

The Assessment of Cognitive Function in Older Adult Patients with Chronic Kidney Disease:
An Integrative Review

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Compliance with Ethical Standards

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- This article does not contain any studies with human participants or animals performed by any of the authors.

Introduction

Chronic kidney disease (CKD) is a common chronic disease, affecting 15.23% of the U.S. population [1]. CKD is especially common in older adults, with an estimated prevalence of 46% in adults over the age of 70 years [2]. Unfortunately, older adults are at risk for other health problems and consequences related to having CKD. One comorbidity commonly experienced by older adult patients with CKD is cognitive impairment. The exact etiology of cognitive impairment in patients with CKD is not fully understood but is likely a combination of factors related to the CKD process itself and micro-vascular changes [3-5]. CKD is thought to confer a specific and unique risk factor for the development of cognitive impairment. Through the complex interaction of clinical factors and the internal vascular milieu, CKD is considered a stimulus for accelerated aging that causes changes in the cerebrovascular-renal axis that leads to cognitive impairment [5]. The readers are referred to a recent review by Bronas et al. [5].

Cognitive impairment has a reported prevalence that ranges anywhere from 13% to 70% in patients with CKD [6,7]. Cognitive impairment in patients with CKD becomes most apparent when a patient's estimated glomerular filtration rate (GFR) is less than 60ml/min/1.73m² (CKD Stage 3) [8]. As the GFR decreases, cognitive function also appears to progressively worsen [9,10]. Cognitive decline escalates even more dramatically when a patient begins dialysis, which makes it critically important that cognitive impairment is identified and addressed prior to the initiation of dialysis [11]. Cognitive impairment occurs in patients with CKD of all ages but is especially common in older adults with CKD [12]. Although cognitive impairment occurs in patients with CKD of all ages, it occurs more commonly in older adults and older age has been associated with high risk of progression of cognitive impairment [12]. It is unclear in current state of the science whether the mechanisms leading to cognitive impairment in patients CKD

and the manifestations are similar in adults under 65 years old, but the physiologic processes that are considered to play a prominent role in the development of cognitive impairment are present in adult patients with CKD of all ages [5]. Older adults with CKD have a 37% higher risk of developing dementia than older adults without CKD [13]. Older adults with CKD and cognitive impairment are at increased risk for hospitalization, morbidity, and mortality [14-16]; therefore, it is essential that cognitive impairment is identified and addressed in this at risk population.

For any patient with suspected cognitive impairment, it is essential that an appropriate and thorough cognitive assessment is conducted. Cognitive function is often evaluated through the assessment of one or more of the six neurocognitive domains- complex attention, executive function, learning and memory, language, perceptual motor, and social cognition [17]. Cognitive function can be assessed with a clinical assessment or, more ideally, with standardized tests to quantify and objectively assess cognitive function [17,18]. There are numerous cognitive function tests available to assess the domains of cognitive function. Examples of common cognitive function tests and their associated domains are displayed in Table 1. In clinical practice when a patient is noted to have a deficit on a cognitive test, they may be diagnosed with mild cognitive impairment (MCI). MCI is a clinical syndrome characterized by a person being at a level of cognitive function between changes normally attributed to aging and those that are characteristic of dementia, and with the impairment not being significant in more than one cognitive domain [18,19,20]. The clinical concept of MCI has assisted providers in identifying patients in the prodementia stage. MCI has been found to progress to Alzheimer's disease and dementia with an incidence as high as 42% at 5 years [18,21]. A person is diagnosed with overt dementia, or a major neurocognitive disorder per the DSM V nomenclature, when they are noted

to have a substantial decline in at least one cognitive domain that interferes with independence in activities of daily life [18].

There is a critical need to identify cognitive impairment in older adults with CKD, so patients can be managed appropriately prior to the initiation of dialysis, when cognitive impairment is expected to dramatically worsen. Unfortunately, cognitive assessment utilizing a standardized cognitive test is not part of the routine care for patients with CKD [22]. This likely contributes to the large variability in prevalence rates of cognitive impairment reported for patients with CKD [23], which suggests that the true depth and breadth of cognitive impairment in this population is still not clear. The current practice of cognitive assessment in patients with CKD needs to be fully evaluated, so recommendations can be made on the ideal method to assess cognitive function in this population. Therefore, the purpose of this integrative review is to explore how cognitive function is currently assessed with cognitive function tests in older adult patients with CKD.

Methods

Given the range of research methods utilized to explore cognitive impairment in CKD, the integrative review methodology of Whittemore and Knafl was applied to capture all data related to the study purpose [24]. A research librarian was consulted regarding database utilization and preferred search language, after a preliminary review of the literature was conducted. Search terms were selected to obtain the broadest scope of literature about evaluation of cognitive function in patients with CKD (Table 2). Five electronic databases were searched to locate studies that evaluated cognitive function in patients with CKD: Medline via Ovid, CINAHL, Embase, Scopus, and PsychInfo. The searches included all available literature from the start of the databases through the final search date of December 2, 2017.

The inclusion criteria were articles that a) evaluated patients with a mean age greater than 65 years old, since cognitive impairment is more common in older adults with CKD [12,25,26] and the World Health Organization and Healthy People 2020 define “older adult” as those over 65years [27,28] b) included patients with CKD Stage 3-5 or the average GFR of the sample being less than $60\text{ml}/\text{min}/1.73\text{m}^2$, which is where cognitive impairment becomes most apparent and occurs most frequently [8] c) conducted cognitive assessment via a standardized test d) and were available in English. Studies were excluded if they a) only evaluated patients with end stage renal disease (ESRD), since the cognitive impairment experienced by patients with ESRD is influenced by unique factors related to the dialysis procedure [29,30] b) only evaluated patients who had received a kidney transplant, since cognitive impairment in this population is influenced by unique factors, including immunosuppressant medications [31], c) or only included a patient’s self-rated cognitive function.

Results

Through the search and analysis strategies, 36 studies were identified that were published in a 12-year period, from 2005 to 2017 (Appendix A). The final search strategy is outlined in the flow diagram [32] displayed in Figure 1.

Purpose

The majority of the included studies had the primary purpose of exploring associations between CKD and cognitive function. The purpose of 26 studies was to explore the relationship between kidney function and cognitive function [12,25,33-56]. Four studies sought to explore the relationship between cognitive function and kidney function in patients with CKD, as well as another diagnosis (stroke, atrial fibrillation, depression, etc.) [57-60]. Two studies evaluated associations between neuroimaging findings and cognitive impairment in patients with CKD

[61,62]. The remaining studies each had a unique purpose in their evaluation of patients with CKD. One study examined the utilization of the Mini-Addenbrooke Cognitive Examination (M-ACE) [63], one examined the influence of uric acid on cognitive function,[64] one evaluated the influence of cognitive impairment on decision making [47] and one evaluated the impact of medication dosage on cognitive impairment [65].

Study Design

The two most commonly utilized designs in the included studies were prospective cohort designs and comparative cross-sectional designs. The design of 15 studies was a prospective cohort design, and these studies sought to evaluate changes in cognitive function over time in patients with CKD [12,25,34,36, 39,41,46,47,49,50,54,59-62,66]. The comparative cross-sectional studies compared patients with CKD with another patient group, and this method was utilized in 15 studies [33,35,37, 40,42-44,48,51-53,55,56,63,64]. Of these studies, 12 utilized patients with a GFR greater than $60\text{ml}/\text{min}/1.73\text{m}^2$ as a comparison group [33,35,40,43,44,48,51-53,55,63,64], one study utilized patients on hemodialysis (HD) as a comparison group [56], and one study utilized both patients with a GFR greater than $60\text{ml}/\text{min}/1.73\text{m}^2$ and patients on renal replacement therapy (HD, peritoneal dialysis, and transplant) as a comparison group [42]. Of the remaining studies, one study utilized a cross-sectional design without a comparison group [58], one study utilized a case report [65], one study utilized a retrospective comparative study [57], one study conducted a post hoc analysis of a randomized controlled trial [38], and one study utilized a population based observational survey [45].

Sample

The samples utilized by the included studies were varied. The mean age of the participants in the included studies was 74.5 years, with a range of patients from age 65 [64] to 83 [53] years. The sample size of the studies ranged from 2 [65] to 33654 [66] (Appendix 1). There were 16 studies that provided the mean estimated GFR for their samples of patients with CKD [12,34,35,37,38,42,43,46,53,57,59,60,62-64,67]. The mean GFR for the samples in these studies was 43.85ml/min/1.73m² (range eGFR 17-59.8ml/min/1.73m²). The remaining studies reported kidney function as stage of CKD (Stage 3, 4, 5) [47,49,58,65] or as a range of GFR (eGFR 15-30, eGFR 30-45, eGFR > or <60, etc.) [25,33,36,39,41,44,45,48,50-52,61,66].

Quality of Studies

Study quality was assessed with a process for studies of varied designs in an integrative review [68]. The mean quality rating of the studies was 9.75 out of 13 (SD=.55). All studies utilized quantitative methods and included a thorough description of the methods. The sampling methods in the studies were convenience, purposive, and cohort. The most prevalent sampling method was purposive sampling or utilization of a cohort, which was utilized in 28 studies. The full quality assessment is displayed in Table 3.

Most Common Test

In the included studies, 36 different types of cognitive screening tests were utilized at varying frequencies (Figure 2). The full details of which tests were utilized in each study are displayed in Appendix B. The most commonly utilized cognitive assessment test was the Mini Mental State Exam (MMSE) which was utilized in 16 of the 36 studies [12,33,44,47-49,51-53,56,59,60,62-65]. The MMSE was used as a singular test to evaluate cognitive function in eight studies [33,47-49,51,53,59,64]. The second most commonly utilized tests were the digit

symbol substitution test, which was utilized in eight of the 36 studies [25,34,35,42,45, 46,52,56], and evaluation of verbal fluency [34,38,40,43,55,56,60,62]. The third most commonly utilized tests were each utilized in studies seven times, which were the Trail Making Test B (TMT-B) [35,40,42, 43,50,55,56]. The number of tests utilized in each study to assess cognitive function were varied. The number of tests utilized in each study ranged from one [33,36,37,41,45,47-49,51,53,54,57-59,64,66-67] to 12 [35] tests. (Figure 3)

The tests utilized in the included studies evaluated various domains of cognitive function. The tests were identified with the domain most evaluated by the test (Appendix B) [69,70]. The most common area assessed in the included studies was global cognition, which was assessed by 13 of the utilized tests (Figure 4). The second most common domain of assessment was tests that evaluated memory, which were 9 of 36 tests utilized in the included studies (Figure 4).

Psychometrics

The authors of some of the included studies reported the psychometrics of the cognitive tests utilized in their study. Sixteen studies provided citations for the validity of the cognitive test utilized in their study, which supported that the tests had adequate validity in assessing cognitive function in the general population [36-39,43,44,46,48,56-61,64,66]. Only Hobson and colleagues assessed test validity of their utilized test, the M-ACE, with their sample of patients with diabetes and CKD through the assessment of criterion validity with a DSM diagnosis of dementia and convergent validity with the MMSE [63]. Two studies provided citations of previously measured reliability for the utilized cognitive tests [44,64]. Hobson and colleagues assessed the reliability of the M-ACE with assessment of internal consistency via Cronbach alpha (.81) [63]. Three studies cited previously reported sensitivity of the cognitive tests [43,50,53], and two studies cited previously reported specificity related to cognitive impairment

[50,53]. Hobson and colleagues assessed the sensitivity and specificity of their utilized test in identifying cognitive impairment in their sample [63].

Findings

Of the 36 studies included in the review, 30 studies explored the relationship between kidney disease and cognitive impairment. Of these studies, 29 found significant relationships between CKD and cognitive impairment [25,33-37,39-46,48-50,52-56,58-62,66,67]. Of these studies, 14 evaluated changes in cognitive function over time and found significant changes over time through the cognitive test utilized in their study [12,25,34,36,39,41,46,49,50,54,60-62,66]. One study did not find a significant relationship between CKD and cognitive impairment with logistic regression, but the authors reported a nonsignificant trend for increased odds of cognitive impairment in patients with GFR less than 48ml/min [51]. The remaining seven studies had findings that supported their study purpose. (Appendix A)

Discussion

Through this review, it has been identified that the cognitive assessment of older adult patients with CKD is vast and varies. There were 36 different tests administered to assess cognitive function in the reviewed articles, with authors utilizing anywhere from one [33,36,37,41,45,47-49,51,53,54,57-59,64,66-67] to 12 [35] tests in each study. This has been similarly found in studies that sought to synthesize associations between CKD and cognitive decline [10] and in studies that evaluated cognitive function in patients on hemodialysis [11].

Research and clinical findings suggest that the domains affected in the cognitive impairment of CKD are unique and may be related to deficits seen in vascular dementia, which are different than the domains of impairment seen in patients with Alzheimer's disease [5]. The cognitive impairment seen in patients with vascular dementia is non-progressive, slowed

cognitive performance that primarily affects executive function and may cause mild impairments in memory [20]. Similarly, patients with CKD are primarily noted to have deficits in executive function [9,40,50,71,72], but have also been found to have deficits in global cognition [9,40,72], memory [40,72], attention and concentration [71,72], and language and naming [40,72]. Patients with Alzheimer's disease primarily have deficits in episodic memory while other domains are conserved [20]. Cognitive decline is considered to be a part of the normal aging process in all older adults, particularly with deficits noted in novel situations that utilize memory, spatial, and executive function [20]. The cognitive impairment noted in patients with CKD is also different than the decline noted with normal aging. This is specifically related to vascular dementia and impaired executive function. These differences emphasize the critical need to assess patients with CKD with cognitive tests that evaluate the appropriate domains. From this review, it was found that composite tests of global cognition are frequently utilized but not every test of global cognition evaluates the domains most affected in patients with CKD, such as executive function [70]. Therefore, it is critically important that patients with CKD are evaluated for cognitive impairment with tests that assess the domains where they most commonly experience cognitive impairment, in addition to evaluating the domains affected by Alzheimer's disease. With an appropriate assessment, there is a greater potential that the full magnitude of cognitive impairment in patients with CKD is understood.

Most Frequently Utilized Tests

The most commonly utilized test identified in this review was the MMSE, which was used in 16 of the 36 studies. When including the utilization of the 3MS, which is a modified version of the MMSE with more items and a revised grade scoring system [73], versions of the MMSE were utilized in 21 studies. The frequent utilization of the MMSE has similarly been

found when cognitive function is assessed in patients on hemodialysis [11]. The MMSE has advantages in its relatively strong sensitivity and specificity in detecting cognitive impairment in the general population, as well as the ability of the test to evaluate five cognitive dimensions-orientation, memory, attention, language, and visuoconstruction [69,70]. The MMSE has limitations in that it is copyrighted and has poor sensitivity in detecting MCI (.18) [69,70,74]. The low sensitivity of the MMSE in detecting MCI is concerning because it may not detect cognitive impairment in its mildest stages, including the deficits found in older adult patients with CKD. The utilization of the MMSE in patients with CKD is also concerning because the MMSE does not assess executive function, which is the cognitive domain where patients with CKD and patients with vascular dementia are often noted to have deficits [9,40,50,71,72]. Eight of the reviewed studies utilized the MMSE as the only test to evaluate cognitive function [33,47-49,51,53,59,64]. It is possible that these studies did not capture all patients with cognitive impairment because executive function was not assessed. Of the 30 studies that sought to find an association between CKD and cognitive impairment, only one study did not find a significant relationship between cognitive impairment and lower GFR [51]. Interestingly, this study only utilized the MMSE to evaluate cognitive function. Given the potential limitations of the utilization of the MMSE in older adult patients with CKD, it is possible that this study did not find a significant relationship because of the limited scope of evaluation of cognitive function with the MMSE.

There were two tests that were utilized in eight studies. The digit symbol substitution test, which is a 90 second test of how many appropriate symbols a participant can place next to a corresponding number according to a key [75], was one of the second most commonly utilized tests. Digit symbol substitution tests evaluate processing speed, which requires the utilization of

the cognitive abilities of attention, memory, and visual scanning [42,76]. Digit symbol substitution tests are often used in research and practice because they are easy to administer in a consistent way [42,75]. One example of this test is the Digit Symbol Substitution Test (DSST) from the Wechsler Adult Intelligence Scale, which has been utilized for over 15 years and has scores that are significantly correlated with the age of the person being evaluated while being independent of educational level [75]. Unfortunately, digit symbol substitution tests have weaknesses. For a person to be accurately evaluated with digit symbol substitution tests, visual acuity, motor coordination, and motor speed need to be intact [77]. Therefore, digit symbol substitution tests cannot be administered to obtain a true assessment of cognitive function if a person has deficits in any of these areas. Symbol familiarity also plays a role in the performance on digital substitution tests for older adults, which can alter the ability of the test to be a factual representation of the patient's cognitive ability [76]. The use of digit symbol substitution tests has limitations in the assessment of cognitive function for older adult patients with CKD. Unfortunately, digit symbol substitution tests do not assess executive function. The digit symbol substitution test was utilized as the singular cognitive test in only one study of this review [45]. Given the lack of assessment of executive function, the use of digit symbol substitution tests as a singular assessment of cognitive function in patients with CKD should be utilized with caution, as it may not evaluate all potential domains of deficit.

Tests of verbal fluency were also utilized in eight of the evaluated studies. Tests of verbal fluency are an assessment of a person's ability to name words beginning with a certain letter or belonging to a certain category [78]. Tests of verbal fluency evaluate language, in addition to semantic memory and working memory, which is considered a component of executive function [40]. Deficits in verbal fluency have been found frequently in patients with

vascular dementia [72]. Unfortunately, tests of verbal fluency have limitations in that there is limited normative data related to gender, age, educational level, and intelligence [78]. In addition, the norms that are available are only applicable to people that are fluent in English [78]. A test of verbal fluency was not utilized as the singular cognitive assessment in any of the included studies, which is appropriate given the limited cognitive domains that are assessed by tests of verbal fluency.

The TMT-B was utilized in seven of the studies of the review. The TMT-B evaluates executive function, as well as mental flexibility, in its assessment of the speed at which a person can complete a number and letter sequence in the correct order [70]. The TMT-B has shown strength as a cognitive test in determining loss of cognitive function in patients at all stages of kidney disease, even those with only minor deficits in cognition [70]. In addition, when utilized in one sample of older adult patients with ESRD, many patients were unable to complete a cognitive battery that included the TMT-B due to visual impairment, lack of motivation, or motor difficulties [79]. The complexity and time limit of this cognitive assessment needs to be considered when it is utilized in older adults with CKD.

Recommendations and Future Research Directions

It is critical that older adult patients with CKD have an appropriate assessment to identify cognitive impairment, so this population can receive care and manage the risks associated with this complication of CKD. Since executive function is commonly affected in patients with CKD [9,40,50,71,72], cognitive function tests that evaluate executive function should be utilized in practice and research that seeks to fully understand cognitive impairment of older adults with CKD. To assure that multiple aspects of cognitive function are evaluated, it is reasonable that patients with CKD are assessed for cognitive impairment with either a composite test or multiple

tests that evaluate different domains of cognitive function, including executive function and other domains commonly affected in patients with CKD [9,40,50,71,72]. This is particularly important when evaluating patients with CKD that have varying levels of GFR, since patients at different levels of kidney impairment may experience deficits in different cognitive domains. As described by Yaffe and colleagues in the Chronic Renal Insufficiency Cohort (CRIC) study, patients with an estimated GFR below 30ml/min/1.73m² were found to have deficits in global cognition, naming, attention, executive function, and delayed memory but had relatively intact category fluency and immediate memory, as compared to patients with estimated GFR above 30ml/min/1.73m² [72]. These findings emphasize that older adults with CKD should be evaluated across multiple cognitive domains, particularly when evaluating groups of patients with different levels of GFR.

Further research is needed on the appropriate way to assess cognitive function in older adult patients with CKD. A large priority is the determination of the ideal cognitive assessment test to utilize with older adult patients with CKD. In the articles reviewed, there were limited reports on the reliability, validity, sensitivity, and specificity of the cognitive assessment tests utilized. Unfortunately, this has led to the assessment of cognitive function in patients with CKD being done in various ways utilizing different tests. Therefore, it is essential that thorough psychometric evaluation of cognitive tests is conducted with older adult patients with CKD to establish an ideal test to utilize with this at-risk population.

Clinical Implications

The findings of this review have very important clinical implications. The reviewed studies highlight the large burden of cognitive impairment experienced by older adult patients with CKD. Assessment of cognitive function should be done for all patients with CKD, and this

review has highlighted the complexity associated with doing this assessment. With many cognitive screening tests available, it is important that clinicians choose appropriate cognitive screening tests for older adults with CKD. Clinical assessments that aim to assess cognitive function in patients with CKD should utilize more than a singular test to assess multiple cognitive domains, including those most commonly affected in patients with CKD. In practice and research, assessing a single cognitive domain in a patient with CKD is likely not sufficient. Executive function should be one of the domains assessed in all older adult patients with CKD with suspected cognitive impairment, since there is support that assessment of executive function is a necessary and sensitive indicator of cognitive impairment in patients with CKD [9].

In clinical practice, it is critically important that older adult patients with CKD are evaluated with cognitive tests that consider the patient's other comorbidities and deficits. As previously described, tests such as the digit symbol substitution test require visual acuity, motor coordination, and motor speed [77]. It is necessary to choose appropriate cognitive tests that consider the patient's other comorbidities and sensory deficits to avoid missing cases and fully capture the magnitude of the problem of cognitive impairment in older adult patients with CKD.

Limitations

Although this review was rigorous and thorough, it does have some limitations. The articles evaluated were those that were available in English, which may have excluded relevant international studies. Although the review was integrative in nature, a full review of grey literature was not conducted, which may have omitted relevant citations [80]. There were some limitations related to the evaluation of tests utilized to assess cognitive function. Every test was not counted individually if it was a derivation of the same test, such as the different versions of digit symbol substitution tests. In addition, composite tests of global cognition were counted as

one test, although they evaluate different cognitive domains. This has similarly been done in other studies that evaluated cognitive assessment in patients with CKD [10]. This may have led to misrepresentation of the number of cognitive tests utilized in each study because if a composite was used, less tests per study may have been utilized. In addition, this may have led to certain cognitive domains not being fully counted. This review also has limitations in that it did not evaluate the full breadth of studies that evaluated cognitive function in patients with CKD, since studies were only evaluated if the mean age of participants was greater than 65 years old to capture studies focused on older adults. The utilization of this cutoff may have eliminated relevant studies of cognitive impairment in patients with CKD. It is possible with the inclusion of studies with patients with a mean age less than 65 years old that the utilization of cognitive function assessments would have been different. However, the purpose of this study was to focus on older adults with a mean age of greater than 65 years of age due to the higher prevalence of cognitive impairment in this population. Future studies should investigate cognitive function assessment in midlife and younger adults. Despite these limitations, a thorough review was conducted that revealed the breadth of assessment tests currently being utilized to evaluate cognitive function in older adult patients with CKD.

Conclusion

Through this integrative review, it has been elucidated that the assessment of cognitive function in older adults with CKD is done in many, inconsistent ways. In the reviewed articles, there were wide variations in the tests chosen, the number of tests utilized, and the cognitive domains assessed. Since there is not a test of cognitive function validated for use in older adult patients with CKD, it is critical in research and practice that assessment of cognitive function in older adult patients with CKD is done thoroughly by assessing various cognitive domains. With

a more comprehensive assessment of cognitive function, the true magnitude of cognitive impairment in older adults with CKD can be understood and interventions can be developed to address this debilitating consequence of CKD.

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Table 1- Examples of Cognitive Tests and their Domain of Assessment

Cognitive Test	Domain
Mini Mental State Exam (MMSE)	Composite Test (Global cognition)
Trail Making Test A (TMT-A)	Complex Attention
Trail Making Test B (TMT-B)	Executive Function
California Learning Test (CVLT)	Learning and Memory
Hopkins Verbal Learning Test (HVLT)	Language
Number Comparison	Perceptual Motor

Table 2-Search terms

Renal insufficiency, chronic kidney disease, kidney failure, chronic renal disease, chronic renal insufficiency

AND

Cognitive function, cognition, cognitive impairment, cognitive dysfunction, mental status, cognitive disorder, mild cognitive impairment

Table 3- Quality Assessment

Author	Year	Study type ^a	Sampling ^b	Method ^c	Statistical analysis	Score
Afsar et al.	2011	4	1	1	3	9
Amano et al.	2013	4	1	1	2	8
Antunes et al.	2014	4	1	1	3	9
Auriel et al.	2016	4	2	1	3	10
Buchman et al.	2009	4	2	1	3	10
Chen et al.	2017	4	2	1	3	10
Corrao et al.	2015	4	2	1	3	10
Darsie et al.	2014	4	2	1	3	10
Elias et al.	2009	4	2	1	3	10
Etgen et al.	2009	4	2	1	3	10
Feng et al.	2013	4	2	1	3	10
Foster et al.	2016	4	2	1	3	10
Hobson et al.	2016	4	2	1	3	10
Iyasere et al.	2017	4	1	1	3	9
Jovanovich et al.	2014	4	2	1	3	10
Khatri et al.	2009	4	2	1	3	10
Kurella, Chertow et al.	2005	4	2	1	3	10
Kurella, Yaffe et al.	2005	4	2	1	3	10
Kuriyam et al.	2013	4	2	1	3	10
Lai et al.	2016	4	1	1	3	9
Lee, Chin et al.	2011	4	2	1	3	10
Lee, Shimada et al.	2015	4	2	1	3	10
Lin et al.	2009	4	2	1	3	10
Murray et al.	2016	4	2	1	3	10
Post et al.	2010	4	1	1	3	9
Pulignano et al.	2014	4	1	1	3	9
Rodriguez Angarita et al.	2016	4	3	1	3	11
Rodriguez Villareal et al.	2014	4	2	1	3	10
Romijn et al.	2015	4	1	1	3	9
Sasaki et al.	2011	4	2	1	3	10
Slinin et al.	2008	4	2	1	3	10
Srivanitchapoom et al.	2013	4	2	1	3	10
Umemura et al.	2013	4	2	1	3	10
Wang et al.	2016	4	2	1	3	10
Weng et al.	2012	4	1	1	3	9
Zammit et al.	2015	4	2	1	3	10
Mean		4	1.778	1	2.972	9.75
Range		4	1 to 3	1	2 to 3	8 to 11

a **Study type:** 3=qualitative design; 4=quantitative descriptive design; 5=mixed qualitative and quantitative descriptive; 6=quantitative experimental and quasi-experimental b **Sampling:** 0=not explained; 1=convenience; 2=purposive or case matching/cohort; 3=random or 100% c **Method:** 1=methods and tools explained; 0=not explained d **Analysis:** 1=narrative statistics; 2=descriptive statistics; 3= inferential statistics¹⁰

Figure 2- Number of Tests Utilized in Each Study

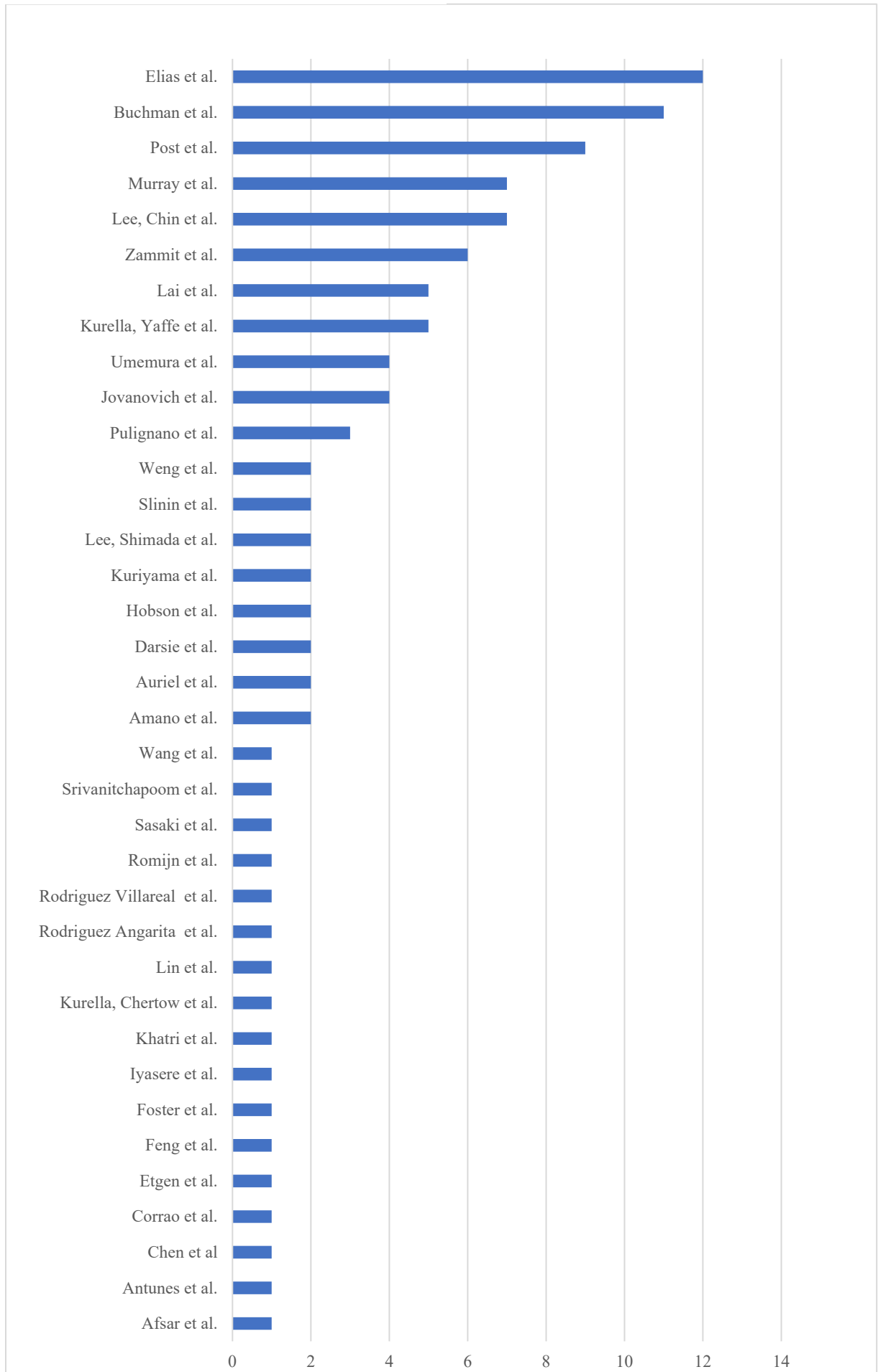


Figure 3-Number of Times Each Test Utilized

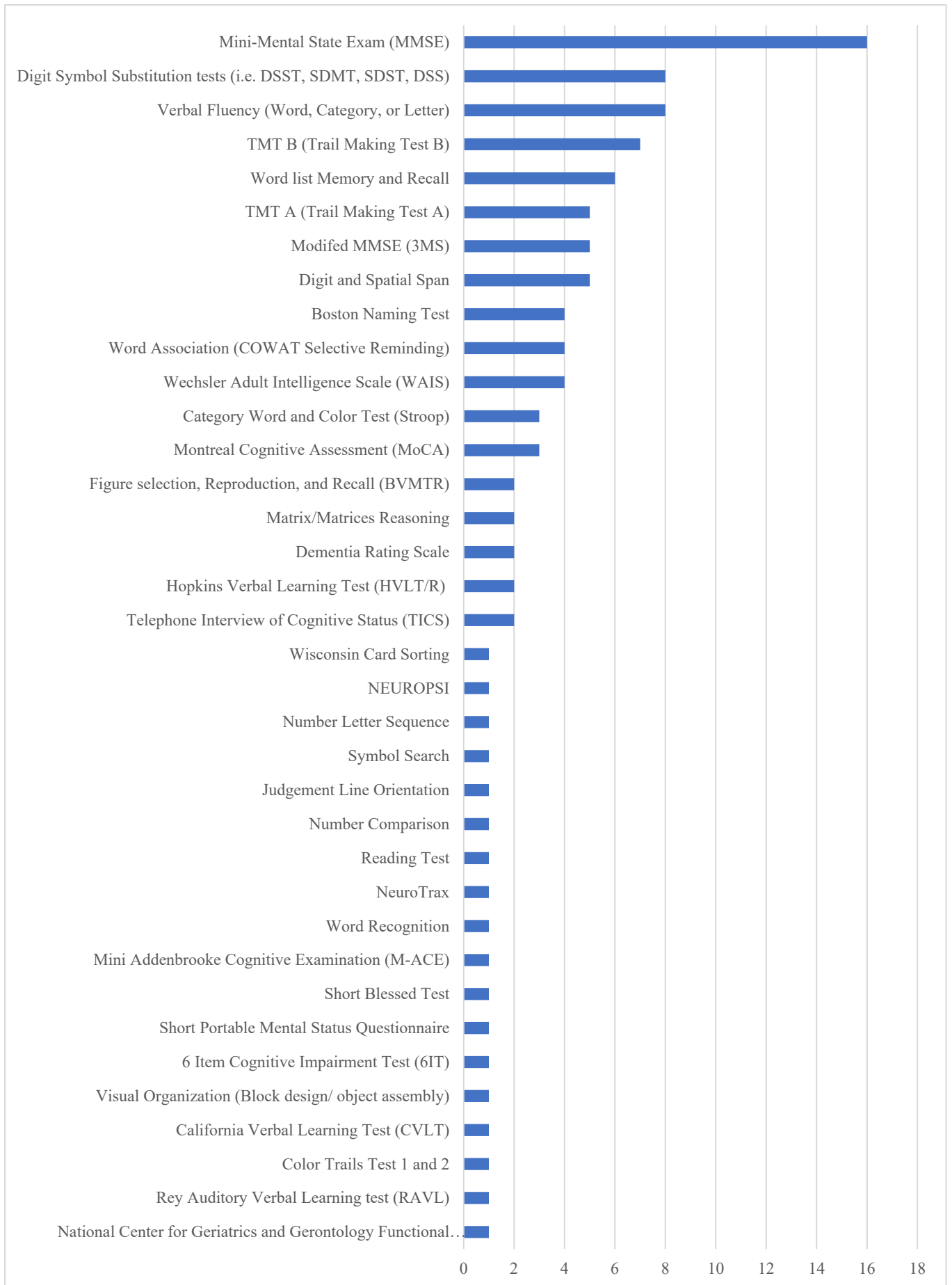
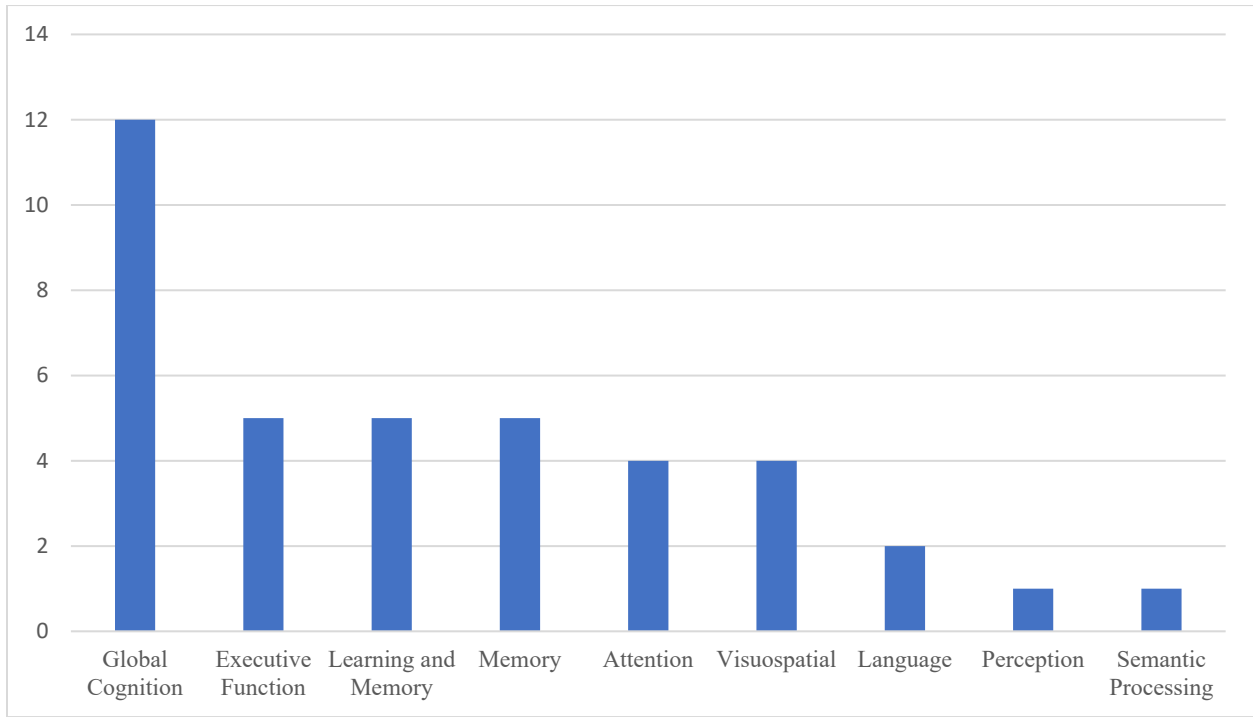


Figure 4- Number of Cognitive Tests per Doman



Author	Year	CKD Stage or GFR	Sample Size	Mean Age (with CKD)	Purpose	Design	Cognitive Tests Utilized	Results- Related to cognitive function tests
Afsar et al.	2011	32.3 +/- 14.3	247	65+/-11	Relationship between uric acid and cognitive impairment in CKD	Cross sectional comparative	Standardized MMSE (SMMSE)	Uric acid is independently and inversely associated with cognitive function in CKD
Amano et al.	2013	2 CKD Stage 5 patients	2	80, 67- two cases (mean not calculated)	Describe the use of Donepezil HCl in CKD patients; 2 case reports	Case report	MMSE; Hasegawa Dementia Rating Scale	Significant increase in concentration with 5mg dose to near toxic level and cognitive function improved most
Antunes et al.	2015	<60	246	75.7+/- 5.61	Evaluate the association of cognitive impairment in CKD	Cross sectional comparative	MMSE	Patients with GFR<60 and >90 had a higher prevalence of cognitive impairment
Auriel et al.	2016	GFR<60	431	74.9+/-8.3	Determine the interrelationship among CKD, markers of cerebral small vessel disease and brain integrity, and cognitive performance in patients after stroke or TIA	Prospective cohort	Questionnaire on Cognitive Decline in the Elderly, NeuroTrax, MoCA	Patients with CrCl<60 performed worse over time on all cognitive tests, as compared with patients with CrCl>60. Patients with CrCl<60 had larger white matter hyperintensities, cortical atrophy, and smaller hippocampal volume. CrCl<60 at baseline is a significant predictor for development of cognitive impairment 2 years after stroke or TIA
Buchman et al.	2009	GFR 59.8 +/- 15.8 entire sample	886	80.6	Assess if impaired kidney function is associated with more rapid decline in cognitive function; Rush Memory and Aging Project	Prospective cohort	Weschler, East Boston Story and Word List memory, Word list recall, word list recognition, Boston naming test, Verbal fluency, 15item reading test, digit span forward and backward, digit ordering, Symbol digit modalities, number comparison, Stroop, Judgement line orientation, Standard progressive matrices	Lower GFR is associated with decreased cognitive function at baseline; Impaired kidney function is associated with more rapid decline in cognitive function
Chen et al.	2017	<60	33654	78.76 +/- 5.83	Determine the influence of the annual percentage change in GFR on cognitive deterioration	Prospective cohort	Short Portable Mental Status Questionnaire	Patients with severe decline in GFR (>20% per year) had an increased risk of cognitive decline when compared with those with stable eGFR

Author	Year	CKD Stage or GFR	Sample Size	Mean Age (with CKD)	Purpose	Design	Cognitive Tests Utilized	Results- Related to cognitive function tests
Corrao et al.	2015	53.3 (patients with AF) and 59.6 (patients without AF)	321	80.8 (with AF); 78.5 (w/o AF)	Impact of cognitive impairment in elderly hospitalized patients with CKD with A Fib	Retrospective, comparative	Short Blessed Test (SBT)	Elderly patients with A Fib are more likely to have cognitive impairment and CKD
Darsie et al.	2014	GFR<60	3907	CKD patients- 77.5+/- 5.9	Association between kidney function and change in cognitive behavior; The Cardiovascular Health Study	Prospective cohort	Digit Symbol Substitution Test (DSST); Modified MMSE	eGFR<60 patients had a .64 decline per year faster than eGFR>60 on MMSE and .42 decline faster on DSST
Elias et al.	2009	49.7+/- 10.7	923	68.5 +/- 11.6	Examine the range of cognitive abilities affected by CKD and whether the associations of cognition and CKD were influenced by CVD risk factors	Cross sectional comparative	Logical memory immediate and delayed recall, Hopkins verbal learning test, visual reproductions immediate and delay recall, matrix reasoning, block design, object assembly, Hooper visual organization, TMT A, TMT B, digit symbol substitution, symbol search, digit span forward and backward, letter-number sequence, controlled oral word associations, similarities	CKD was related to lower cognitive performance in the areas of global, visual-spatial organization/memory, and scanning and tracking
Etgen et al.	2009	Ccr 45-59 and <45	3679	73.7+/-8 (Ccr 45-59); 79.2+/-7.9 (Ccr<45)	Examine the relationship between decreased renal function and cognitive impairment at baseline and 2yr f/u; Invade Study	Prospective cohort	6 Item cognitive impairment test (6CIT)	Incidence at 2yrs of cognitive impairment was 5.8 for GFR>60, 9.9% for GFR 45-59, 21.5% for GFR <45
Feng et al.	2013	51.0+/-8.3	362	70.3 +/- 7.8	Examine the prevalence of depressive symptoms and their influence on QOL, mortality, and what is correlated with depressive symptoms in CKD patients; Singapore Longitudinal aging study	Prospective cohort	MMSE	Cognitive impairment present in 23.8% of depressed patients and 10.6% non-depressed patients with CKD

Author	Year	CKD Stage or GFR	Sample Size	Mean Age (with CKD)	Purpose	Design	Cognitive Tests Utilized	Results- Related to cognitive function tests
Foster et al.	2016	19 (14-25)	385	68 (56-78)	Examine cognitive impairment (CI) in pre-dialysis CKD patients	Cross sectional comparative	MOCA	61% of CKD 4-5 patients had cognitive impairment; lower in all domains- especially recall, attention, and visual/executive function; Factors associated with CI- older age, recent history of falls or stroke
Hobson et al.	2016	No cognitive impairment 29.9+/-9.6, MCI 29.7+/-7.9, Dementia 31.9+/-11.7	118	77.1+/-7.9	To evaluate utility of the mini-Addenbrooke's Cognitive Examination (M-ACE) in older adults with CKD and DM	Cross sectional comparative	Mini-Addenbrooke's Cognitive Examination (M-ACE); MMSE	M-ACE has good sensitivity and specificity to capture and assist diagnosis of MCI or dementia in CKD and DM
Iyasere et al.	2017	17+/-0.9	102	72.5+/-1.5	Cognitive function amongst CKD, HD, PD patients and relationship between CI and decision-making capacity	Prospective cohort study	MOCA	Cognition declines faster in HD compared with CKD and in HD compared with PD. Cognitive impairment affects decision making capacity in patients with advanced kidney disease
Jovanovich et al.	2014	18.3ml/min (+/-6.3)	2056	66.2 (+/-11/5) placebo, 65.4 (+/-12) vitamin group	Examine the association between mineral metabolites and cognitive function in the VA HOSTCOG study	Post hoc analysis of a randomized controlled trial evaluating prospective associations; Comparison group ESRD patients	Telephone: TICS-m (telephone interview for cognitive status), forced choice recognition trial, Digit span forward and backward, Index of attention and working memory, verbal fluency	There was no effect of treatment with high dose Vitamin B on cognitive function tests in patients with CKD and ESRD.
Khatri et al.	2009	GFR<60	2172	76+/-9.4	Longitudinal study of cognitive decline in CKD; Northern Manhattan study	Prospective cohort	Telephone: TICS-m (telephone interview for cognitive status)	Decreased kidney function is associated with greater cognitive decline over time at all levels of CKD

Author	Year	CKD Stage or GFR	Sample Size	Mean Age (with CKD)	Purpose	Design	Cognitive Tests Utilized	Results- Related to cognitive function tests
Kurella, Chertow et al.	2005	GFR 45-59 and GFR<45	3034	73.9+/-2.8 and 74.3+/-2.9	Longitudinal course of cognitive impairment different for patients with CKD; Health ABC	Prospective cohort	3MS	CKD is associated with increased risk of cognitive impairment in the elderly
Kurella, Yaffe et al.	2005	eGFR 57+/- 14	1015	66.7+/-6.4	Evaluate the relation between CKD and cognitive impairment; Heart Estrogen/Progestin Replacement Study	Cross sectional comparative	3MS, TMT B, Modified Boston Naming, Verbal Fluency test, Word List Memory and Word List Recall	eGFR was associated significantly with impairment in global cognition, executive function, language, and memory (15-25% increase in risk for cognitive impairment for each 10ml/min lower GFR), results independent of age/race
Kuriyama et al.	2013	53.8 ± 13.3	273	66.6+/-7.1	Relationship between deep white matter lesions and cognitive impairment in CKD, 5yr follow-up	Prospective cohort	MMSE, letter fluency test, word fluency task	CKD is associated with deep white matter lesions and their progression and with cognitive impairment
Lai et al.	2016	25.5+/-9.1	74	67+/-15.2	Assess cognitive, neurological, and psychological imbalance in patients with CKD (no RRT, HD, PD, post-transplant) compared to healthy controls	Cross sectional, comparative	TMT A, TMT B, Digit Span test (DST), Symbol digit modalities test (SDMT), Grooved Pegboard Test (GPT)	Patients with CKD had abnormalities in their psychological profiles and these results are associated with decreased cognitive function scores. (paranoia correlated with scores on DST, SDMT, TMT)
Lee, Chin et al.	2011	Two groups: eGFR 54.4+/-3.8, 37.6+/-5.0	529	74.1+/- 7.8; 79.6+/-8.4	Investigate frontal lobe dysfunction in patients with CKD +/- depression	Cross sectional comparative	Word list memory task, word list recall test, word list recognition test, modified Boston naming test, lexical fluency test, TMT-A, TMT-B, Wisconsin card sorting test	Frontal dysfunction, particularly perseverative errors and responses, was associated with moderate to severe CKD

Author	Year	CKD Stage or GFR	Sample Size	Mean Age (with CKD)	Purpose	Design	Cognitive Tests Utilized	Results- Related to cognitive function tests
Lee, Shimada et al.	2015	Two groups eGFR 45-59, eGFR <45	4686	73.4+/- 6.1, 77.2+/-7.4	Evaluate the relationship between CKD and cognitive decline	Cross sectional comparative	MMSE; National Center for Geriatrics and Gerontology functional assessment tool (NCGG-FAT)	Lower GFR associated with lower cognitive performance in attention and processing speed
Lin et al.	2009	Groups eGFR30-59, 15-30, <15	2431	71+/- 7.6 overall mean age, no reference to age of CKD	To examine relationships between CKD, atherosclerosis, and functional performance in the elderly; NHANES 1999-2002	Population based observational survey	Digit symbol subtest (DSST)	Renal impairment was independently associated with physical and cognitive function after adjustment of potential confounding factors
Murray et al.	2016	45.5+/- 23.5	554	70.4 (no sd given)	Identify mechanisms that contribute to increased risk for cognitive impairment in CKD	Prospective cohort	3MSE, Hopkins Verbal Learning Test-Revised(HVLTR) , Brief Visuospatial Memory Test-Revised (BVMTR, Symbol Digit Modalities Test (SDMT), Controlled Oral Word Association Test (COWAT), Color Trails Tests 1 and 2 (CTT-1 and CTT-2), Wechsler Digit Span	Cognitive function significantly worse in patients with GFR<30

Author	Year	CKD Stage or GFR	Sample Size	Mean Age (with CKD)	Purpose	Design	Cognitive Tests Utilized	Results- Related to cognitive function tests
Post et al.	2010	CKD Stage 3 and 4	51	72+/-12	Assess cognitive function in CKD and HD pts with no h/o stroke or dementia	Cross sectional comparative	MMSE, CVLT, Controlled oral word association, animal category fluency, digit span, symbol digit modality test (SDMT), TMT A, TMT B, Stroop word and color test, Short category test (SCT)	All patients had normal MMSE; but there was a high prevalence of MCI in both groups
Pulignano et al.	2014	eGFR 41.3+/-16.2	199	77+/-5.1	Determine if anemia and cognitive impairment are independent predictors of cognitive impairment in patients with heart failure	Prospective cohort	MMSE, Verbal fluency, Wechsler adult intelligence scale digit symbol (WDS)	Cognitive impairment is common in elderly heart failure patients and associated with anemia and renal dysfunction
Rodriguez Angarita et al.	2014	CKD Stage 4 and 5	251	79+/-4.98	Examine which factors influence decision making on whether to start HD or not in older adult patients with CKD	Cross sectional	MMSE	Predictive factors for patients to choose conservative care (no HD) were age, pre-frailty on multivariate analysis
Rodriguez Villareal et al.	2016	Stage 3,4	56	76.3+/-7.9	Prevalence of cognitive impairment and depression in patients with CKD >55	Prospective cohort	NEUROPSI (orientation, attention, concentration, language, memory, visual motor skills, executive functions, reading, writing, and computing)	The overall prevalence of cognitive impairment was 51%
Romijn et al.	2015	eGFR 45-60, eGFR <45	581	81+/-7, 81+/-8	Relationship between renal function and cognition	Cross sectional comparative	MMSE	Significant relationship between mild CKD and impaired cognitive function
Sasaki et al.	2011	CKD 3-5	497	80.5+/-7.6	Examine the relationship between incident dementia and CKD	Prospective cohort	MMSE	CKD was strongly associated with the incidence of dementia

Author	Year	CKD Stage or GFR	Sample Size	Mean Age (with CKD)	Purpose	Design	Cognitive Tests Utilized	Results- Related to cognitive function tests
Slinin et al.	2008	Group eGFR 45-59, eGFR<45	5529	>65 for entire sample; not specified for CKD group	Examine the association of kidney function and cognitive impairment/decline in older men	Prospective cohort	3MS, TMT B	Independent association between kidney function decline/reduction and poor executive function at baseline (not global function or risk of decline)
Srivanitchapoom et al.	2013	eGFR 30-59, eGFR<30	317	73.62+/-6.47, 76.86+/-7.44	Relationship of CrCl and cognitive function in older adults in Thailand	Cross sectional comparative	MMSE (Thai version)	No statistically significant association of cognitive impairment and lower GFR; trend for CrCl<48 to be associated with cognitive impairment
Umemura et al.	2013	eGFR<60	79	79+/-6.7	Evaluate if CKD is associated with cognitive impairment independently of cerebral small vessel disease in elderly diabetic patients	Cross sectional comparative	Stroop color word, Digit symbol substitution , MMSE, word recall	Low GFR associated with low digit symbol and albuminuria associated with low Stroop color word; no association GFR/albuminuria and MMSE, word recall
Wang et al.	2016	eGFR 50.2+/-7.8	395	83+/-2.6	Assess impact of CKD and eGFR on cognitive impairment in 80yo Chinese patients with untreated HTN	Cross sectional comparative	MMSE	CKD and GFR associated with cognitive impairment in HTN patients >80
Weng et al.	2012	48.2+/-14	356	78.1+/-3.6	Prospective study to investigate factors affecting progression of cognitive dysfunction in the elderly at different levels of kidney function	Prospective cohort	MMSE, Clinical dementia rating (CDR) scale	Age, MMSE, and plasminogen activator inhibitor-1 was associated with high risk for cognitive dysfunction at different levels of CKD
Zammit et al.	2015	eGFR 45-59, eGFR<45	649	80.7+/-5.5, 82.3+/-6.1	Assessment of renal and cognitive function in community based older adults	Cross sectional comparative	Free and cued selective reminding test, Wechsler memory scale-revised, Wechsler adult intelligence (WASI) III, TMT A, TMT B, Category fluency, controlled oral word fluency test, Boston naming task	Low GFR is associated with reduced performance on executive function