

# Validation of the Kidney Disease Quality of Life (KDQOL) Cognitive Function subscale

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## Validation of the Kidney Disease Quality of Life (KDQOL) Cognitive Function subscale.

**Background.** Formal cognitive function testing is cumbersome, and no self-administered instruments for estimating cognitive function in persons with chronic kidney disease (CKD) and end-stage renal disease (ESRD) have been validated. The goal of this study was to determine the validity of the Kidney Disease Quality of Life Cognitive Function scale (KDQOL-CF) for the assessment of cognitive impairment in persons with kidney disease.

**Methods.** We administered the KDQOL-CF to 157 subjects, 79 with ESRD and 78 with CKD participating in a cross-sectional study of cognitive function. Scores on the Modified Mini-Mental State Exam (3MS) were considered the gold standard measure of global cognitive function. Performance characteristics of the KDQOL-CF were assessed using correlation coefficients, Bland-Altman plots, and receiver operating characteristic curves.

**Results.** Median scores on the KDQOL-CF were 73 (interquartile range 60–87) for subjects with ESRD and 87 (interquartile range 73–100) for subjects with CKD ( $P < 0.0001$ ). Scores on the KDQOL-CF were directly correlated with scores on the 3MS ( $r = 0.31$ ,  $P = 0.0001$ ). Defining global cognitive impairment as a 3MS score  $< 80$ , a cut-point of 60 on the KDQOL-CF accurately classified 76% of subjects, with 52% sensitivity and 81% specificity. On multivariable analysis, cerebral and peripheral vascular disease, benzodiazepine use, and higher serum phosphorus concentrations were associated with lower KDQOL-CF scores, while beta blocker use, education, and higher serum albumin concentrations were associated with higher KDQOL-CF scores.

**Conclusion.** The KDQOL-CF is a valid instrument for estimating cognitive function in patients with CKD and ESRD. KDQOL-CF screening followed by 3MS testing in selected individuals may prove to be an effective and efficient strategy for identifying cognitive impairment in patients with kidney disease.

**Key words:** chronic kidney disease, cognitive impairment, end-stage renal disease.

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Cognitive impairment is a common, often unrecognized condition in persons with end-stage renal disease (ESRD) [1]. Cognitive impairment is associated with more frequent hospitalizations and greater utilization of health care resources in patients with ESRD [1]; in the general population dementia carries an increased risk of death and higher health care costs [2]. Little is known about cognitive impairment in persons with chronic kidney disease (CKD) not yet requiring dialysis. Nevertheless, accurate identification of patients with cognitive impairment is central to reducing the considerable morbidity associated with this condition. Formal cognitive function testing requires trained personnel and can be time consuming, even when employing screening tests of global cognitive function, such as the Mini-Mental Status Examination (MMSE). A reliable self-administered questionnaire for the identification of cognitive impairment would be extremely valuable for physicians and others caring for persons with CKD and ESRD.

The Kidney Disease Quality of Life (KDQOL) instrument is a self-administered questionnaire designed to assess health-related quality of life in persons with kidney disease. The KDQOL contains eight subscales derived from the Medical Outcomes Study SF-36 [3], as well as 12 kidney disease targeted subscales, including cognitive function [4]. There are several potential advantages of such an instrument to assess cognitive function, including its brevity and ease of administration and interpretation. Additionally, the KDQOL has been used to assess quality of life in several ongoing and recently completed cohort studies in CKD and ESRD [5–7], facilitating comparisons among different patient groups. Despite widespread use of the KDQOL, the cognitive function subscale has not been validated against objective measures of cognitive function.

Therefore, we sought to determine the sensitivity, specificity, and positive and negative predictive values of the KDQOL cognitive function scale (KDQOL-CF) compared with an objective measure of global cognitive function, the Modified Mini-Mental State Exam (3MS) in

subjects with CKD and ESRD. Using performance characteristics of the KDQOL-CF and the 3MS and a broad range of prevalence estimates for cognitive impairment in CKD and ESRD, we then determined the expected diagnostic efficiency of a two-step screening strategy employing the KDQOL-CF and 3MS in sequence.

## METHODS

We recruited subjects from three dialysis units and ambulatory nephrology practices affiliated with the University of California San Francisco (UCSF) to participate in a cross-sectional study of cognitive function. These practices serve an ethnically and socioeconomically diverse population generally from within the city of San Francisco. Subjects with ESRD received in-center hemodialysis three times per week, using ultrafiltration controlled machines, bicarbonate-based dialysate, and high-flux polysulfone dialyzers for 3 to 4 hours per session. Estimated GFR was calculated for subjects with CKD using the six variable Modification of Diet in Renal Disease (MDRD) study equation incorporating age, black versus non-black race, sex, serum creatinine, urea nitrogen, and albumin concentrations [8]. Subjects with CKD were eligible to participate if they had an estimated GFR  $<60$  mL/min/1.73 m<sup>2</sup> on at least two occasions during the past 12 months. Subjects not fluent in English or with significant hearing impairment were excluded. Participation rates were  $>95\%$  for screened subjects with ESRD. Potential subjects with CKD were screened by the treating nephrologist, and referred to the study if eligible; thus, participation rates were not determined for subjects with CKD. The UCSF Committee on Human Research approved the study, and all subjects signed informed consent.

### Cognitive function tests

Subjects underwent a battery of cognitive function tests administered by two trained personnel. The 3MS is a brief test of global cognitive function with components for orientation, attention, language, and memory. The 3MS has a maximum score of 100 (scores range from 0–100), and is considered to be more sensitive for mild cognitive impairment compared with the traditional 30-point Mini-Mental Status Exam (MMSE) [9]. A 3MS  $<80$  was reported to have a sensitivity of 91% and specificity of 97% for detecting dementia in the general population [9]. The 3MS was administered to subjects with ESRD during a midweek hemodialysis session, avoiding the beginning or end of each treatment. Subjects with CKD underwent cognitive function testing during a clinic visit. Subjects also completed the cognitive function subscale of the Kidney Disease Quality of Life (KDQOL-CF) short form and the Geriatric Depression Scale short form (GDS). The cognitive subscale of the KDQOL consists

of three questions: During the past 4 weeks, did you react slowly to things that were said or done? Did you have difficulty concentrating or thinking? Did you become confused? Subject responses on a qualitative 6-point scale were weighted and transformed to scores ranging from 0 to 100, with higher scores indicating better self-assessed cognitive function [4]. The GDS is a 12-item scale measuring symptoms of depression, with higher scores indicating greater depressive symptoms [10]. The GDS has been validated as a screen for depression among elderly subjects, and specifically among those with cognitive impairments [11]. Compared to the more widely used Beck Depression Inventory (BDI), the GDS is shorter and contains fewer items (one of 12) querying somatic symptoms.

### Statistical analysis

Continuous variables were expressed as mean  $\pm$  standard deviation or median with interquartile range. Categorical variables were expressed as proportions. Between-group differences were compared with Student *t* test, the Wilcoxon rank-sum test, or the chi-square test, where appropriate. Correlation was assessed with the Pearson product moment coefficient. We used multivariable linear regression analysis to determine independent predictors of the KDQOL-CF score. Companion analyses stratified by the severity of kidney disease (i.e., ESRD vs. CKD) were also performed. Based on the stratified analyses, we considered several multiplicative interaction terms to evaluate for effect modification by ESRD versus CKD status. Variables that were not significantly associated with the KDQOL-CF score were added back to the model individually to evaluate for residual confounding. Residual plots showed normal distributions and no significant outliers. We constructed a Bland-Altman plot to determine agreement between the KDQOL-CF and 3MS [12]. A receiver operator characteristic (ROC) curve was constructed to determine the sensitivity and specificity of the KDQOL-CF using different cut-points to define self-reported cognitive impairment. Finally, we considered two hypothetical screening strategies for cognitive impairment—one in which all potential participants were screened with the 3MS, and another in which all potential participants were screened with the KDQOL-CF and those with low KDQOL-CF scores were subsequently screened with the 3MS. We calculated positive and negative predictive values and hypothetical costs over a wide range of prevalence estimates. For all analyses, two-tailed *P* values  $< 0.05$  were considered significant. All analyses were performed with STATA 8.0 (College Station, TX, USA).

## RESULTS

A total of 160 subjects were enrolled in the study; 157 completed the 3MS and KDQOL-CF. Subject

**Table 1.** Characteristics of study subjects with chronic kidney disease (CKD) and end-stage renal disease (ESRD)

Characteristic	CKD (N = 78)	ESRD (N = 79)	P value
Age years	63.8 ± 14.2	61.2 ± 14.4	0.25
Female %	23%	41%	0.02
Race %			
Caucasian	54%	17%	<0.0001
Black	26%	52%	
Asian	17%	25%	
Other	4%	6%	
High school graduate %	93%	81%	0.04
Diabetes %	40%	54%	0.08
CHF %	21%	49%	<0.0001
PVD %	18%	22%	0.57
Stroke %	27%	20%	0.32
Beta-blocker %	60%	63%	0.70
Benzodiazepine %	9%	9%	0.98
Opiate %	12%	20%	0.17
Antidepressant %	18%	11%	0.25
Weight kg	79.1 ± 16.7	73.5 ± 29.3	0.16
SBP mm Hg	137 ± 22	153 ± 26	<0.0001
DBP mm Hg	74 ± 13	82 ± 16	0.001
Vintage months	—	40.9 ± 36.2	—
eGFR mL/min/1.73m <sup>2</sup>	26.6 ± 11.5	—	—
Creatinine mg/dL	3.1 ± 2.0	9.4 ± 3.5	<0.0001
BUN mg/dL	51.2 ± 22.5	62.2 ± 21.2	0.002
Hemoglobin mg/dL	12.1 ± 1.5	11.9 ± 1.2	0.38
Calcium mg/dL	9.1 ± 0.8	9.2 ± 0.8	0.28
Phosphorus mg/dL	4.4 ± 1.1	5.6 ± 1.9	<0.0001
PTH ng/L	186 ± 139	388 ± 268	<0.0001
Geriatric Depression Scale	3 ± 3	5 ± 3	0.0008

Abbreviations are: CHF, congestive heart failure; PVD, peripheral vascular disease; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone.

characteristics are shown in Table 1 stratified by CKD status (CKD vs. ESRD). The mean age of all subjects was 62.5 ± 14.3 years. For subjects with CKD, the mean estimated GFR was 26.6 ± 11.5 mL/min/1.73 m<sup>2</sup>. Subjects with ESRD were more likely to be female, nonwhite, and less likely to have graduated high school. Subjects with ESRD also had a higher prevalence of congestive heart failure, and a trend toward more diabetes mellitus. As expected, there were significant differences in blood pressure and serum concentrations of creatinine, urea nitrogen, phosphorus, and parathyroid hormone between the ESRD and CKD groups.

### Scores on KDQOL-CF and 3MS

Median scores on the KDQOL-CF were 73 (range 0–100) for ESRD subjects, and 87 (range 20–100) in CKD subjects ( $P < 0.0001$ ). Eleven percent of subjects with ESRD and 26% of subjects with CKD had scores at the test ceiling on the KDQOL-CF. Only one subject with ESRD, and no subjects with CKD, had KDQOL-CF scores at the test floor. Median scores on the 3MS were 86 (range 45–99) for subjects with ESRD, and 94 (range 60–100) for subjects with CKD ( $P < 0.0001$ ). Six percent of subjects with CKD, and no subjects with ESRD, had scores at the test ceiling on the 3MS; no subjects had scores at the test floor.

There was a modest direct correlation between the summary KDQOL-CF score and 3MS score ( $r = 0.31$ ,  $P = 0.0001$ ). Item 3 querying symptoms of confusion was most strongly correlated with 3MS score ( $r = 0.34$ ,  $P < 0.0001$ ). The KDQOL-CF was more strongly correlated with the GDS ( $r = -0.56$ ,  $P < 0.0001$ ) than with the 3MS. Among subjects with CKD, KDQOL-CF scores were inversely correlated with benzodiazepine use, serum phosphorus, and calcium × phosphorus product, and directly correlated with years of education and serum albumin (Table 2). Among subjects with ESRD, KDQOL-CF scores were inversely correlated with the GDS, benzodiazepine use, and stroke, and directly correlated with beta-blocker use.

### Predictors of the KDQOL-CF score

Table 3 shows the final multivariable model predicting the KDQOL-CF score. ESRD status, stroke, peripheral vascular disease, benzodiazepine use, higher serum phosphorus, and lower serum albumin concentrations were associated with lower KDQOL-CF scores. Beta-blocker use and additional education were associated with higher KDQOL-CF scores. The associations of education and albumin with KDQOL-CF scores were dependent on ESRD status. No other ESRD × covariate interaction terms were statistically significant, suggesting a relatively uniform association by stage of kidney disease. The model explained 42% of the variance in KDQOL-CF score.

Since depression and cognitive function are closely linked, we fit companion models including the GDS score. With addition of the GDS, 52% of the variation in KDQOL-CF was explained. The parameter coefficients and  $P$  values were essentially unchanged, except that the fixed effect of serum albumin ( $P = 0.07$ ) and the ESRD × education interaction term ( $P = 0.06$ ) were no longer statistically significant by the  $P < 0.05$  criterion.

### Bland-Altman plot and ROC curve

A Bland-Altman plot suggested systematic differences between KDQOL-CF scores and 3MS scores (Fig. 1). Those with low 3MS scores tended to overestimate cognitive function on the KDQOL-CF, whereas those with high 3MS scores tended to underestimate cognitive function on the KDQOL-CF. Considering a 3MS <80 as indicative of cognitive impairment, a KDQOL-CF cut-point of 33 correctly classified the largest number of subjects (83%). The specificity of the cut-point at 33 was 98%, but the sensitivity was only 15% (Fig. 2). If the KDQOL-CF cut-point were raised to 60, 76% of subjects were correctly classified, with an acceptable specificity of 82% and a much higher sensitivity of 52%. The performance characteristics varied slightly by ESRD status. Among ESRD subjects, a cut-point of 60 had a specificity of 69% and a sensitivity of 57%. Among CKD subjects, a cut-point of

**Table 2.** Correlates of kidney disease Quality of Life Cognitive Function score stratified by chronic kidney disease (CKD) versus end-stage renal disease (ESRD) status

CKD			ESRD		
Variable	Correlation coefficient	P value	Variable	Correlation coefficient	P value
Benzodiazepine use	-0.35	0.002	Geriatric Depression Scale	-0.54	<0.0001
Albumin	0.30	0.007	Benzodiazepine use	-0.40	0.0003
Phosphorus	-0.30	0.008	Stroke	-0.31	0.005
Calcium × Phosphorus	-0.24	0.04	Beta-blocker use	0.23	0.04
Education	0.24	0.03			

**Table 3.** Multivariable predictors of Kidney Disease Quality of Life Cognitive Function score

Variable	$\beta \pm SE$	P value
ESRD	79.95 ± 26.92	0.003
Benzodiazepine use	-22.43 ± 4.59	<0.001
Stroke	-9.75 ± 3.12	0.002
PVD	-8.49 ± 3.31	0.01
Phosphorus per mg/dL	-2.87 ± 0.87	0.001
Albumin per mg/dL	10.44 ± 3.59	0.004
Beta-blocker use	8.81 ± 2.75	0.002
Education per year	3.76 ± 1.12	0.001
Albumin × ESRD	-14.77 ± 4.93	0.003
Education × ESRD	-2.86 ± 1.40	0.04
Intercept	11.32 ± 21.35	0.60

Note: model  $R^2 = 0.42$ ;  $\beta$ , linear regression coefficient, SE, standard error.

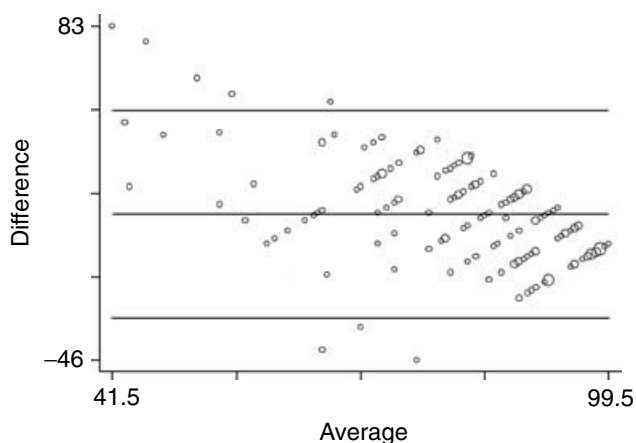
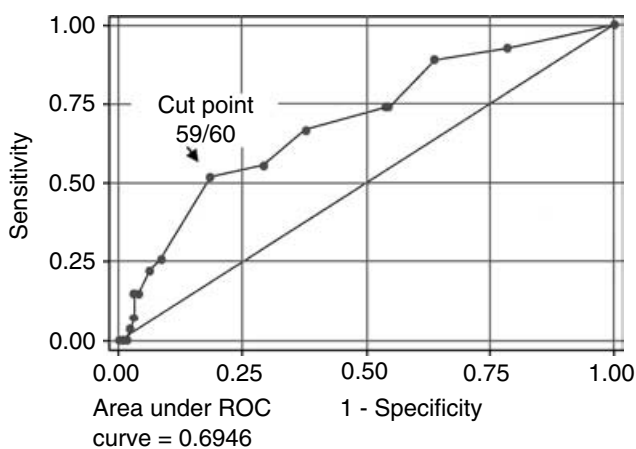
60 had a higher specificity of 92%, but a lower sensitivity of only 33%. Raising the cut-point to 80 in subjects with CKD improved the sensitivity to 56%, with a somewhat lower specificity of 83%.

### Comparing alternative screening strategies

Employing a screening strategy of 3MS testing only in patients with a KDQOL-CF score <60 enhanced the positive predictive value (PPV) and slightly decreased the negative predictive value (NPV) compared to a strategy of screening with the 3MS in all patients (Table 4). For example, if the prevalence of dementia were 10%, prescreening with the KDQOL-CF increased the PPV from 77% to 91%, and decreased the NPV from 99% to 94%. Such a strategy would miss 44 additional cases of dementia, and would avoid additional (perhaps unnecessary) testing in 786 patients per 1000 patients screened. Assuming formal cognitive function testing costs \$20, a strategy that included prescreening with the KDQOL-CF would result in a cost savings of \$15,720 per 1000 patients screened. The benefits of prescreening diminished somewhat as the estimated prevalence of dementia increased.

### DISCUSSION

Effectively identifying patients with cognitive impairment requires an accurate screening tool that can be easily implemented in clinical practice. In this study, we assessed the validity of the KDQOL-CF subscale, a simple self-administered questionnaire, with the 3MS, a

**Fig. 1.** Bland-Altman plot of average Kidney Disease Quality of Life Cognitive Function and 3MS scores versus difference in scores. Horizontal bands represent mean difference  $\pm 2$  SD.**Fig. 2.** Receiver operating characteristics (ROC) curve for Kidney Disease Quality of Life Cognitive Function Scale (3MS <80 as gold standard).

measure of global cognitive function used widely in epidemiologic studies [13, 14]. Our results suggest the KDQOL-CF is a valid instrument for assessing cognitive function.

We identified several significant predictors of self-assessed cognitive impairment by the KDQOL-CF, including a number of factors and/or conditions associated

**Table 4.** Positive and negative predictive values for strategies of dementia screening

Dementia prevalence	Strategy 1 3MS testing in all			Strategy 2 KDQOL-CF followed by 3MS if positive			Additional dementia cases missed <sup>a</sup>	Additional tests avoided <sup>a</sup>
	PPV	NPV	False negatives <sup>a</sup>	PPV	NPV	False negatives <sup>a</sup>		
2.5%	44%	99%	2	69%	99%	13	11	812
5%	61%	99%	5	82%	97%	26	21	803
7.5%	71%	99%	7	87%	96%	42	35	795
10%	77%	99%	9	91%	94%	53	44	786
15%	84%	98%	14	94%	91%	79	66	769
20%	88%	98%	18	96%	88%	105	87	752

Abbreviations are: 3MS, Modified Mini-Mental State Exam; KDQOL-CF, Kidney Disease Quality of Life Cognitive Function Scale; PPV, positive predictive value; NPV, negative predictive value. Note: assuming 3MS cut-point <80 has sensitivity of 91% and specificity of 97% and KDQOL-CF cut-point <60 has sensitivity 52% and specificity 82%.

<sup>a</sup>Per 1000 patients screened.

with vascular disease, such as stroke, peripheral vascular disease, hyperphosphatemia, and hypoalbuminemia. The relation between hypoalbuminemia and self-assessed cognitive function varied by stage of kidney disease, suggesting malnutrition is a much stronger predictor of cognitive impairment in ESRD versus CKD. Drugs were also related to KDQOL-CF scores. Specifically, beta-blockers were associated with higher, and benzodiazepines associated with lower, KDQOL-CF scores. There was a non-significant association between beta-blocker use and 3MS score ( $P = 0.07$  after adjusting for age, sex, race, and education). In contrast, there was no association between benzodiazepine use and 3MS score ( $P = 0.57$ ). There was no association between the use of opiates or antidepressants and 3MS, KDQOL-CF, or GDS scores.

Interestingly, there were no associations among age, sex, and race and the KDQOL-CF score (explaining less than 1% of the variation), in contrast to the 3MS, where demographics account for 15% of the score's variation. The absence of age, sex, and race biases in the KDQOL-CF may be advantageous. If confirmed in larger studies, this characteristic of the KDQOL-CF could prove very useful in socioeconomically and ethnically diverse populations with CKD and ESRD. The dominant effects of age and race on the 3MS and other objective tests of cognitive function have lessened enthusiasm for their widespread use in screening for dementia [15, 16].

Despite only modest correlation between scores on the KDQOL-CF and 3MS, the KDQOL-CF accurately classified 76% of subjects using a cut-point of 60 with reasonable sensitivity and specificity. Exploratory analysis suggested an alternate cut-point of 33 had high specificity for diagnosing cognitive impairment. The largest discrepancies between the two instruments occurred at the extremes, such that the KDQOL-CF underestimated impairment at the lowest 3MS scores, and overestimated impairment at the highest 3MS scores. One would expect these discrepancies with most self-administered instruments when compared with objective non-self-administered tests. Persons with poorer cognitive func-

tion may not recognize their own limitations. In contrast, persons with little or no cognitive impairment may interpret decrements in function (possibly related to physical disability) as decrements in cognition. Thus, optimal use of the KDQOL-CF in clinical practice may be as the first step in a staged evaluation, or in selected patients with risk factors for cognitive impairment. Such an approach would maximize efficiency, targeting labor-intensive formal cognitive function testing and associated resources toward those with a high likelihood of impairment.

Indeed, a strategy of performing 3MS testing only in those with KDQOL-CF scores <60 would result in considerable improvement in the PPV of dementia screening with relatively little change in the NPV over a wide range of prevalence estimates. Although we did not consider the downstream costs of missing a case of dementia with these screening strategies (or the considerable costs of a comprehensive dementia evaluation), prescreening would substantially reduce unneeded formal cognitive function testing. If the prevalence of dementia in persons with CKD and ESRD were over 25% or more than twice the age-matched prevalence in the general population, prescreening would provide less incremental benefit over 3MS testing alone.

There are several limitations of this study. We used scores on the 3MS rather than clinical diagnosis of dementia as the gold standard. The presence of cognitive impairment is associated with an increased risk of dementia and mortality in the general population [17, 18]. However, longitudinal studies of cognitive impairment in CKD and ESRD are lacking; thus, whether the presence of cognitive impairment, and by extension, low 3MS scores, carry the same prognosis in persons with kidney disease is unknown. We did not include a control group in the current study. However, age-, race-, and education-matched normative data for the 3MS are available from published sources [19–21]. Each instrument was administered only once, although the reliability of both the 3MS and KDQOL-CF has previously been reported to be high [4, 9].

We used the GDS, rather than the more widely used BDI, to adjust for depressive symptoms because of the brevity of the GDS. In addition, although not specifically validated in persons with CKD, its use in persons with cognitive impairment is well accepted [11]. The strong correlation between the GDS and KDQOL-CF suggests overlap between depressive symptoms and cognitive impairment symptoms. Alternatively, the two conditions may frequently coexist in persons with CKD and ESRD. Because a more comprehensive depression evaluation was not performed, this finding deserves further study before firm conclusions can be reached. Our CKD subjects were predominantly male, reflecting the large ambulatory nephrology clinic population at one of the study sites (San Francisco Veterans Affairs Medical Center). We had relatively few CKD patients with an estimated GFR  $>45$  mL/min/1.73 m<sup>2</sup>. Thus, these results may not be generalizable to persons with mild CKD. Finally, our study population, while demographically similar to the United States ESRD population, may represent a more highly functional population than average.

The optimal time for administering cognitive tests in subjects with ESRD is not known. Studies examining temporal fluctuations in cognitive performance are difficult to interpret due to differences in study design. Some studies suggest cognitive performance 24 hours after dialysis is better than nondialyzed ESRD subjects [22], and not different than medical controls [23]. In a recent study of hemodialysis and peritoneal dialysis subjects, the authors found significant decrements in the cognitive performance of hemodialysis subjects at 67 hours, but not 24 hours, postdialysis [24]. In contrast, cognitive performance in peritoneal dialysis subjects was unchanged, or in some cases, slightly improved. Others have found no evidence of temporal changes in cognitive function [25]. Moreover, whether testing should be conducted on or off dialysis has not been resolved. In the current study, we chose to test subjects during hemodialysis for several reasons. First, the largest study of cognitive function in hemodialysis patients performed cognitive function testing during hemodialysis, thus permitting direct comparison to our population's test results [1]. Second, testing for all patients were standardized to a midweek hemodialysis day, minimizing potential fluctuations due to uremic symptoms. Finally, although the optimal timing is debatable, administration of the 3MS during dialysis is clinically most practical. Thus, we hoped to mimic the realities of clinical practice in the current study.

## CONCLUSION

We assessed the validity of the KDQOL-CF subscale using measured global cognitive function on the 3MS as the gold standard. Our results provide support for use of the KDQOL-CF as a screening tool to assess cognitive

impairment in patients with CKD and ESRD, and should facilitate comparisons of cognitive function among different patient groups in epidemiologic studies utilizing the KDQOL-CF. Further studies are needed to determine whether a two-tiered diagnostic approach, or use of additional instruments, could improve the accuracy of assessing cognitive function in persons with ESRD and CKD.

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