitude of neurocognitive dysfunction in patients with kidney disease. Therefore, using tools designed to detect and quantify subtle neurocognitive impairment are ideal to study this population of patients. By truly understanding the impairment experienced by patients with kidney disease, health care professionals will be better equipped to monitor the progression of the impairment experienced by these patients. It may also dictate who is eligible for home RRT, raise ethical concerns regarding ability to provide informed consent for treatments and procedures, and will ensure that adequate measures are instituted so that these patients can

understand and maintain the complex fluid, dietary, and medication regimes required of them[61].

Since the systemic review and meta-analysis was conducted almost three years prior to this thesis write up, an updated search of the literature was conducted. Although this search was not as in depth as the systematic review and meta-analysis, it did highlight some notable findings. Firstly like our previous findings, there is still an over reliance on dementia screening tools, in particular the MMSE. Additionally, neurocognitive impairment is commonly reported in those experiencing kidney disease. New research however is beginning to shift its investigation into biomarkers which may be related to neurocognitive impairment in those with kidney disease[307–310], and the importance of mental health in neurocognitive functioning, specifically depression[238,311,312]. There is also a trend to encourage early screening of neurocognitive impairment in this population that is desperately needed[313].

6.3 Attention, Executive Function, and Perceptual-Motor/Visuomotor Impairments are Common in Patients with Kidney Disease

Novel state of the art robotic technology (Kinarm) was used to characterize neurocognitive impairment across the spectrum of kidney disease. In order to determine the efficacy of the use of Kinarm in patients with CKD, its performance was compared to a traditional screening tool (RBANS). Although Kinarm is not a substitute for a trained neuropsychological assessment, it was able to quantify more impairment than the RBANS in the domains of attention and executive function. It also demonstrated that a high proportion of individuals were impaired on the visuomotor/perceptual-motor domain, which has not been previously described in this population.

These findings indicate that impairments in attention, executive function, and visuomotor frequently occur in patients with CKD. Impairments in these specific domains may influence if patients are able to complete their treatments at home when RRT is needed, along with significant implications on quality of life. Previous research has described that patients with CKD have subjectively rated their quality of life as being worse than non-CKD controls, and that this rating drops further once dialysis is initiated[314]. Additional research is needed to assess the relationship between neurocognitive impairment and quality of life in patients with CKD.

Additionally, Kinarm was used to quantify impairments in patients who recently experienced an episode of AKI. Like patients with CKD, attention, executive function, and visuomotor impairments were described when performance was compared to healthy controls. Furthermore, the AKI population also performed significantly worse on attention and visuomotor domains when compared to patients who were matched for cardiovascular risk factors. Notably, this was the first prospective study to actively measure the

neurocognitive status of patients who have had an episode of AKI. While generating a novel hypothesis regarding the neurocognitive consequences of AKI, this study was limited by its low sample size due to difficulties in recruiting during the COVID-19 pandemic. Although the true extent of the neurocognitive outcomes of AKI remains unclear, this study provides a solid foundation for which assessments may prove useful and what domains should be a priority when assessing those who experience AKI.

6.4 Longitudinal rSO2 Values Are Associated with Hemodynamic and Dialysis Dependent Parameters in Patients Undergoing Hemodialysis

NIRS (a tool that measures rSO2) was used to investigate the feasibility of serially monitoring rSO2 once a week for a patient's first year of HD. This schedule was selected in order to assess whether repetitive hypoperfusion was related to the accelerated neurocognitive decline described in this cohort[18]. As such, relationships between rSO2, dialysis, and hemodynamic parameters were investigated. Although the study was deemed unfeasible due to low recruitment rates, interesting findings were suggested with regards to specific hemodynamic and dialysis parameters and rSO2. For instance, positive correlations were apparent in all the patients between rSO2 and MAP. This may indicate that cerebral autoregulation may be impacted by either CKD or the process of dialysis itself. Additionally, there were significant correlations between rSO2 and dialysis vintage, as well as between rSO2 and fluid removal.

Although low recruitment rates limited a more rigorous analysis of this data, this work was the first to serially monitor rSO2 during a patient's first year of HD. It lays the foundation for future studies to investigate this process, as the study protocol itself was feasible (high data capture rates were obtained, and no adverse events were reported), but larger sample sizes are needed. With larger sample sizes, analyses can be performed to determine if repetitive hypoperfusion contributes to the accelerated neurocognitive decline described in those undergoing HD[18].

6.5 Conclusions

This thesis has created the foundation for a completely novel program of research aimed at characterizing neurocognitive impairments in patients with all stages of kidney disease. I have demonstrated that 1) there is currently no gold standard for the assessment of neurocognitive impairment in patients with kidney disease, 2) the use of dementia screening tools may provide an unreliable description of the magnitude and scope of the neurocognitive impairment found in those with kidney disease, and 3) that objective robotic technology identifies novel visuospatial and perceptual-motor impairments in patients with kidney disease. Furthermore, this thesis also indicates that NIRS is suitable for measuring rSO2 during dialysis. rSO2 was also identified as a potentially useful target for determining dialysis limits for fluid removal and optimal MAPs during these sessions. However, further research is needed in order to determine the exact influence of HD on rSO2 and how it relates to dialysis and treatment outcomes and neurocognitive performance.

References

1. Hill NR, Fatoba ST, Oke JL, et al. Global Prevalence of Chronic Kidney Disease – A Systematic Review and Meta-Analysis. Remuzzi G, ed. *PLoS One*. 2016;11(7):e0158765. doi:10.1371/journal.pone.0158765

2. Zhang QL, Rothenbacher D. Prevalence of chronic kidney disease in population-based studies: Systematic review. *BMC Public Health*. 2008;8(1):1-13. doi:10.1186/1471-2458-8-117

3. Bello AK, Ronksley PE, Tangri N, et al. Prevalence and Demographics of CKD in Canadian Primary Care Practices: A Cross-sectional Study. *Kidney Int Reports*. 2019;4(4):561-570. doi:10.1016/j.ekir.2019.01.005

4. Levey AS, Coresh J, Balk E, et al. National Kidney Foundation Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. *Ann Intern Med*. 2003;139(2):137. doi:10.7326/0003-4819-139-2-200307150-00013

5. Ryan JJ, Souheaver GT, DeWolfe AS. Halstead-Reitan Test results in chronic hemodialysis. *J Nerv Ment Dis*. 1981;169:311-314. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med2&NEWS=N&AN=7217942.

6. Tonelli M, Wiebe N, Culleton B, et al. Chronic kidney disease and mortality risk: A systematic review. *J Am Soc Nephrol*. 2006;17(7):2034-2047. doi:10.1681/ASN.2005101085

7. Tonelli M, Wiebe N, Guthrie B, et al. Comorbidity as a driver of adverse outcomes in people with chronic kidney disease. *Kidney Int.* 2015;88(4):859-866. doi:10.1038/ki.2015.228

8. Hsu CY, Ordõez JD, Chertow GM, Fan D, McCulloch CE, Go AS. The risk of acute renal failure in patients with chronic kidney disease. *Kidney Int*. 2008;74(1):101-107. doi:10.1038/ki.2008.107

9. Hsu RK, Hsu C yuan. The Role of Acute Kidney Injury in Chronic Kidney Disease. *Semin Nephrol*. 2016;36(4):283-292. doi:10.1016/j.semnephrol.2016.05.005

10. Ostermann M, Joannidis M. Acute kidney injury 2016: Diagnosis and diagnostic workup. *Crit Care*. 2016;20(1):1-13. doi:10.1186/s13054-016-1478-z

11. Cartin-Ceba R, Kashiouris M, Plataki M, Kor DJ, Gajic O, Casey ET. Risk factors for development of acute kidney injury in critically ill patients: A systematic review and meta-analysis of observational studies. *Crit Care Res Pract*. 2012;2012. doi:10.1155/2012/691013

12. Parolari A, Pesce LL, Pacini D, et al. Risk factors for perioperative acute kidney injury after adult cardiac surgery: Role of perioperative management. *Ann Thorac Surg*. 2012;93(2):584-591. doi:10.1016/j.athoracsur.2011.09.073

13. Susantitaphong P, Cruz DN, Cerda J, et al. World incidence of AKI: A meta-analysis. *Clin J Am Soc Nephrol*. 2013;8(9):1482-1493. doi:10.2215/CJN.00710113

14. Robert AM, Kramer RS, Dacey LJ, et al. Cardiac surgery-associated acute kidney

injury: A comparison of two consensus criteria. *Ann Thorac Surg*. 2010;90(6):1939-1943. doi:10.1016/j.athoracsur.2010.08.018

15. Kurella Tamura M, Xie D, Yaffe K, et al. Vascular risk factors and cognitive impairment in chronic kidney disease: the Chronic Renal Insufficiency Cohort (CRIC) study. *Clin J Am Soc Nephrol*. 2011;6:248-256. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20930087.

16. Watanabe K, Watanabe T, Nakayama M. Cerebro-renal interactions: Impact of uremic toxins on cognitive function. *Neurotoxicology*. 2014;44:184-193. doi:10.1016/j.neuro.2014.06.014

17. Tamura MK, Yaffe K. Dementia and cognitive impairment in ESRD: Diagnostic and therapeutic strategies. *Kidney Int*. 2011;79(1):14-22. doi:10.1038/ki.2010.336

18. Tiffin-Richards FE, Costa AS, Holschbach B, et al. The Montreal Cognitive Assessment (MoCA) - a sensitive screening instrument for detecting cognitive impairment in chronic hemodialysis patients. *PLoS One*. 2014;9:e106700. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=25347578.

19. Wolcott DL, Wellisch DK, Marsh JT, Schaeffer J, Landsverk J, Nissenson AR. Relationship of dialysis modality and other factors to cognitive function in chronic dialysis patients. *Am J Kidney Dis*. 1988;12:275-284. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed88&NEWS=N&AN=1988258514.

20. Maugeri D, Malaguarnera M, Panebianco P, et al. Assessment of cognitive and affective disorders in an elderly population undergoing hemodialysis. *Arch Gerontol Geriatr*. 2000;29:239-248. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed5&NEWS=N&AN=1999411292.

21. Rozeman CA, Jonkman EJ, Poortvliet DC, et al. Encephalopathy in patients on continuous ambulatory peritoneal dialysis and patients on chronic haemodialysis. *Nephrol Dial Transplant*. 1992;7:1213-1218. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=1337162.

22. Sanchez-Roman S, Ostrosky-Solis F, Morales-Buenrostro LE, Nogues-Vizcaino MG, Alberu J, McClintock SM. Neurocognitive profile of an adult sample with chronic kidney disease. *J Int Neuropsychol Soc*. 2011;17:80-90. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21062523.

23. Tsai CF, Wang SJ, Fuh JL. Moderate chronic kidney disease is associated with reduced cognitive performance in midlife women. *Kidney Int*. 2010;78(6):605-610. doi:10.1038/ki.2010.185

24. Vanderlinden JA, Ross-White A, Holden R, Shamseddin MK, Day A, Boyd JG. Quantifying cognitive dysfunction across the spectrum of end-stage kidney disease: A systematic review and meta-analysis. *Nephrology*. 2019;24(1). doi:10.1111/nep.13448

25. Weiner DE, Seliger SL. Cognitive and physical function in chronic kidney disease. *Curr Opin Nephrol Hypertens*. 2014;23(3):291-297. doi:10.1097/01.mnh.0000444821.87873.7b

26. Bishop NA, Lu T, Yankner BA. Neural mechanisms of ageing and cognitive decline. *Nature*. 2010;464(7288):529-535. doi:10.1038/nature08983

27. Kodl CT, Seaquist ER. Cognitive dysfunction and diabetes mellitus. *Endocr Rev*. 2008;29(4):494-511. doi:10.1210/er.2007-0034

28. Ferreira ST, Clarke JR, Bomfim TR, De Felice FG. Inflammation, defective insulin signaling, and neuronal dysfunction in Alzheimer's disease. *Alzheimer's Dement*. 2014;10(1 SUPPL.):S76-S83. doi:10.1016/j.jalz.2013.12.010

29. Tamura MK, Xie D, Yaffe K, et al. Vascular risk factors and cognitive impairment in chronic kidney disease: The Chronic Renal Insufficiency Cohort (CRIC) study. *Clin J Am Soc Nephrol*. 2011;6(2):248-256. doi:10.2215/CJN.02660310

30. Weiner DE, Seliger SL. Cognitive and physical function in chronic kidney disease. *Curr Opin Nephrol Hypertens*. 2014;23(3):291-297. doi:10.1097/01.mnh.0000444821.87873.7b

31. Murray AM. Cognitive Impairment in the Aging Dialysis and Chronic Kidney Disease Populations: An Occult Burden. *Adv Chronic Kidney Dis*. 2008;15(2):123-132. doi:10.1053/j.ackd.2008.01.010

32. Brouns R, De Deyn PP. Neurological complications in renal failure: A review. *Clin Neurol Neurosurg*. 2004;107(1):1-16. doi:10.1016/j.clineuro.2004.07.012

33. Tsai H-H, Yen R-F, Lin C-L, Kao C-H. Increased risk of dementia in patients

hospitalized with acute kidney injury: A nationwide population-based cohort study. Burdmann EA, ed. *PLoS One*. 2017;12(2):e0171671. doi:10.1371/journal.pone.0171671

34. Kao CC, Wu CH, Lai CF, et al. Long-Term risk of dementia following acute kidney injury: A population-based study. *Tzu Chi Med J*. 2017;29(4):201-207. doi:10.4103/tcmj.tcmj_40_17

35. Conroy AL, Opoka RO, Bangirana P, et al. Acute kidney injury is associated with impaired cognition and chronic kidney disease in a prospective cohort of children with severe malaria. *BMC Med*. 2019;17(1):98. doi:10.1186/s12916-019-1332-7

36. Lombardi R, Ferreiro A. Risk Factors Profile for Acute Kidney Injury after Cardiac Surgery Is Different According to the Level of Baseline Renal Function. *Ren Fail*. 2008;30(2):155-160. doi:10.1080/08860220701808129

37. Malek M. Brain consequences of acute kidney injury: Focusing on the hippocampus. *Kidney Res Clin Pract*. 2018;37(4):315-322. doi:10.23876/j.krcp.18.0056

38. Scott JP, Hoffman GM. Near-infrared spectroscopy: exposing the dark (venous) side of the circulation. Wolf A, ed. *Pediatr Anesth*. 2014;24(1):74-88. doi:10.1111/pan.12301

39. Ikeda K, MacLeod DB, Grocott HP, Moretti EW, Ames W, Vacchiano C. The accuracy of a near-infrared spectroscopy cerebral oximetry device and its potential value for estimating jugular venous oxygen saturation. *Anesth Analg*. 2014;119(6):1381-1392. doi:10.1213/ANE.0000000000000463

40. Soul JS, Du Plessis AJ. Near-infrared spectroscopy. *Semin Pediatr Neurol*. 1999;6(2):101-110. doi:10.1016/S1071-9091(99)80036-9

41. Wolfgram DF. Intradialytic cerebral hypoperfusion as mechanism for cognitive impairment in patients on hemodialysis. *J Am Soc Nephrol*. 2019;30(11):2052-2058. doi:10.1681/ASN.2019050461

42. Taussky, P., O'Neal, B., Daugherty, W. P., Luke, S., Thorpe, D., Pooley, R. A., ... & Freeman WD (2012). Validation of frontal near-infrared spectroscopy as noninvasive bedside monitoring for regional cerebral blood flow in brain-injured patients in: Neurosurgical Focus Volume 32 Issue 2 (2012). *Neurosurg Focus*. 2012;32(2). https://thejns-org.proxy.queensu.ca/focus/view/journals/neurosurg-focus/32/2/2011.12.focus11280.xml. Accessed July 24, 2020.

43. Taillefer, M. C., & Denault AY. Cerebral near-infrared spectroscopy in adult heart surgery: systematic review of its clinical efficacy. *Can J Anesth*. 2005;52(1):79-87.

44. Hoshino T, Ookawara S, Goto S, et al. Evaluation of Cerebral Oxygenation in Patients Undergoing Long-Term Hemodialysis. *Nephron Clin Pract*. 2014;126(1):57-61. doi:10.1159/000358432

45. Prohovnik I, Post J, Uribarri J, Lee H, Sandu O, Langhoff E. Cerebrovascular effects of hemodialysis in chronic kidney disease. *J Cereb Blood Flow Metab*. 2007;27(11):1861-1869. doi:10.1038/sj.jcbfm.9600478

46. Malik J, Kudlicka J, Lachmanova J, et al. Tissue ischemia worsens during hemodialysis in end-stage renal disease patients. *J Vasc Access*. 2017;18(1):47-51. doi:https://dx.doi.org/10.5301/jva.5000630

47. Malik J, Kudlicka J, Lachmanova J, et al. Tissue ischemia worsens during hemodialysis in end-stage renal disease patients. *J Vasc Access*. 2017;18(1):47-51. doi:10.5301/jva.5000630

48. Ito K, Ookawara S, Ueda Y, et al. Factors Affecting Cerebral Oxygenation in Hemodialysis Patients: Cerebral Oxygenation Associates with pH, Hemodialysis Duration, Serum Albumin Concentration, and Diabetes Mellitus. Jeyaseelan K, ed. *PLoS One*. 2015;10(2):e0117474. doi:10.1371/journal.pone.0117474

49. Eldehni MT, Odudu A, Mcintyre CW. Brain white matter microstructure in end-stage kidney disease, cognitive impairment, and circulatory stress. *Hemodial Int*. 2019;23(3):356-365. doi:10.1111/hdi.12754

50. Findlay MD, Dawson J, Dickie DA, et al. Investigating the relationship between cerebral blood flow and cognitive function in hemodialysis patients. *J Am Soc Nephrol*. 2019;30(1):147-158. doi:10.1681/ASN.2018050462

51. Berger A. Magnetic resonance imaging. *BMJ*. 2002;324(7328):35. doi:10.1136/bmj.324.7328.35

52. RBANS Assessment of Neuropsychological Status Update. https://www.pearsonassessments.com/store/usassessments/en/Store/Professional-Assessments/Cognition-%26-Neuro/Repeatable-Battery-for-the-Assessment-of-Neuropsychological-Status-Update/p/100000726.html. Accessed December 5, 2020.

53. Kinarm Standard Tests. https://kinarm.com/kinarm-products/kinarm-standard-tests/#download_kst. Accessed September 2, 2020.

54. Kinarm End-Point Lab. https://kinarm.com/kinarm-products/kinarm-end-point-lab/. Accessed July 24, 2020.

55. Mang CS, Whitten TA, Cosh MS, et al. Test-retest reliability of the KINARM end-point robot for assessment of sensory, motor and neurocognitive function in young adult athletes. 2018. doi:10.1371/journal.pone.0196205

56. Little CE, Emery C, Black A, et al. Test-retest reliability of KINARM robot sensorimotor and cognitive assessment: in pediatric ice hockey players. 2012. doi:10.1186/s12984-015-0070-0

57. Claes AJ, Mertens G, Gilles A, et al. The repeatable battery for the assessment of neuropsychological status for hearing impaired individuals (RBANS-H) before and after cochlear implantation: A protocol for a prospective, longitudinal cohort study. *Front Neurosci*. 2016;10(NOV). doi:10.3389/fnins.2016.00512

58. User Guides & Documentation. https://kinarm.com/support/user-guides-documentation/. Accessed July 24, 2020.

59. Hedgeman E, Lipworth L, Lowe K, Saran R, Do T, Fryzek J. International Burden of Chronic Kidney Disease and Secondary Hyperparathyroidism: A Systematic Review of the Literature and Available Data. *Int J Nephrol*. 2015;2015:1-15. doi:10.1155/2015/184321

60. Madero M, Gul A, Sarnak MJ. Cognitive function in chronic kidney disease. *Semin Dial*. 2008;21(1):29-37. doi:10.1111/j.1525-139X.2007.00384.x

61. Tiffin-Richards FE, Costa AS, Holschbach B, et al. The Montreal Cognitive Assessment (MoCA) - A Sensitive Screening Instrument for Detecting Cognitive

Impairment in Chronic Hemodialysis Patients. Herholz K, ed. *PLoS One*. 2014;9(10):e106700. doi:10.1371/journal.pone.0106700

62. Tamura MK, Xie D, Yaffe K, et al. Vascular risk factors and cognitive impairment in chronic kidney disease: The Chronic Renal Insufficiency Cohort (CRIC) study. *Clin J Am Soc Nephrol*. 2011;6:248-256. http://cjasn.asnjournals.org/content/6/2/248.full.pdf+html.

63. Souheaver GT, Ryan JJ, DeWolfe AS. Neuropsychological patterns in uremia. *J Clin Psychol*. 1982;38:490-496. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med2&NEWS=N&AN=7050178.

64. Williams MA, Sklar AH, Burright RG, Donovick PJ. Temporal effects of dialysis on cognitive functioning in patients with ESRD. *Am J Kidney Dis*. 2004;43:705-711. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=15042548.

65. O'Lone E, Connors M, Masson P, et al. Cognition in People With End-Stage Kidney Disease Treated With Hemodialysis: A Systematic Review and Meta-analysis. *Am J Kidney Dis*. 2016;67(6):925-935. doi:https://dx.doi.org/10.1053/j.ajkd.2015.12.028

66. Tsai C-F, Wang S-J, Fuh J-L. Moderate chronic kidney disease is associated with reduced cognitive performance in midlife women. *Kidney Int*. 2010;78:605-610. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=

N&AN=20571474.

67. Institute. JB. *Joanna Briggs Institute Reviewers' Manual*.; 2011.

68. Finding What Works in Health Care: Standards for Systematic Reviews - Institute of Medicine, Board on Health Care Services, Committee on Standards for Systematic Reviews of Comparative Effectiveness Research - Google Books. https://books.google.ca/books?hl=en&lr=&id=JgFGxzdBckEC&oi=fnd&pg=PT17&dq=16.%09Morton,+S.,+Berg,+A.,+Levit,+L.,+%26+Eden,+J.+(Eds.).+(2011).+Finding+What+Works+in+Health+Care:+Standards+for+Systematic+Reviews.+National+Academies+Press.&ots=eHxjdJfkfC&sig=UC467ZihriSrkPXS4QYQLKdu3XI#v=onepage&q=16.%09Morton%2C S.%2C Berg%2C A.%2C Levit%2C L.%2C %26 Eden%2C J. (Eds.). (2011). Finding What Works in Health Care%3A Standards for Systematic Reviews. National Academies Press.&f=false. Accessed December 7, 2020.

69. Weissenborn K, Rückert N, Hecker H, Manns MP. The number connection tests A and B: Interindividual variability and use for the assessment of early hepatic encephalopathy. *J Hepatol*. 1998;28(4):646-653. doi:10.1016/S0168-8278(98)80289-4

70. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14(1):1-13. doi:10.1186/1471-2288-14-135

71. Folstein, M. F., Folstein, S. E., & McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*.

1975;12(3):189-198.

72. Teng, E. L., & Chui HC. The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry*. 1987;48(8):314-318.

73. McDowell I, Hill G, Lindsay J, et al. Canadian Study of Health and Aging: Study methods and prevalence of dementia. *CMAJ*. 1994;150(6):899-912. /pmc/articles/PMC1486712/?report=abstract. Accessed December 7, 2020.

74. Rossetti HC, Lacritz LH, Munro Cullum C, Weiner MF. Normative data for the Montreal Cognitive Assessment (MoCA) in a population-based sample. *Neurology*. 2011;77(13):1272-1275. doi:10.1212/WNL.0b013e318230208a

75. Zakzanis KK, Mraz R, Graham SJ. An fMRI study of the Trail Making Test. *Neuropsychologia*. 2005;43(13):1878-1886. doi:10.1016/j.neuropsychologia.2005.03.013

76. Tombaugh TN. Trail Making Test A and B: Normative data stratified by age and education. *Arch Clin Neuropsychol*. 2004;19(2):203-214. doi:10.1016/S0887-6177(03)00039-8

77. Pena-Casanova J, Quinones-Ubeda S, Quintana-Aparicio M, et al. Spanish Multicenter Normative Studies (NEURONORMA Project): Norms for Verbal Span, Visuospatial Span, Letter and Number Sequencing, Trail Making Test, and Symbol Digit Modalities Test. *Arch Clin Neuropsychol*. 2009;24(4):321-341. doi:10.1093/arclin/acp038

78. Kessels RPC, Van Den Berg E, Ruis C, Brands AMA. The backward span of the corsi block-tapping task and its association with the WAIS-III digit span.

Assessment. 2008;15(4):426-434. doi:10.1177/1073191108315611

79. Kreiner DS, Ryan JJ. Memory and motor skill components of the WAIS-III Digit Symbol-Coding subtest. *Clin Neuropsychol*. 2001;15(1):109-113. doi:10.1076/clin.15.1.109.1906

80. Hoyer WJ, Stawski RS, Wasylyshyn C, Verhaeghen P. Adult Age and Digit Symbol Substitution Performance: A Meta-Analysis. *Psychol Aging*. 2004;19(1):211-214. doi:10.1037/0882-7974.19.1.211

81. Etgen T, Sander D, Chonchol M, et al. Chronic kidney disease is associated with incident cognitive impairment in the elderly: The INVADE study. *Nephrol Dial Transplant*. 2009;24(10):3144-3150. doi:10.1093/ndt/gfp230

82. Sasaki Y, Marioni R, Kasai M, Ishii H, Yamaguchi S, Meguro K. Chronic Kidney Disease: A Risk Factor for Dementia Onset: A Population-Based Study. The Osaki-Tajiri Project. *J Am Geriatr Soc*. 2011;59(7):1175-1181. doi:10.1111/j.1532-5415.2011.03477.x

83. Bugnicourt JM, Godefroy O, Chillon JM, Choukroun G, Massy ZA. Cognitive disorders and dementia in CKD: The neglected kidney-brain axis. *J Am Soc Nephrol*. 2013;24(3):353-363. doi:10.1681/ASN.2012050536

84. Freedman BI, Sink KM, Hugenschmidt CE, et al. Associations of Early Kidney Disease With Brain Magnetic Resonance Imaging and Cognitive Function in African Americans With Type 2 Diabetes Mellitus. *Am J Kidney Dis*. 2017;70(5):627-637. doi:https://dx.doi.org/10.1053/j.ajkd.2017.05.006

85. McDowell I, Hill G, Lindsay J, et al. Canadian Study of Health and Aging: Study

methods and prevalence of dementia. *Cmaj*. 1994;150(6):899-912.

86. Murea M, Hsu FC, Cox AJ, et al. Structural and functional assessment of the brain in European Americans with mild-to-moderate kidney disease: Diabetes Heart Study-MIND. *Nephrol Dial Transplant*. 2015;30(8):1322-1329. doi:10.1093/ndt/gfv030

87. Murray AM, Bell EJ, Tupper DE, et al. The brain in kidney disease (BRINK) cohort study: Design and baseline cognitive function. *Am J Kidney Dis*. 2016;67(4):593-600. doi:10.1053/j.ajkd.2015.11.008

88. Palmer ND, Sink KM, Smith SC, et al. Kidney disease and cognitive function: African American-diabetes heart study MIND. *Am J Nephrol*. 2014;40(3):200-207. doi:10.1159/000367669

89. Pi HC, Xu YF, Xu R, et al. Cognitive Impairment and Structural Neuroimaging Abnormalities Among Patients with Chronic Kidney Disease. *Kidney Blood Press Res*. 2016;41(6):986-996. doi:https://dx.doi.org/10.1159/000452603

90. Slinin Y, Paudel ML, Ishani A, et al. Kidney function and cognitive performance and decline in older men. *J Am Geriatr Soc*. 2008;56:2082-2088. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=18795984.

91. Kurella M, Chertow GM, Luan J, Yaffe K. Cognitive impairment in chronic kidney disease. *J Am Geriatr Soc*. 2004;52(11):1863-1869. doi:10.1111/j.1532-5415.2004.52508.x

92. Yaffe K, Ackerson L, Tamura MK, et al. Chronic kidney disease and cognitive

function in older adults: Findings from the chronic renal insufficiency cohort cognitive study. *J Am Geriatr Soc*. 2010;58:338-345. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=2010084497.

93. Yaffe K, Ackerson L, Hoang TD, et al. Retinopathy and cognitive impairment in adults with CKD. *Am J Kidney Dis*. 2013;61(2):219-227. doi:http://dx.doi.org/10.1053/j.ajkd.2012.10.006

94. Lee JJ, Chin HJ, Byun MS, et al. Impaired frontal executive function and predialytic chronic kidney disease. *J Am Geriatr Soc*. 2011;59(9):1628-1635. doi:http://dx.doi.org/10.1111/j.1532-5415.2011.03562.x

95. Fastenau PS, Denburg NL, Mauer BA. Parallel short forms for the Boston naming test: Psychometric properties and norms for older adults. *J Clin Exp Neuropsychol*. 1998;20(6):828-834. doi:10.1076/jcen.20.6.828.1105

96. Martini A, Ammirati A, Garcia C, et al. Evaluation of quality of life, physical, and mental aspects in longevous patients with chronic kidney disease. *Int Urol Nephrol*. 2018;50(4):725-731. doi:http://dx.doi.org/10.1007/s11255-018-1813-1

97. Torres R V, Elias MF, Seliger S, Davey A, Robbins MA. Risk for cognitive impairment across 22 measures of cognitive ability in early-stage chronic kidney disease. *Nephrol Dial Transplant*. 2017;32(2):299-306. doi:https://dx.doi.org/10.1093/ndt/gfw005

98. Yaffe K, Kurella-Tamura M, Ackerson L, et al. Higher levels of cystatin C are associated with worse cognitive function in older adults with chronic kidney

disease: the chronic renal insufficiency cohort cognitive study. *J Am Geriatr Soc*. 2014;62(9):1623-1629. doi:http://dx.doi.org/10.1111/jgs.12986

99. Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. *Arch Clin Neuropsychol*. 1999;14(2):167-177. doi:10.1016/S0887-6177(97)00095-4

100. Yeh Y-C, Huang M-F, Hwang S-J, et al. Association of homocysteine level and vascular burden and cognitive function in middle-aged and older adults with chronic kidney disease. *Int J Geriatr Psychiatry*. 2016;31(7):723-730. doi:http://dx.doi.org/10.1002/gps.4383

101. Post JB, Jegede AB, Morin K, Spungen AM, Langhoff E, Sano M. Cognitive profile of chronic kidney disease and hemodialysis patients without dementia. *Nephron Clin Pract*. 2010;116:c247--55. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=20606486.

102. Szerlip HM, Edwards ML, Williams BJ, Johnson LA, Vintimilla RM, O'Bryant SE. Association between cognitive impairment and chronic kidney disease in Mexican Americans. *J Am Geriatr Soc*. 2015;63(10):2023-2028. doi:10.1111/jgs.13665

103. Norman MA, Evans JD, Miller SW, Heaton RK. Demographically corrected norms for the California verbal learning test. *J Clin Exp Neuropsychol*. 2000;22(1):80-94. doi:10.1076/1380-3395(200002)22:1;1-8;FT080

104. Chang CY, Lin CC, Tsai CF, et al. Cognitive impairment and hippocampal atrophy

in chronic kidney disease. *Acta Neurol Scand*. 2017;136(5):477-485. doi:http://dx.doi.org/10.1111/ane.12753

105. Hart RP, Pederson JA, Czerwinski AW, Adams RL. Chronic renal failure, dialysis, and neuropsychological function. *J Clin Neuropsychol*. 1983;5:301-312. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed1a&NEWS=N&AN=1984064341.

106. Kaya Y, Ozturkeri OA, Benli US, Colak T. Evaluation of the cognitive functions in patients with chronic renal failure before and after renal transplantation. *Acta Neurol Belg*. 2013;113:147-155. http://www.springerlink.com/content/2240-2993.

107. Paraizo Mde A, Almeida AL, Pires LA, et al. Montreal Cognitive Assessment (MoCA) screening mild cognitive impairment in patients with chronic kidney disease (CKD) pre-dialysis. *J Bras Nefrol*. 2016;38(1):31-41. doi:https://dx.doi.org/10.5935/0101-2800.20160006

108. Seidel UK, Gronewold J, Volsek M, et al. The prevalence, severity, and association with HbA1c and fibrinogen of cognitive impairment in chronic kidney disease. *Kidney Int*. 2014;85(3):693-702. doi:http://dx.doi.org/10.1038/ki.2013.366

109. Nasser MET, Shawki S, El Shahawy Y, Sany D. Assessment of cognitive dysfunction in kidney disease. *Saudi J Kidney Dis Transpl*. 2012;23:1208-1214. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=23168850.

110. Chen HJ, Qi R, Kong X, et al. The impact of hemodialysis on cognitive dysfunction in patients with end-stage renal disease: a resting-state functional MRI

study. *Metab Brain Dis*. 2015;30(5):1247-1256. doi:10.1007/s11011-015-9702-0

111. Jiang XL, Wen JQ, Zhang LJ, et al. Cerebral blood flow changes in hemodialysis and peritoneal dialysis patients: an arterial-spin labeling MR imaging. *Metab Brain Dis*. 2016;31(4):929-936. doi:https://dx.doi.org/10.1007/s11011-016-9829-7

112. Lin C-Y, Lin L-Y, Kuo H-K, Lin J-W. Chronic kidney disease, atherosclerosis, and cognitive and physical function in the geriatric group of the National Health and Nutrition Survey 1999-2002. *Atherosclerosis*. 2009;202:312-319. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=18533156.

113. Luo S, Qi RF, Wen JQ, et al. Abnormal Intrinsic Brain Activity Patterns in Patients with End-Stage Renal Disease Undergoing Peritoneal Dialysis: A Resting-State Functional MR Imaging Study. *Radiology*. 2016;278(1):181-189. doi:10.1148/radiol.2015141913

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

115. Amodio P, Campagna F, Olianas S, et al. Detection of minimal hepatic encephalopathy: Normalization and optimization of the Psychometric Hepatic Encephalopathy Score. A neuropsychological and quantified EEG study. *J Hepatol*. 2008;49(3):346-353. doi:10.1016/j.jhep.2008.04.022

116. Afsar B. Relationship between total testosterone, cognitive function, depressive

behavior, and sleep quality in chronic kidney disease patients not on dialysis. *Clin Exp Nephrol*. 2013;17(1):59-65. doi:http://dx.doi.org/10.1007/s10157-012-0652-0

117. Afsar B, Elsurer R, Covic A, Johnson RJ, Kanbay M. Relationship between uric acid and subtle cognitive dysfunction in chronic kidney disease. *Am J Nephrol*. 2011;34:49-54. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21659739.

118. Bai K, Pan Y, Lu F, Zhao Y, Wang J, Zhang L. Kidney function and cognitive decline in an oldest-old Chinese population. *Clin Interv Aging*. 2017;12:1049-1054. doi:https://dx.doi.org/10.2147/CIA.S134205

119. Driessen M, Wetterling T, Wedel T, Preuss R. Secondary hyperparathyroidism and depression in chronic renal failure. *Nephron*. 1995;70:334-339. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed3&NEWS=N&AN=1995204703.

120. Helmer C, Stengel B, Metzger M, et al. Chronic kidney disease, cognitive decline, and incident dementia: the 3C Study. *Neurology*. 2011;77(23):2043-2051. doi:http://dx.doi.org/10.1212/WNL.0b013e31823b4765

121. Hobson P, Rohoma KH, Wong SP, Kumwenda MJ. The Utility of the Mini-Addenbrooke's Cognitive Examination as a Screen for Cognitive Impairment in Elderly Patients with Chronic Kidney Disease and Diabetes. *Dement Geriatr Cogn Dis Extra*. 2016;6(3):541-548. doi:http://dx.doi.org/10.1159/000450784

122. Ito H, Antoku S, Mori T, et al. Association between chronic kidney disease and the

cognitive function in subjects without overt dementia. *Clin Nephrol*. 2018;89(5):330-335. doi:http://dx.doi.org/10.5414/CN109188

123. Lee SC, Shimada H, Park H, et al. The Association Between Kidney Function and Cognitive Decline inCommunity-Dwelling, Elderly Japanese People. *J Am Med Dir Assoc*. 2015;16(4):349.e1-349.e5. doi:10.1016/j.jamda.2014.12.009

124. Madan P, Kalra OP, Agarwal S, Tandon OP. Cognitive impairment in chronic kidney disease. *Nephrol Dial Transplant*. 2007;22:440-444. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=17023495.

125. Miwa K, Tanaka M, Okazaki S, et al. Chronic kidney disease is associated with dementia independent of cerebral small-vessel disease. *Neurology*. 2014;82(12):1051-1057. doi:http://dx.doi.org/10.1212/WNL.0000000000000251

126. Wang H, Fang C, Cai L, Dong B, Deng J. Chronic kidney disease and cognitive impairment among the very old in China. *Aging-Clinical Exp Res*. 2016;28(3):475-482. doi:https://dx.doi.org/10.1007/s40520-015-0433-1

127. Wang H, Liu T, Cai YY, Jiang H, Liu HX, Lin C. Kidney Function and Cognitive Impairment in People Aged 80 Years and Over with Untreated Hypertension: A Cross-Sectional Survey. *Kidney Blood Press Res*. 2016;41(1):70-77. doi:https://dx.doi.org/10.1159/000368550

128. Wang F, Zhang L, Liu L, Wang H. Level of kidney function correlates with cognitive decline. *Am J Nephrol*. 2010;32:117-121. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=

N&AN=20714128.

129. Wang J, Li XB, Huang P, Huang MY, Gu XJ. Change of Peripheral Blood Treg/Thl7 in Cognitive Impairment with Chronic Renal Failure Patients. *Cell Physiol Biochem*. 2018;45(1):281-290. doi:https://dx.doi.org/10.1159/000486809

130. Weng SC, Shu KH, Tang YJ, et al. Progression of cognitive dysfunction in elderly chronic kidney disease patients in a veteran's institution in central Taiwan: a 3-year longitudinal study. *Intern Med*. 2012;51(1):29-35. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=22214620.

131. Yao H, Miwa Y, Takashima Y, et al. Chronic kidney disease and subclinical lacunar infarction are independently associated with frontal lobe dysfunction in community-dwelling elderly subjects: the Sefuri brain MRI study. *Hypertens Res*. 2011;34:1023-1028. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21697852.

132. Yao H, Araki Y, Takashima Y, Uchino A, Yuzuriha T, Hashimoto M. Chronic Kidney Disease and Subclinical Brain Infarction Increase the Risk of Vascular Cognitive Impairment: The Sefuri Study. *J Stroke Cerebrovasc Dis*. 2017;26(2):420-424. doi:https://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2016.10.002

133. Iyasere O, Okai D, Brown E. Cognitive function and advanced kidney disease: Longitudinal trends and impact on decision-making. *Clin Kidney J*. 2017;10(1):89-

94. doi:http://dx.doi.org/10.1093/ckj/sfw128

134. Gale SD, Baxter L, Connor DJ, Herring A, Comer J. Sex differences on the Rey Auditory Verbal Learning Test and the Brief Visuospatial Memory Test-Revised in the elderly: Normative data in 172 participants. *J Clin Exp Neuropsychol*. 2007;29(5):561-567. doi:10.1080/13803390600864760

135. Peña-Casanova J, Gramunt-Fombuena N, Quiñones-Úbeda S, et al. Spanish multicenter normative studies (NEURONORMA project): Norms for the rey-osterrieth complex figure (copy and memory), and free and cued selective reminding test. *Arch Clin Neuropsychol*. 2009;24(4):371-393. doi:10.1093/arclin/acp041

136. Van Der Elst W, Van Boxtel MPJ, Van Breukelen GJP, Jolles J. The stroop color-word test: Influence of age, sex, and education; and normative data for a large sample across the adult age range. *Assessment*. 2006;13(1):62-79. doi:10.1177/1073191105283427

137. Tsuruya K, Yoshida H, Haruyama N, Fujisaki K, Hirakata H, Kitazono T. Clinical Significance of Fronto-Temporal Gray Matter Atrophy in Executive Dysfunction in Patients with Chronic Kidney Disease: The VCOHP Study. *PLoS One*. 2015;10(12):1-16. doi:10.1371/journal.pone.0143706

138. Troyer AK. Normative data for clustering and switching on verbal fluency tasks. *J Clin Exp Neuropsychol*. 2000;22(3):370-378. doi:10.1076/1380-3395(200006)22:3;1-V;FT370

139. Dixon BS, Vanburen JM, Rodrigue JR, et al. Cognitive changes associated with

switching to frequent nocturnal hemodialysis or renal transplantation Dialysis and Transplantation. *BMC Nephrol*. 2016;17(1):1-11. doi:10.1186/s12882-016-0223-9

140. Kalirao P, Pederson S, Foley RN, et al. Cognitive impairment in peritoneal dialysis patients. *Am J Kidney Dis*. 2011;57:612-620. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=2011163397.

141. McAdams-Demarco MA, Tan J, Salter ML, et al. Frailty and cognitive function in incident hemodialysis patients. *Clin J Am Soc Nephrol*. 2015;10(12):2181-2189. doi:10.2215/CJN.01960215

142. Shavit L, Mikeladze I, Torem C, Slotki I. Mild hyponatremia is associated with functional and cognitive decline in chronic hemodialysis patients. *Clin Nephrol*. 2014;82:313-319. http://www.dustri.com/index.php?id=8?no_cache=1&magId=20&volId=168&issueId=12775.

143. Kurella Tamura M, Larive B, Unruh ML, et al. Prevalence and correlates of cognitive impairment in hemodialysis patients: the Frequent Hemodialysis Network trials. *Clin J Am Soc Nephrol*. 2010;5:1429-1438. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=20576825.

144. Kurella Tamura M, Unruh ML, Nissenson AR, et al. Effect of more frequent hemodialysis on cognitive function in the frequent hemodialysis network trials. *Am J Kidney Dis*. 2013;61(2):228-237.

doi:http://dx.doi.org/10.1053/j.ajkd.2012.09.009

145. Jassal S V., Devins GM, Chan CT, Bozanovic R, Rourke S. Improvements in cognition in patients converting from thrice weekly hemodialysis to nocturnal hemodialysis: A longitudinal pilot study. *Kidney Int*. 2006;70(5):956-962. doi:10.1038/sj.ki.5001691

146. Benedict RHB, Groninger L, Schretlen D, Dobraski M, Shpritz B. Revision of the brief visuospatial memory test: Studies of normal performance, reliability, and, validity. *Psychol Assess*. 1996;8(2):145-153. doi:10.1037/1040-3590.8.2.145

147. Murray AM, Pederson SL, Tupper DE, et al. Acute Variation in Cognitive Function in Hemodialysis Patients: A Cohort Study With Repeated Measures. *Am J Kidney Dis*. 2007;50:270-278. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=2007359372.

148. Brown WS, Marsh JT, Wolcott D, et al. Cognitive function, mood and P3 latency: effects of the amelioration of anemia in dialysis patients. *Neuropsychologia*. 1991;29:35-45. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=2017307.

149. Marsh JT, Brown WS, Wolcott D, et al. rHuEPO treatment improves brain and cognitive function of anemic dialysis patients. *Kidney Int*. 1991;39:155-163. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=2002629.

150. Oaksford K, Oaksford M, Ashraf M, Fitzgibbon G. Comparing neuropsychological function before and during haemodialysis: A habituating selective deficit for prose recall. *Br J Health Psychol*. 2008;13:273-289. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=2008257987.

151. Pliskin NH, Yurk HM, Ho LT, Umans JG. Neurocognitive function in chronic hemodialysis patients. *Kidney Int*. 1996;49:1435-1440. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed4&NEWS=N&AN=1996151973.

152. Sarnak MJ, Tighiouart H, Scott TM, et al. Frequency of and risk factors for poor cognitive performance in hemodialysis patients. *Neurology*. 2013;80(5):471-480. doi:http://dx.doi.org/10.1212/WNL.0b013e31827f0f7f

153. Tamura MK, Meyer JB, Saxena AB, Terri Huh JW, Wadley VG, Schiller B. Prevalence and significance of stroke symptoms among patients receiving maintenance dialysis. *Neurology*. 2012;79:981-987. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=psyc9&NEWS=N&AN=2012-27294-010.

154. Wolfgram D, Vogt E, Jahn AL, et al. Hemodynamics During Dialysis and Changes in Cognitive Performance. *WMJ*. 2016;115(6):311-316. https://proxy.queensu.ca/login?url=http://ovidsp.ovid.com?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=29094868 http://dw2zn6fm9z.search.serialssolutions.com/?url_ver=Z39.88-

2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:medl&rft.genre=ar.

155. Drew DA, Tighiouart H, Scott TM, et al. Cognitive performance before and during hemodialysis: a randomized cross-over trial. *Nephron*. 2013;124(3-4):151-158. doi:http://dx.doi.org/10.1159/000356393

156. George S, Holt S, Medford N, Hildick-Smith D. Does a patent foramen ovale influence cognitive function in dialysis patients? *Nephron*. 2013;123(1-2):1-6. doi:http://dx.doi.org/10.1159/000351191

157. Anwar W, Ezzat H, Mohab A. Comparative study of impact of hemodialysis and renal transplantation on cognitive functions in ESRD patients. *Nefrologia*. 2015;35(6):567-571. doi:https://dx.doi.org/10.1016/j.nefro.2015.07.004

158. Gallai V, Alberti A, Buoncristiani U, Firenze C, Mazzotta G. Changes in auditory P3 event-related potentials in uremic patients undergoing haemodialysis. *Electromyogr Clin Neurophysiol*. 1994;34:397-402. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=7859667.

159. O'Connor SM, Jardine AG, Millar K. The prediction of self-care behaviors in end-stage renal disease patients using Leventhal's Self-Regulatory Model. *J Psychosom Res*. 65:191-200. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=psyc6&NEWS=N&AN=2008-10640-018.

160. Ratner DP, Adams KM, Levin NW, Rourke BP. Effects of hemodialysis on the

cognitive and sensory-motor functioning of the adult chronic hemodialysis patient. *J Behav Med*. 1983;6:291-311. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med2&NEWS=N&AN=6663616.

161. Umans JG, Pliskin NH. Attention and mental processing speed in hemodialysis patients. *Am J Kidney Dis*. 1998;32:749-751. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed4&NEWS=N&AN=1998382716.

162. Chen HJ, Wang YF, Qi R, et al. Altered Amygdala Resting-State Functional Connectivity in Maintenance Hemodialysis End-Stage Renal Disease Patients with Depressive Mood. *Mol Neurobiol*. 2017;54(3):2223-2233. doi:http://dx.doi.org/10.1007/s12035-016-9811-8

163. Giang LM, Tighiouart H, Lou K V, et al. Measures of blood pressure and cognition in dialysis patients. *Hemodial Int*. 2013;17(1):24-31. doi:http://dx.doi.org/10.1111/j.1542-4758.2012.00718.x

164. Kong X, Wen JQ, Qi RF, et al. Diffuse interstitial brain edema in patients with end-stage renal disease undergoing hemodialysis: A tract-based spatial statistics study. *Med (United States)*. 2014;93:e313. http://journals.lww.com/md-journal.

165. Pereira AA, Weiner DE, Scott T, et al. Subcortical cognitive impairment in dialysis patients. *Hemodial Int*. 2007;11:309-314. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=17576295.

166. Kurella Tamura M, Chertow GM, Depner TA, et al. Metabolic Profiling of Impaired Cognitive Function in Patients Receiving Dialysis. *J Am Soc Nephrol*. 2016;27(12):3780-3787. https://proxy.queensu.ca/login?url=http://ovidsp.ovid.com?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medc&AN=27444566 http://dw2zn6fm9z.search.serialssolutions.com/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:medc&rft.genre=ar.

167. Weiner DE, Scott TM, Giang LM, et al. Cardiovascular disease and cognitive function in maintenance hemodialysis patients. *Am J Kidney Dis*. 2011;58:773-781. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21778003.

168. Afsar B. Sociodemographic, clinical, and laboratory parameters related with presence of regular toothbrushing in hemodialysis patients. *Ren Fail*. 2013;35(2):179-184. doi:http://dx.doi.org/10.3109/0886022X.2012.747131

169. Afsar B, Elsurer R. Association between serum bicarbonate and pH with depression, cognition and sleep quality in hemodialysis patients. *Ren Fail*. 2015;37(6):957-960. doi:10.3109/0886022X.2015.1038476

170. Badzek L, Hines SC, Moss AH. Inadequate self-care knowledge among elderly hemodialysis patients: assessing its prevalence and potential causes. *ANNA J*. 1998;25:293-300.

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=9801485.

171. Bae JS, Park SS. Contingent negative variation before and after hemodialysis among patients with end-stage renal disease. *J Neurol Sci*. 2008;267:70-75. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=2008081479.

172. Bossola M, Antocicco M, Di Stasio E, et al. Mini Mental State Examination over time in chronic hemodialysis patients. *J Psychosom Res*. 2011;71:50-54. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21665013.

173. Bossola M, Di Stasio E, Giungi S, Rosa F, Tazza L. Fatigue is associated with serum interleukin-6 levels and symptoms of depression in patients on chronic hemodialysis. *J Pain Symptom Manage*. 2015;49:578-585. www.elsevier.com/locate/jpainsymman.

174. Chai C, Zhang M, Long M, et al. Increased brain iron deposition is a risk factor for brain atrophy in patients with haemodialysis: A combined study of quantitative susceptibility mapping and whole brain volume analysis. *Metab Brain Dis*. 2015;30(4):1009-1016. doi:10.1007/s11011-015-9664-2

175. Chiu E, Markowitz SN, Cook WL, Jassal S V. Visual Impairment in Elderly Patients Receiving Long-term Hemodialysis. *Am J Kidney Dis*. 2008;52:1131-1138. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS

=N&AN=2008539929.

176. Costa AS, Tiffin-Richards FE, Holschbach B, et al. Clinical predictors of individual cognitive fluctuations in patients undergoing hemodialysis. *Am J Kidney Dis*. 2014;64(3):434-442. doi:http://dx.doi.org/10.1053/j.ajkd.2014.02.012

177. Cukor D, Ver Halen N, Rosenthal Asher D, Goldberg MA, Slyker J, Kimmel PL. A pilot investigation of cognitive improvement across a single hemodialysis treatment. *J Nephrol*. 2013;26(2):323-330. doi:http://dx.doi.org/10.5301/jn.5000148

178. da Silva ST avare., Ribeiro R de CL ane., Rosa C de OB arbos., Cotta RMM itr. Cognitive capacity in individuals with chronic kidney disease: relation to demographic and clinical characteristics. *J Bras Nefrol 'orgão Of Soc Bras e Latino-Americana Nefrol*. 2014;36(2):163-170. doi:10.5935/0101-2800.20140026

179. Dahbour SS, Wahbeh AM, Hamdan MZ. Mini mental status examination (MMSE) in stable chronic renal failure patients on hemodialysis: The effects of hemodialysis on the MMSE score. A prospective study. *Hemodial Int*. 2009;13:80-85. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=2009054959.

180. Dixit A, Dhawan S, Raizada A, Yadav A, Vaney N, Kalra OP. Attention and information processing in end stage renal disease and effect of hemodialysis: a bedside study. *Ren Fail*. 2013;35(9):1246-1250. doi:http://dx.doi.org/10.3109/0886022X.2013.819768

181. Fadili W, Al Adlouni A, Louhab N, Habib Allah M, Kissani N, Laouad I. Prevalence and risk factors of cognitive dysfunction in chronic hemodialysis patients. *Aging Ment Health*. 2014;18(2):207-211. doi:http://dx.doi.org/10.1080/13607863.2013.823375

182. Fazekas G, Fazekas F, Schmidt R, Kapeller P, Offenbacher H, Krejs GJ. Brain MRI findings and cognitive impairment in patients undergoing chronic hemodialysis treatment. *J Neurol Sci*. 1995;134:83-88. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=8747848.

183. Gencoz F, Gencoz T, Soykan A. Psychometric properties of the Hamilton Depression Rating Scale and other physician-rated psychiatric scales for the assessment of depression in ESRD patients undergoing hemodialysis in Turkey. *Psychol Health Med*. 2007;12:450-459. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=17620209.

184. Grimm G, Stockenhuber F, Schneeweiss B, Madl C, Zeitlhofer J, Schneider B. Improvement of brain function in hemodialysis patients treated with erythropoietin. *Kidney Int*. 1990;38:480-486. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=2232491.

185. Harciarek M, Michalowski J, Biedunkiewicz B, et al. Disorders of the anterior attentional-intentional system in patients with end stage renal disease: Evidence

from reaction time studies. *Brain Cogn*. 2016;107:1-9. doi:https://dx.doi.org/10.1016/j.bandc.2016.05.005

186. Hsieh RL, Lee WC, Chang CH. Maximal Cardiovascular Fitness and Its Correlates in Ambulatory Hemodialysis Patients. *Am J Kidney Dis*. 2006;48:21-27. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed7&NEWS=N&AN=2006293274.

187. Huertas-Vieco MP, Perez-Garcia R, Albalate M, et al. Psychosocial factors and adherence to drug treatment in patients on chronic haemodialysis. *Nefrologia*. 2014;34(6):737-742. doi:https://dx.doi.org/10.3265/Nefrologia.pre2014.Jul.12477

188. Jones DJW, Butler LT, Harris JP, Vaux EC. Latent learning in End Stage Renal Disease (ESRD). *Physiol Behav*. 142:42-47. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=psyc11&NEWS=N&AN=2015-08846-010.

189. Jung S, Lee YK, Choi SR, Hwang SH, Noh JW. Relationship between cognitive impairment and depression in dialysis patients. *Yonsei Med J*. 2013;54(6):1447-1453. doi:http://dx.doi.org/10.3349/ymj.2013.54.6.1447

190. Kim JK, Choi SR, Choi MJ, et al. Prevalence of and factors associated with sarcopenia in elderly patients with end-stage renal disease. *Clin Nutr*. 2014;33(1):64-68. doi:http://dx.doi.org/10.1016/j.clnu.2013.04.002

191. Kitaguchi N, Hasegawa M, Ito S, et al. A prospective study on blood Aβ levels and the cognitive function of patients with hemodialysis: a potential therapeutic strategy for Alzheimer's disease. *J Neural Transm*. 2015;122(11):1593-1607.

doi:10.1007/s00702-015-1431-3

192. Kobayashi S, Mochida Y, Ishioka K, et al. The effects of blood pressure and the renin-angiotensin-aldosterone system on regional cerebral blood flow and cognitive impairment in dialysis patients. *Hypertens Res*. 2014;37:636-641. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=24694648.

193. Kramer L, Madl C, Stockenhuber F, et al. Beneficial effect of renal transplantation on cognitive brain function. *Kidney Int*. 1996;49:833-838. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=8648927.

194. Li C, Su HH, Qiu YW, et al. Regional homogeneity changes in hemodialysis patients with end stage renal disease: In Vivo resting-state functional MRI Study. *PLoS One*. 2014;9. http://www.plosone.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pone.0087114&representation=PDF.

195. Lux S, Mirzazade S, Kuzmanovic B, et al. Differential activation of memory-relevant brain regions during a dialysis cycle. *Kidney Int*. 2010;78:794-802. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=20668428.

196. Prelevic V, Radunovic D, Antunovic T, et al. Increased Serum Level of IGF-1 Correlates With Better Cognitive Status in End-Stage Renal Disease Patients Undergoing Hemodialysis. *Ther Apher Dial*. 2018;22(2):118-123.

doi:http://dx.doi.org/10.1111/1744-9987.12610

197. Sithinamsuwan P, Niyasom S, Nidhinandana S, Supasyndh O. Dementia and depression in end stage renal disease: comparison between hemodialysis and continuous ambulatory peritoneal dialysis. *J Med Assoc Thai*. 2005;88 Suppl 3:S141--7. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=16858952.

198. Sorensen EP, Sarnak MJ, Tighiouart H, et al. The kidney disease quality of life cognitive function subscale and cognitive performance in maintenance hemodialysis patients. *Am J Kidney Dis*. 2012;60(3):417-426. doi:http://dx.doi.org/10.1053/j.ajkd.2011.12.029

199. Soysal P, Isik AT, Buyukaydin B, Kazancioglu R. A comparison of end-stage renal disease and Alzheimer's disease in the elderly through a comprehensive geriatric assessment. *Int Urol Nephrol*. 2014;46:1627-1632. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=24848882.

200. Tasmoc A, Donciu MD, Veisa G, Nistor I, Covic A. Increased arterial stiffness predicts cognitive impairment in hemodialysis patients. *Hemodial Int*. 2016;20(3):463-472. doi:https://dx.doi.org/10.1111/hdi.12406

201. Tholen S, Schmaderer C, Kusmenkov E, et al. Variability of cognitive performance during hemodialysis: Standardization of cognitive assessment. *Dement Geriatr Cogn Disord*. 2014;38:31-38.

www.karger.com/journals/dem/dem_jh.htm.

202. Tholen S, Schmaderer C, Chmielewski S, et al. Reduction of Amyloid-beta Plasma Levels by Hemodialysis: An Anti-Amyloid Treatment Strategy? *J Alzheimer's Dis*. 2016;50(3):791-796. doi:https://dx.doi.org/10.3233/JAD-150662

203. Tilki HE, Akpolat T, Tunali G, Kara A, Onar MK. Effects of haemodialysis and continuous ambulatory peritoneal dialysis on P300 cognitive potentials in uraemic patients. *Ups J Med Sci*. 2004;109:43-48. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=15124952.

204. Zhang R, Liu K, Yang L, Zhou T. Reduced white matter integrity and cognitive deficits in maintenance hemodialysis ESRD patients : A diffusion-tensor study. 2015:661-668. doi:10.1007/s00330-014-3466-5

205. Angermann S, Baumann M, Steubl D, et al. Cognitive impairment in hemodialysis patients: Implementation of cut-off values for the Montreal Cognitive Assessment (MoCA)-test for feasible screening. *PLoS ONE [Electronic Resour*. 2017;12(10):e0184589. doi:https://dx.doi.org/10.1371/journal.pone.0184589

206. Dasgupta I, Patel M, Mohammed N, et al. Cognitive Function Declines Significantly during Haemodialysis in a Majority of Patients: A Call for Further Research. *Blood Purif*. 2018;45(4):347-355. doi:http://dx.doi.org/10.1159/000485961

207. Li P, Ding D, Ma XY, Zhang HW, Liu JX, Zhang M. Altered intrinsic brain activity and memory performance improvement in patients with end-stage renal

disease during a single dialysis session. *Brain Imaging Behav*. 2018:1-10. doi:http://dx.doi.org/10.1007/s11682-018-9828-x

208. Smith BC, Winslow EH. Cognitive changes in chronic renal patients during hemodialysis. *ANNA J*. 1990;17:283-287. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=2396853.

209. Musolino R, de Domenico P, Troilo G, Blandino A, et Al. Cerebral atrophy and cognitive impairment in long-term haemodialyzed patients. *New Trends Exp Clin Psychiatry*. 1992;8:119-125. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=psyc3&NEWS=N&AN=1993-34745-001.

210. Temple RM, Langan SJ, Deary IJ, Winney RJ. Recombinant erythropoietin improves cognitive function in chronic haemodialysis patients. *Nephrol Dial Transplant*. 1992;7:240-245. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=1314997.

211. Temple RM, Deary IJ, Winney RJ. Recombinant erythropoietin improves cognitive function in patients maintained on chronic ambulatory peritoneal dialysis. *Nephrol Dial Transplant*. 1995;10:1733-1738. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=8559497.

212. Griva K, Newman SP, Harrison MJ, et al. Acute neuropsychological changes in

hemodialysis and peritoneal dialysis patients. *Health Psychol*. 2003;22:570-578. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=14640853.

213. Radić J, Ljutic D, Radić M, Kovacic V, Ćurković KD, Sain M. Cognitive-psychomotor functions and nutritional status in maintenance hemodialysis patients: Are they related? *Ther Apher Dial*. 2011;15(6):532-539. doi:10.1111/j.1744-9987.2011.00995.x

214. SchneiDer SM, Malecki AK, Müller K, et al. Effect of a single dialysis session on cognitive function in CKD5D patients: A prospective clinical study. *Nephrol Dial Transplant*. 2015;30(9):1551-1559. doi:10.1093/ndt/gfv213

215. Wolcott DL, Marsh JT, La Rue A, Carr C, Nissenson AR. Recombinant human erythropoietin treatment may improve quality of life and cognitive function in chronic hemodialysis patients. *Am J Kidney Dis*. 1989;14:478-485. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed2&NEWS=N&AN=1990058239.

216. Brickman AL, Yount SE, Blaney NT, Rothberg S, De-Nour AK. Pathogenesis of cognitive complaints in patients on hemodialysis. *Gen Hosp Psychiatry*. 1996;18:36-43. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed4&NEWS=N&AN=1996077972.

217. Neumann D, Mau W, Wienke A, Girndt M. Peritoneal dialysis is associated with better cognitive function than hemodialysis over a one-year course. *Kidney Int*.

2018;93(2):375-389. doi:http://dx.doi.org/10.1016/j.kint.2017.07.022

218. Dong J, Pi HC, Xiong ZY, et al. Depression and Cognitive Impairment in Peritoneal Dialysis: A Multicenter Cross-sectional Study. *Am J Kidney Dis*. 2016;67(1):111-118. doi:10.1053/j.ajkd.2015.06.025

219. Li Y, Tian X, Xiong ZY, et al. Performance of the modified mini-mental state examination (3MS) in assessing specific cognitive function in patients undergoing peritoneal dialysis. *PLoS One*. 2016;11 (12) (n(e0166470). doi:http://dx.doi.org/10.1371/journal.pone.0166470

220. Isshiki R, Kobayashi S, Iwagami M, et al. Cerebral blood flow in patients with peritoneal dialysis by an easy Z-score imaging system for brain perfusion single-photon emission tomography. *Ther Apher Dial Off Peer-Reviewed J Int Soc Apher Japanese Soc Apher Japanese Soc Dial Ther*. 2014;18(3):291-296. doi:http://dx.doi.org/10.1111/1744-9987.12107

221. Li JSC. Prevalence of cognitive impairment among elderly Chinese continuous ambulatory peritoneal dialysis patients. *Hong Kong J Nephrol*. 2004;6(1):22-30. doi:10.1016/S1561-5413(09)60122-8

222. Shea YF, Lam MF, Lee MS, et al. Prevalence of CMMSE defined cognitive impairment among peritoneal dialysis patients and its impact on peritonitis. *Clin Exp Nephrol*. 2016;20(1):126-133. doi:https://dx.doi.org/10.1007/s10157-015-1127-x

223. Harciarek M, Biedunkiewicz B, Lichodziejewska-Niemierko M, Debska-Slizien A, Rutkowski B. Cognitive performance before and after kidney transplantation: a

prospective controlled study of adequately dialyzed patients with end-stage renal disease. *J Int Neuropsychol Soc*. 2009;15:684-694. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=19570307.

224. Liang X, Wen J, Ni L, et al. Altered pattern of spontaneous brain activity in the patients with end-stage renal disease: a resting-state functional MRI study with regional homogeneity analysis. *PLoS ONE [Electronic Resour*. 2013;8(8):e71507. doi:http://dx.doi.org/10.1371/journal.pone.0071507

225. Ni L, Wen J, Zhang LJ, et al. Aberrant default-mode functional connectivity in patients with end-stage renal disease: a resting-state functional MR imaging study. *Radiology*. 2014;271(2):543-552. doi:http://dx.doi.org/10.1148/radiol.13130816

226. Zhang LJ, Wen J, Ni L, et al. Predominant gray matter volume loss in patients with end-stage renal disease: a voxel-based morphometry study. *Metab Brain Dis*. 2013;28(4):647-654. doi:http://dx.doi.org/10.1007/s11011-013-9438-7

227. Afsar B. The Relationship of Serum Cortisol Levels with Depression, Cognitive Function and Sleep Disorders in Chronic Kidney Disease and Hemodialysis Patients. *Psychiatr Q*. 2014;85(4):479-486. doi:10.1007/s11126-014-9307-5

228. Frasnelli JA, Temmel AF, Quint C, Oberbauer R, Hummel T. Olfactory function in chronic renal failure. *Am J Rhinol*. 2002;16:275-279. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed5&NEWS=N&AN=2002410702.

229. Harciarek M, Williamson JB, Biedunkiewicz B, Lichodziejewska-Niemierko M,

Debska-Slizien A, Rutkowski B. Risk factors for selective cognitive decline in dialyzed patients with end-stage renal disease: evidence from verbal fluency analysis. *J Int Neuropsychol Soc*. 2012;18(1):162-167. doi:http://dx.doi.org/10.1017/S1355617711001445

230. Lee JG, Park MK, Kim YW, et al. The correlations among depressive symptoms, cognitive performance and serum BDNF levels in the patients with chronic kidney disease. *Psychiatry Investig*. 2018;15(2):186-192. doi:http://dx.doi.org/10.30773/pi.2017.03.09

231. Tyrrell J, Paturel L, Cadec B, Capezzali E, Poussin G. Older patients undergoing dialysis treatment: cognitive functioning, depressive mood and health-related quality of life. *Aging Ment Health*. 2005;9:374-379. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=16019295.

232. Sharma A, Yabes J, Al Mawed S, et al. Impact of Cognitive Function Change on Mortality in Renal Transplant and End-Stage Renal Disease Patients. *Am J Nephrol*. 2016;44(6):462-472. https://proxy.queensu.ca/login?url=http://ovidsp.ovid.com?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=27798939 http://dw2zn6fm9z.search.serialssolutions.com/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:medl&rft.genre=ar.

233. Gupta A, Lepping RJ, Yu AS, et al. Cognitive Function and White Matter Changes

Associated with Renal Transplantation. *Am J Nephrol*. 2016;43(1):50-57. doi:https://dx.doi.org/10.1159/000444334

234. Murray AM, Tupper DE, Knopman DS, et al. Cognitive impairment in hemodialysis patients is common. *Neurology*. 2006;67(2):216-223. doi:10.1212/01.wnl.0000225182.15532.40

235. Etgen T, Chonchol M, Förstl H, Sander D. Chronic Kidney Disease and Cognitive Impairment: A Systematic Review and Meta-Analysis. *Am J Nephrol*. 2012;35(5):474-482. doi:10.1159/000338135

236. Sachdev PS, Blacker D, Blazer DG, Ganguli M, Jeste D V, Paulsen JS. Classifying neurocognitive disorders : the DSM - 5 approach. 2014;(April 2016). doi:10.1038/nrneurol.2014.181

237. Viggiano D, Wagner CA, Martino G, et al. Mechanisms of cognitive dysfunction in CKD. *Nat Rev Nephrol*. 2020;16(8):452-469. doi:10.1038/s41581-020-0266-9

238. Viggiano D, Wagner CA, Blankestijn PJ, et al. Mild cognitive impairment and kidney disease: Clinical aspects. *Nephrol Dial Transplant*. 2020;35(1):10-17. doi:10.1093/ndt/gfz051

239. Baek MJ, Kim K, Park YH, Kim S. The Validity and Reliability of the Mini-Mental State Examination-2 for Detecting Mild Cognitive Impairment and Alzheimer's Disease in a Korean Population. Chen K, ed. *PLoS One*. 2016;11(9):e0163792. doi:10.1371/journal.pone.0163792

240. Wouters H, van Gool WA, Schmand B, Zwinderman AH, Lindeboom R. Three sides of the same coin: measuring global cognitive impairment with the MMSE,

ADAS-cog and CAMCOG. *Int J Geriatr Psychiatry*. 2009;25(8):770-779. doi:10.1002/gps.2402

241. Arevalo-Rodriguez I, Smailagic N, Roquéi Figuls M, et al. Mini-Mental State Examination (MMSE) for the detection of Alzheimer's disease and other dementias in people with mild cognitive impairment (MCI). *Cochrane Database Syst Rev*. 2015;2015(3). doi:10.1002/14651858.CD010783.pub2

242. Cabel DW, Cisek P, Scott SH. Neural Activity in Primary Motor Cortex Related to Mechanical Loads Applied to the Shoulder and Elbow During a Postural Task. *J Neurophysiol*. 2001;86(4):2102-2108. doi:10.1152/jn.2001.86.4.2102

243. Desrochers PC, Brunfeldt AT, Kagerer FA. Neurophysiological Correlates of Adaptation and Interference during Asymmetrical Bimanual Movements. *Neuroscience*. 2020;432:30-43. doi:10.1016/j.neuroscience.2020.01.044

244. Tyryshkin K, Coderre AM, Glasgow JI, et al. A robotic object hitting task to quantify sensorimotor impairments in participants with stroke. 2014:1-12.

245. Wood MD, Maslove DM, Muscedere J, et al. Robotic technology provides objective and quanti fi able metrics of neurocognitive functioning in survivors of critical illness : A feasibility study. 2018;48:228-236. doi:10.1016/j.jcrc.2018.09.011

246. Debert CT, Herter TM, Scott SH, Dukelow S. Robotic Assessment of Sensorimotor Deficits After Traumatic Brain Injury. 2012:58-67. doi:10.1097/NPT.0b013e318254bd4f

247. Simmatis L, Atallah G, Scott SH, et al. Degeneration The feasibility of using

robotic technology to quantify sensory , motor , and cognitive impairments associated with ALS. *Amyotroph Lateral Scler Front Degener*. 2019;20(1-2):43-52. doi:10.1080/21678421.2018.1550515

248. Semrau JS, Scott SH, Hamilton AG, et al. Quantified pre - operative neurological dysfunction predicts outcome after coronary artery bypass surgery. *Aging Clin Exp Res*. 2019;(0123456789). doi:10.1007/s40520-019-01184-9

249. Randolph C, Tierney MC, Mohr E, et al. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Preliminary Clinical Validity The Repeatable Battery for the Assessment of Neuro- psychological Status (RBANS): Preliminary Clinical Validity *. 2010;3395. doi:10.1076/jcen.20.3.310.823

250. Simmatis LER, Early S, Moore KD, Appaqaq S, Scott SH. Statistical measures of motor, sensory and cognitive performance across repeated robot-based testing. *J Neuroeng Rehabil*. 2020;17(1):86. doi:10.1186/s12984-020-00713-2

251. Glickman ME, Rao SR, Schultz MR. False discovery rate control is a recommended alternative to Bonferroni-type adjustments in health studies. *J Clin Epidemiol*. 2014;67(8):850-857. doi:10.1016/j.jclinepi.2014.03.012

252. van Hooren SAH, Valentijn AM, Bosma H, Ponds RWHM, van Boxtel MPJ, Jolles J. Cognitive Functioning in Healthy Older Adults Aged 64–81: A Cohort Study into the Effects of Age, Sex, and Education. *Aging, Neuropsychol Cogn*. 2007;14(1):40-54. doi:10.1080/138255890969483

253. van den Berg E, Kloppenborg RP, Kessels RPC, Kappelle LJ, Biessels GJ. Type 2

diabetes mellitus, hypertension, dyslipidemia and obesity: A systematic comparison of their impact on cognition. *Biochim Biophys Acta - Mol Basis Dis*. 2009;1792(5):470-481. doi:10.1016/j.bbadis.2008.09.004

254. Vanderploeg RD, Axelrod BN, Sherer M, Scott J, Adams RL. The importance of demographic adjustments on neuropsychological test performance: A response to Reitan and Wolfson (1995). *Clin Neuropsychol*. 1997;11(2):210-217. doi:10.1080/13854049708407054

255. R Core Team (2016) R: a language and environment... - Google Scholar. https://scholar-google-ca.proxy.queensu.ca/scholar?hl=en&as_sdt=0%2C5&q=R+Core+Team+%282016%29+R%3A+a+language+and+environment+for+statistical+computing.+Vienna%2C+Austria%3A+R+foundation+for+statistical+computing.&btnG=. Accessed July 24, 2020.

256. Hellberg M, Hoglund P, Svensson P, Abdulahi H, Clyne N. Decline in measured glomerular filtration rate is associated with a decrease in endurance, strength, balance and fine motor skills. *Nephrology*. 2017;22(7):513-519. doi:http://dx.doi.org/10.1111/nep.12810

257. Ng CL, Ho DD, Chow SP. The Moberg pickup test: Results of testing with a standard protocol. *J Hand Ther*. 1999;12(4):309-312. doi:10.1016/S0894-1130(99)80069-6

258. Erken E, Altunoren O, Senel ME, et al. Impaired cognition in hemodialysis patients: The Montreal Cognitive Assessment (MoCA) and important clues for

testing. *Clin Nephrol*. 2019;91(5):275-283. doi:10.5414/CN109506

259. Kepecs DM, Glick L, Silver SA, Yuen DA. Does Chronic Kidney Disease – Induced Cognitive Impairment Affect Driving Safety ? 2018. doi:10.1177/2054358118777133

260. Vancouver JB, Thompson CM, Williams AA. The Changing Signs in the Relationships Among Self-Efficacy , Personal Goals , and Performance. 2001;86(4). doi:10.1037//0021-9010.86.4.605

261. Kluger AN, DeNisi A. The effects of feedback interventions on performance: A historical review, a meta-analysis, and a preliminary feedback intervention theory. *Psychol Bull*. 1996;119(2):254-284. doi:10.1037/0033-2909.119.2.254

262. Tanaka S, Okusa MD. Crosstalk between the nervous system and the kidney. *Kidney Int*. 2020;97(3):466-476. doi:10.1016/j.kint.2019.10.032

263. Śnchez-Roḿn S, Ostrosky-Soĺs F, Morales-Buenrostro LE, Nogús-Vizcáno MG, Albeŕ J, McClintock SM. Neurocognitive profile of an adult sample with chronic kidney disease. *J Int Neuropsychol Soc*. 2011;17(1):80-90. doi:10.1017/S1355617710001219

264. Vanderlinden JA, Holden RM, Scott SH, Boyd JG. Robotic technology quantifies novel perceptual-motor impairments in patients with chronic kidney disease. *J Nephrol*. 2021;(0123456789). doi:10.1007/s40620-020-00912-z

265. Silver SA, Harel Z, Harvey A, et al. Improving Care after Acute Kidney Injury: A Prospective Time Series Study. *Nephron*. 2015;131(1):43-50. doi:10.1159/000438871

266. Siew ED, Alp Ikizler T, Matheny ME, et al. Estimating baseline kidney function in hospitalized patients with impaired kidney function. *Clin J Am Soc Nephrol*. 2012;7(5):712-719. doi:10.2215/CJN.10821011

267. Semrau JS, Scott SH, Hamilton AG, et al. Road to recovery: A study protocol quantifying neurological outcome in cardiac surgery patients and the role of cerebral oximetry. *BMJ Open*. 2019;9(12):1-6. doi:10.1136/bmjopen-2019-032935

268. Browndyke JN, Berger M, Harshbarger TB, et al. Resting-State Functional Connectivity and Cognition After Major Cardiac Surgery in Older Adults without Preoperative Cognitive Impairment: Preliminary Findings. *J Am Geriatr Soc*. 2017;65(1):e6-e12. doi:10.1111/jgs.14534

269. Simmatis LER, Early S, Moore KD, Appaqaq S, Scott SH. Statistical measures of motor, sensory and cognitive performance across repeated robot-based testing. *J Neuroeng Rehabil*. 2020;17(1):86. doi:10.1186/s12984-020-00713-2

270. Kashani K, Rosner MH, Haase M, et al. Quality improvement goals for acute kidney injury. *Clin J Am Soc Nephrol*. 2019;14(6):941-953. doi:10.2215/CJN.01250119

271. Liu M, Liang Y, Chigurupati S, et al. Acute kidney injury leads to inflammation and functional changes in the brain. *J Am Soc Nephrol*. 2008;19(7):1360-1370. doi:10.1681/ASN.2007080901

272. https://www12.statcan.gc.ca/nhs-enm/2011/dp-pd/prof/details/page.cfm?Lang=E&Geo1=CMA&Code1=521&Data=Count&SearchText=K7L5E1&SearchType=Begins&SearchPR=01&A1=All&B1=All&Custo

m=&TABID=2.

273. Murray AM, Tupper DE, Knopman DS, et al. Cognitive impairment in hemodialysis patients is common. *Neurology*. 2006;67:216-223. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=16864811.

274. Kurella Tamura M, Larive B, Unruh ML, et al. Prevalence and correlates of cognitive impairment in hemodialysis patients: The frequent hemodialysis network trials. *Clin J Am Soc Nephrol*. 2010;5(8):1429-1438. doi:10.2215/CJN.01090210

275. Sehgal AR, Grey SF, DeOreo PB, Whitehouse PJ. Prevalence, recognition, and implications of mental impairment among hemodialysis patients. *Am J Kidney Dis*. 1997;30(1):41-49. doi:10.1016/S0272-6386(97)90563-1

276. Post JB, Morin KG, Sano M, Jegede AB, Langhoff E, Spungen AM. Increased presence of cognitive impairment in hemodialysis patients in the absence of neurological events. *Am J Nephrol*. 2012;35(2):120-126. doi:http://dx.doi.org/10.1159/000334871

277. Murray AM, Seliger S, Lakshminarayan K, Herzog CA, Solid CA. Incidence of Stroke Before and After Dialysis Initiation in Older Patients. *J Am Soc Nephrol*. 2013;24(7):1166-1173. doi:10.1681/ASN.2012080841

278. Mcintyre CW. Recurrent Circulatory Stress : The Dark Side of Dialysis. *Semin Dial*. 2010;23(5):449-451. doi:10.1111/j.1525-139X.2010.00782.x

279. Qian Q. Acid-base alterations in ESRD and effects of hemodialysis. 2018:226-235. doi:10.1111/sdi.12659

280. Nakatani T, Naganuma T, Uchida J, Masuda C. Silent Cerebral Infarction in Hemodialysis Patients. *Am J Nephrol*. 2003;23(2):86-90. doi:10.1159/000068034

281. De Pasquale C, Conti D, Pistorio ML, Fatuzzo P, Veroux M, Nuovo SD. Comparison of the CBA-H and SF-36 for the screening of the psychological and behavioural variables in chronic dialysis patients. *PLoS One*. 2017;12 (6) (no(e0180077). doi:http://dx.doi.org/10.1371/journal.pone.0180077

282. Soul, J. S., & du Plessis AJ. Near-Infrared Spectroscopy. *Semin Pediatr Neurol*. 1999;6(2):101-110.

283. Ito K, Ookawara S, Ueda Y, Goto S, Miyazawa H. Factors Affecting Cerebral Oxygenation in Hemodialysis Patients : Cerebral Oxygenation Associates with pH , Hemodialysis Duration , Serum Albumin Concentration , and Diabetes Mellitus. 2015;(Dm):1-11. doi:10.1371/journal.pone.0117474

284. Polinder-Bos HA, García DV, Kuipers J, et al. Hemodialysis induces an acute decline in cerebral blood flow in elderly patients. *J Am Soc Nephrol*. 2018;29(4):1317-1325. doi:10.1681/ASN.2017101088

285. ForeSight Elite tissue oximetry sensor | Edwards Lifesciences. https://www.edwards.com/devices/hemodynamic-monitoring/ForeSight#tabs-0. Accessed July 24, 2020.

286. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Erlbaum; 1988.

287. Selewski DT, Herreshoff EG, Gipson DS. Optimizing enrollment of patients into nephrology research studies. *Clin J Am Soc Nephrol*. 2016;11(3):512-517.

doi:10.2215/CJN.00500115

288. Davis MM, Clark SJ, Butchart AT, Singer DC, Shanley TP, Gipson DS. Public Participation in, and Awareness about, Medical Research Opportunities in the Era of Clinical and Translational Research. *Clin Transl Sci*. 2013;6(2):88-93. doi:10.1111/cts.12019

289. Hori Y, Naitoh I, Nakazawa T, et al. Feasibility of endoscopic retrograde cholangiopancreatography-related procedures in hemodialysis patients. *J Gastroenterol Hepatol*. 2014;29(3):648-652. doi:10.1111/jgh.12336

290. Thomas Z, Novak M, Platas SGT, et al. Brief mindfulness meditation for depression and anxiety symptoms in patients undergoing hemodialysis a pilot feasibility study. *Clin J Am Soc Nephrol*. 2017;12(12):2008-2015. doi:http://dx.doi.org/10.2215/CJN.03900417

291. Birdee GS, Rothman RL, Sohl SJ, et al. Feasibility and Safety of Intradialysis Yoga and Education in Maintenance Hemodialysis Patients. *J Ren Nutr*. 2015;25(5):445-453. doi:10.1053/j.jrn.2015.02.004

292. Friedman AN, Saha C, Watkins BA. Feasibility Study of Erythrocyte Long-Chain Omega-3 Polyunsaturated Fatty Acid Content and Mortality Risk in Hemodialysis Patients. *J Ren Nutr*. 2008;18(6):509-512. doi:10.1053/j.jrn.2008.08.007

293. Chen JLT, Godfrey S, Ng TT, et al. Effect of intra-dialytic, low-intensity strength training on functional capacity in adult haemodialysis patients: A randomized pilot trial. *Nephrol Dial Transplant*. 2010;25(6):1936-1943. doi:10.1093/ndt/gfp739

294. Weitzel, W. F., Rubin, J. M., Swartz, R. D., Woltmann, D. J., & Messana JM.

Variable Flow Doppler for Hemodialysis Access Evaluation: Theory and Clinical Feasibility. *Asaio J*. 2000;46(1):65-69. https://journals-lww-com.proxy.queensu.ca/asaiojournal/Fulltext/2000/01000/Variable_Flow_Doppler_for_Hemodialysis_Access.18.aspx. Accessed August 11, 2020.

295. Kalantar-Zadeh K, Braglia A, Chow J, et al. An anti-inflammatory and antioxidant nutritional supplement for hypoalbuminemic hemodialysis patients: A pilot/feasibility study. *J Ren Nutr*. 2005;15(3):318-331. doi:10.1016/j.jrn.2005.04.004

296. Chin AI, Appasamy S, Carey RJ, Madan N. Feasibility of Incremental 2-Times Weekly Hemodialysis in Incident Patients With Residual Kidney Function. *Kidney Int Reports*. 2017;2(5):933-942. doi:10.1016/j.ekir.2017.06.005

297. Nonoyama ML, Brooks D, Ponikvar A, et al. Exercise program to enhance physical performance and quality of life of older hemodialysis patients: A feasibility study. *Int Urol Nephrol*. 2010;42(4):1125-1130. doi:10.1007/s11255-010-9718-7

298. Friedli K, Guirguis A, Almond M, et al. Sertraline versus placebo in patients with major depressive disorder undergoing hemodialysis: A randomized, controlled feasibility trial. *Clin J Am Soc Nephrol*. 2017;12(2):280-286. doi:10.2215/CJN.02120216

299. Hernandez R, Burrows B, Wilund K, Cohn M, Xu S, Moskowitz JT. Feasibility of an Internet-based positive psychological intervention for hemodialysis patients with symptoms of depression. *Soc Work Health Care*. 2018;57(10):864-879.

doi:10.1080/00981389.2018.1523268

300. Schell JO, Patel UD, Steinhauser KE, Ammarell N, Tulsky JA. Discussions of the kidney disease trajectory by elderly patients and nephrologists: A qualitative study. *Am J Kidney Dis*. 2012;59(4):495-503. doi:10.1053/j.ajkd.2011.11.023

301. Wood M, Song A, Maslove D, et al. Brain Tissue Oxygenation in Patients with Septic Shock: A Feasibility Study. *Can J Neurol Sci*. 2015;43(1):65-73. doi:10.1017/cjn.2015.280

302. Lambert K, Mullan J, Mansfield K, Lonergan M. Comparison of the extent and pattern of cognitive impairment among predialysis, dialysis and transplant patients: A cross-sectional study from Australia. *Nephrology*. 2017;22(11):899-906. doi:10.1111/nep.12892

303. Scott SH. A Functional Taxonomy of Bottom-Up Sensory Feedback Processing for Motor Actions. *Trends Neurosci*. 2016;39(8):512-526. doi:10.1016/j.tins.2016.06.001

304. Khatri M, Wright CB, Nickolas TL, et al. Chronic kidney disease is associated with white matter hyperintensity volume: The Northern Manhattan Study (NOMAS). *Stroke*. 2007;38(12):3121-3126. doi:10.1161/STROKEAHA.107.493593

305. Takahashi W, Tsukamoto Y, Takizawa S, Kawada S, Takagi S. Relationship between chronic kidney disease and white matter hyperintensities on magnetic resonance imaging. *J Stroke Cerebrovasc Dis*. 2012;21(1):18-23. doi:10.1016/j.jstrokecerebrovasdis.2010.03.015

306. Berger I, Wu S, Masson P, et al. Cognition in chronic kidney disease: a systematic review and meta-analysis. *BMC Med*. 2016;14(1):206. https://proxy.queensu.ca/login?url=http://ovidsp.ovid.com?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med8&AN=27964726 http://dw2zn6fm9z.search.serialssolutions.com/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:med8&rft.genre=ar.

307. Burns CM, Knopman DS, Tupper DE, et al. Prevalence and Risk of Severe Cognitive Impairment in Advanced Chronic Kidney Disease. *Journals Gerontol Ser A*. 2018;73(3):393-399. doi:10.1093/gerona/glx241

308. Sacre JW, Magliano DJ, Zimmet PZ, et al. Associations of Chronic Kidney Disease Markers with Cognitive Function: A 12-Year Follow-Up Study. *J Alzheimer's Dis*. 2019;70(s1):S19-S30. doi:10.3233/JAD-180498

309. Mazumder MK, Phukan BC, Bhattacharjee A, Borah A. Disturbed purine nucleotide metabolism in chronic kidney disease is a risk factor for cognitive impairment. *Med Hypotheses*. 2018;111:36-39. doi:http://dx.doi.org/10.1016/j.mehy.2017.12.016

310. Miyazawa H, Ookawara S, Ito K, et al. Association of cerebral oxygenation with estimated glomerular filtration rate and cognitive function in chronic kidney disease patients without dialysis therapy. Isaka Y, ed. *PLoS One*. 2018;13(6):e0199366. doi:10.1371/journal.pone.0199366

311. Jung S, Lee YK, Choi SR, Hwang SH, Noh JW. Relationship between cognitive

impairment and depression in dialysis patients. *Yonsei Med J*. 2013;54(6):1447-1453. doi:10.3349/ymj.2013.54.6.1447

312. Guenzani D, Buoli M, Caldiroli L, et al. Malnutrition and inflammation are associated with severity of depressive and cognitive symptoms of old patients affected by chronic kidney disease. *J Psychosom Res*. 2019;124:109783. doi:10.1016/j.jpsychores.2019.109783

313. Otobe Y, Hiraki K, Hotta C, et al. Mild cognitive impairment in older adults with pre-dialysis patients with chronic kidney disease: Prevalence and association with physical function. *Nephrology*. 2019;24(1):50-55. doi:10.1111/nep.13173

314. Perlman RL, Finkelstein FO, Liu L, et al. Quality of life in Chronic Kidney Disease (CKD): A cross-sectional analysis in the Renal Research Institute-CKD study. *Am J Kidney Dis*. 2005;45(4):658-666. doi:10.1053/j.ajkd.2004.12.021

Appendix A

Research Ethics Approval

Both the Queen's University and the Affiliated Hospital Health Sciences Research ethics boards approved this study before any consent was obtained from the patients. The official letter of approval is provided below, along with the most recent renewal.

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD-DELEGATED REVIEW
April 30, 2015

Dr. J. G. Boyd
Department of Medicine
Kingston General Hospital

Dear Dr. Boyd
Study Title: DMED-1784-15 Cerebral hypo perfusion during hemodialysis contributes to long-term neurological dysfunction in patients with end-stage renal disease
File # 6015214
Co-Investigators: Dr. R. Holden
Date of Expiry: April 29, 2016

I am writing to acknowledge receipt of your recent ethics submission. We have examined the protocol, case report form and revised information/consent form (Version 1.1 – April 27, 2015) for your project (as stated above) and consider it to be ethically acceptable. This approval is valid for one year from the date of the Chair's signature below. This approval will be reported to the Research Ethics Board. Please attend carefully to the following listing of ethics requirements you must fulfill over the course of your study:

Reporting of Amendments: If there are any changes to your study (e.g. consent, protocol, study procedures, etc.), you must submit an amendment to the Research Ethics Board for approval. Please use event form: HSREB Multi-Use Amendment/Full Board Renewal Form associated with your post review file # **6015214** in your Researcher Portal (https://eservices.queensu.ca/romeo_researcher/)

Reporting of Serious Adverse Events: Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information. Serious Adverse Event forms are located with your post-review file **6015214** in your Researcher Portal (https://eservices.queensu.ca/romeo_researcher/)

Reporting of Complaints: Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of becoming aware of the complaint. Note: All documents supplied to participants must have the contact information for the Research Ethics Board.

Annual Renewal: Prior to the expiration of your approval (which is one year from the date of the Chair's signature below), you will be reminded to submit your renewal form along with any new changes or amendments you wish to make to your study. If there have been no major changes to your protocol, your approval may be renewed for another year.

Yours sincerely,

Albert J. Clark.

Chair, Health Sciences Research Ethics Board
April 30, 2015

Investigators please note that if your trial is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD

The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards and operates in compliance with the Tri-Council Policy Statement; Part C Division 5 of the Food and Drug Regulations, OHRP, and U.S DHHS Code of Federal Regulations Title 45, Part 46 and carries out its functions in a manner consistent with Good Clinical Practices.

Federalwide Assurance Number: #FWA00004184, #IRB00001173

Current 2015 membership of the Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board:

Dr. A.F. Clark, Emeritus Professor, Department of Biomedical and Molecular Sciences, Queen's University (Chair)

Dr. H. Abdollah, Professor, Department of Medicine, Queen's University

Dr. R. Brison, Professor, Department of Emergency Medicine, Queen's University

Dr. D. Groll, Assistant Professor, Department of Psychiatry, Queen's University

Ms. J. Hudacin, Community Member

Mr. D. McNaughton, Community Member

Ms. S. Rohland, Privacy Officer, ICES-Queen's Health Services Research Facility, Research Associate, Division of Cancer Care and Epidemiology, Queen's Cancer Research Institute

Dr. M. Sawhney, Assistant Professor, School of Nursing, Queen's University

Ms. J. Sheldrick, Community Member

Dr. A. Singh, Professor, Department of Psychiatry, Queen's University

Dr. J. Thorpe, Clinical Research Associate, Department of Anesthesiology and Perioperative Medicine, Queen's University

Ms. K. Weisbaum, LL.B. and Adjunct Instructor, Department of Family Medicine (Bioethics)

Dr. J. Whiteley, Community Member

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD (HSREB)

HSREB Renewal of Ethics Clearance

April 17, 2020

Dr. J. Gordon Boyd
Department of Medicine
Queen's University

TRAQ #: 6015214
Department Code: DMED-1784-15
Study Title: "DMED-1784-15 Cerebral hypo perfusion during hemodialysis contributes to long-term neurological dysfunction in patients with end-stage renal disease"
Review Type: Delegated
Date Ethics Clearance Effective: April 17, 2020
Ethics Clearance Expiry Date: April 17, 2021

Dear Dr. Boyd:

The Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (HSREB) has reviewed the application. This study, including all currently approved documentation has been granted ethical clearance until the expiry date noted above.

Prior to the expiration of your ethics clearance, you will be reminded to submit your renewal report through TRAQ. Any lapses in ethical clearance will be documented below.

Lapse in Ethics Clearance: 2017/05/01 – 2017/05/10

NOTE: In-person contact should be eliminated due to COVID-19. If you wish to continue data collection for your research that currently involves in-person contact, submit an amendment event form to outline methods for remote data collection, including all privacy and security considerations. There are human participant research policies, in relation to hospital and non-hospital based research, that are being continually updated. Many restrictions are now in place with respect to in-person research. For the most current information on the COVID-19 impact on research, please visit https://www.queensu.ca/vpr/covid-19. For information directly related to GREB/HSREB please visit the Research Ethics FAQs.

Regards,

Albert F. Clark, PhD
Chair, Queen's University Health Sciences and Affiliated Teaching Hospitals Ethics Board

The HSREB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council

Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the international Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Product Regulations; Part 3 of the Medical Devices Regulations, and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is qualified through the CTO REB Qualification Program and is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP). Federalwide Assurance Number: FWA#: 00004184, IRB#: 00001173

HSREB members involved in the research project do not participate in the review, discussion or decision.