The Montreal Cognitive Assessment (MoCA) - A Sensitive Screening Instrument for Detecting Cognitive Impairment in Chronic Hemodialysis Patients

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Abstract

Background: Chronic kidney disease (CKD) patients undergoing hemodialysis (HD) therapy have an increased risk of developing cognitive impairment and dementia, which are known relevant factors in disease prognosis and therapeutic success, but still lack adequate screening in clinical routine. We evaluated the Montreal Cognitive Assessment (MoCA) for suitability in assessing cognitive performance in HD patients in comparison to the commonly used Mini-Mental State Examination (MMSE) and a detailed neuropsychological test battery, used as gold standard.

Methods: 43 HD patients and 42 healthy controls with an average age of 58 years, were assessed with the MoCA, the MMSE and a detailed neuropsychological test battery, covering the domains of memory, attention, language, visuospatial and executive functions. Composite scores were created for comparison of cognitive domains and test results were analyzed using Spearman’s correlation and linear regression. Cognitive dysfunction was defined using z-score values and predictive values were calculated. Sensitivity and specificity of the MoCA were determined using receiver operating characteristic (ROC) analysis.

Results: HD patients performed worse in all cognitive domains, especially in memory recall and executive functions. The MoCA correlated well with the detailed test battery and identified patients with cognitive impairment with a sensitivity of 76.7% and specificity of 78.6% for a cut-off value of \( \leq 24 \) out of 30 points. In the detailed assessment executive functions accounted significantly for performance in the MoCA. The MMSE only discriminated weakly between groups.

Conclusions: The MoCA represents a suitable cognitive screening tool for hemodialysis patients, demonstrating good sensitivity and specificity levels, and covering executive functions, which appear to play an important role in cognitive performance of HD patients.

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Introduction

The association of cognitive impairment and a higher incidence of dementia in patients with chronic kidney disease (CKD) has been increasingly acknowledged over the last few years [1–3] and represents an important issue in an already vulnerable population. The prevalence of cognitive impairment in chronic hemodialysis (HD) patients has been estimated at 30–80% [4–7]. In addition to being associated with cerebrovascular disease and potentially other types of brain injury [8], cognitive impairment may jeopardize treatment adherence by affecting the efficiency of every-day tasks, including correct medication and dietary rules [9]. Moreover, cognitive impairment is a significant predictor of mortality in HD patients [5].

The call for early detection of cognitive impairment in patients with CKD has yet to be translated to everyday clinical practice. The necessity has, however, been voiced in earlier studies and the use of short and easy-to-apply cognitive screening tools has been suggested [5,10]. The Montreal Cognitive Assessment (MoCA) [11] is a screening test for cognitive impairment that covers major
cognitive domains including episodic memory, language, attention, orientation, visuospatial ability and executive functions, while remaining brief and easy to administer. It is generally considered superior to the well-established Mini-Mental State Examination (MMSE) screening test [12,13], since the MoCA not only assesses executive functioning, which may be particularly important in the CKD population [14,15], but also presents a higher sensitivity for mild cognitive impairment. Accordingly, the MoCA has been evaluated and found to be an adequate screening tool in various clinical populations, e.g. Alzheimer’s dementia (AD) [16], cerebral small vessel disease [17], and other medical conditions such as cardiovascular disease [18], as well as being able to discriminate between mild cognitive impairment and elderly controls [19]. Recently, the MoCA was also recommended as a standardized approach to cognitive assessment in patients undergoing HD [20]. Therefore our primary goal was to further evaluate the MoCA as a brief screening tool for cognitive impairment in HD patients in comparison to a comprehensive cognitive testing. To achieve this, the ability to distinguish between HD patients with and without cognitive impairment, the sensitivity, specificity and predictive values of the MoCA were assessed. Additionally, psychometric criteria such as concurrent and criterion validity of performance on the MoCA, a comprehensive neuropsychological test battery and the standard brief cognitive screening test MMSE were evaluated.

Subjects and Methods

Ethics Statement

The research project was carried out in accordance with the latest version of the Declaration of Helsinki and approved by the ethics committee of the Medical Faculty of the RWTH Aachen University in Germany (EK 179/11). All participants gave informed, written consent before participating.

Study population

Between February 2012 and March 2013, forty-eight patients on hemodialysis treatment were recruited from the Division of Nephrology of the RWTH Aachen University Hospital in Germany and three community based dialysis centers in the Aachen region. Forty-two matching healthy controls of varied intellectual and educational level, but without specific experience in neuropsychology, were recruited from the community and staff of the RWTH Aachen University. All participants with a history of neurological or psychiatric disease were excluded. In two cases of severe visual or motor impairment, specific tasks were not administered and therefore considered missing values. These cases included one patient with residual eye sight of 30% due to diabetic retinopathy and glaucoma and one patient with a disabling hand tremor.

Clinical and demographic data

Medical history and demographic data were gained via self-report and/or from medical records. Patients’ clinical data included medical history, current medication, CKD etiology, dialysis vintage, serum values of sodium, potassium, hemoglobin, hematocrit, creatinine, pH value and blood sugar and were obtained from routine clinical blood samples taken at the beginning of each dialysis treatment. The duration of dialysis treatment, ultrafiltration volume, pre-dialysis blood pressure values and intradialytic hypotensive episodes, defined as systolic blood pressure \(< 90\) mmHg and/or diastolic blood pressure \(< 50\) mmHg, were collected from the dialysis protocols. Cardiovascular risk factors, including nicotine consumption, body mass index (BMI), serum cholesterol and high blood pressure were rated using the SCORE risk charts of the European Society of Cardiology [21] using the low risk chart for the German population. Hypertension was defined as the prescription of antihypertensive medication. Comorbidities were quantified using the Charlson Comorbidity Index (CCI) [22] corrected for dialysis [23], or age in the healthy control group [22].

Neuropsychological testing

The neuropsychological test battery was administered to all subjects on a dialysis-free day by a psychologist or trained assistants. It consisted of two cognitive screening tests, the MoCA and the MMSE, as well as a detailed cognitive test battery that evaluated memory, language, attention, visuospatial ability and executive functions. As participants were partaking in a cross-sectional observational study with a repeated-measures design [24], previously validated alternate versions of the MoCA [25], as well as from other tests, were used to avoid practice effects. For all patients and controls the same order of test administration was used. The alternate versions of tests were contra-balanced in a pseudo-randomized order. Although all patients and controls underwent two rounds of testing, only the data of the first assessment was used in the current analyses and therefore not all participants completed the exact same version of all tests. Testing was performed in a quiet room with a low distraction level, but in cases of reduced mobility, testing was also performed in patients’ hospital rooms. For the order of test administration, view List S1 in File S1.

The MoCA [11] is a brief screening tool assessing visuospatial and executive functions, attention, short-term memory, language and orientation, has been translated and adapted into several languages and is available freely on the Internet [http://www.mocatest.org]. It includes tasks such as trail making test – part B, cube copying, clock drawing, naming, digit span backwards and forwards, serial subtraction, selective attention, sentence repetition, phonemic word fluency, verbal abstraction, a 5-word learning and delayed recall task, and spatial and temporal orientation. Completion time is approximately 10 to 15 minutes and a maximum of 30 points can be obtained.

The ability of the MoCA to screen for cognitive impairment in HD patients was to be evaluated through the comparison to a well-known screening test, the MMSE, and a detailed neuropsychological test battery. Given that our emphasis lay on the evaluation of the MoCA, detailed group analyses, such as correlation analysis, were not performed with the MMSE and the detailed neuropsychological battery.

The MMSE is a ten-minute screening test including questions to spatial and temporal orientation, immediate and delayed recall, language ability and oral command comprehension, serial subtraction and tasks to visuospatial ability. Here the German adaptation was used for all participants [12].

A more detailed analysis of the cognitive domains and psychometric characteristics, such as sensitivity, specificity and concurrent validity, of the MoCA was achieved by comparison to a detailed neuropsychological test battery. In the detailed neuropsychological test battery, verbal memory was examined using the California Verbal Learning Test (CVLT) [26], a word list recall task, and non-verbal memory was assessed with the Medical College of Georgia Complex Figures (MCCGF) test [27]. Attention was evaluated through a computer-based cued and uncued reaction time (phasic and intrinsic alertness) task [28] and digit span forwards. Processing speed and executive functions were assessed using the Trail Making Task (TMT) forms A and B [29], phonemic and semantic word fluency [30], digit span backwards
deviation (SD) below the norm and severe cognitive impairment in cognitive domains of the MoCA. For further analysis, cognitive dysfunction could be classified as mild cognitive impairment and for 19 patients (46%) as severe cognitive impairment.

Based on the median of z-scores of the individual tests, we calculated standard z-scores for each cognitive test, using the healthy control group as the reference group and without replacing missing values. No significant differences could be identified between groups in respect to visuospatial tasks, naming, level of attention (as tested in the letter cancellation and number subtraction tasks) or temporal and spatial orientation.

In the patient group there was a negative association between the MoCA total score and age (r = −.38, p < .05), which was not found in the control group. There was a positive association between the MoCA and education (r = .28, p < .01) within the MoCA and education. From the association analysis between clinical variables and performance on the MoCA, only the CCI score for dialysis patients correlated negatively with the MoCA total scores (r = −.53, p < .001), indicating that patients with a higher comorbidity score achieved lower results in the MoCA.

Performance on the detailed neuropsychological test battery

In the detailed neuropsychological testing, patients performed worse than the control group in all cognitive domains (Table 2). Patient performance was worse in tasks such as immediate and delayed verbal and visual memory, semantic and phonemic word fluency, as well as performance on the TMT, reaction-timed alertness and the Stroop interference task. Cognitive dysfunction was identified in 29 patients (70%), whereby for 10 patients (24%) cognitive dysfunction could be classified as mild cognitive impairment and for 19 patients (46%) as severe cognitive impairment.

Correlation analysis showed that the composite scores of the MoCA and the test battery correlated in the domains of executive functions (r = .60, p < .001) and memory (r = .53, p < .001), whereas the attention, language and visuospatial composites revealed no significant association. The MoCA and the MMSE total scores showed a moderate positive correlation (r = .54, p < .001).

Association between the MoCA and the detailed neuropsychological assessment

Linear regression analysis revealed that the composite score including executive functions tasks explained 39% (β = 0.62,
Table 1. Demographic and health characteristics.

| Demographics                  | Patients     | Controls    | p\(^{e}\) |
|-------------------------------|--------------|-------------|-----------|
| Age                           | 58.3±13.9    | 57.9±11.8   | .96       |
| Gender Male 52.1% (25)        | Male 47.6% (20) |            | .67       |
| Education (years)             | 12.0 (2.0)   | 13.0 (3.3)  | .01       |
| Comorbidities                 |              |             |           |
| BMI                           | 24.4 (6.7)   | 25.2±3.8    | .71       |
| Hypertension                  | 83.3% (40)   | 33.3% (14)  | <.001     |
| Diabetes                      | 45.8% (22)   | 4.8% (2)    | <.001     |
| Nicotine consumption          | 25.0% (12)   | 7.1% (3)    | .02       |
| Hypercholesterolemia          | 31.3% (15)   | 0%          | <.001     |
| Cardiovascular Score (ESC - SCORE) | 1.0 (4.0)   | -           |           |
| Charlson Comorbidity Index (CCI\(^{a}\)) | 4.0 (3.0)   | -           |           |
| Hemodialysis                  |              |             |           |
| Dialysis Vintage (months)     | 36.0 (47.0)  | -           | -         |
| Time on dialysis (hours)      | 4.0 (0.0)    | -           | -         |
| Ultrafiltration volume (l)    | 1.2 (2.1)    | -           | -         |
| Etiology of renal disease     |              |             |           |
| Diabetic nephropathy          | 27.1% (13)   | -           | -         |
| Glomerulonephritis and systemic diseases | 27.1% (13) | - | - |
| Vascular (hypertensive) kidney disease | 14.6% (7) | - | - |
| Other causes\(^{b}\)          | 12.5% (6)    | -           | -         |
| Polycystic kidney disease     | 10.4% (5)    | -           | -         |
| Unknown                       | 8.3% (4)     | -           | -         |
| Secondary diseases            |              |             |           |
| Renal anemia                  | 38.5% (20)   | -           | -         |
| Secondary hyperparathyroidism | 34.6% (18)   | -           | -         |
| Renovascular hypertension     | 19.2% (10)   | -           | -         |
| Kidney transplant in medical history | 13.5% (7)   | -           | -         |
| Medication                    |              |             |           |
| Antihypertensive Medication (total number) | 3.0 (4.0) | 0.0 (0.0) | <.001 |
| ACE* inhibitors               | 37.2% (16)   | 7.1% (3)    | <.001     |
| Beta blockers                 | 67.4% (29)   | 16.7% (7)   | <.001     |
| Calcium channel blockers      | 48.8% (21)   | 7.1% (3)    | <.001     |
| Angiotensin receptor blockers | 20.9% (9)    | 4.8% (2)    | .03       |
| Alpha-1 blockers              | 25.6% (11)   | 0%          | <.001     |
| Adrenergic alpha agonists     | 23.3% (10)   | 0%          | <.001     |
| Direct vasodilators           | 9.3% (4)     | 0%          | .04       |
| Diuretics                     | 46.5% (20)   | 4.8% (2)    | <.001     |
| Antidiabetics\(^{c}\)         | 37.2% (16)   | 2.4% (1)    | <.001     |
| Thyroid drugs                 | 30.2% (13)   | 7.1% (3)    | .01       |
| Psychostimulant drugs\(^{d}\) | 23.3% (10)   | 0%          | .02       |
| Analgesics                    | 16.3% (7)    | 2.4% (1)    | .01       |
| Glucocorticoids               | 25.6% (11)   | 0%          | <.001     |

Notes. Values are presented as mean ± SD for normally distributed continuous variables, median (interquartile range) for non-normally distributed continuous variables and % (N) for percentages.

\(^{a}\) History of cerebral disease found in two cases;

\(^{b}\) Other causes include progression of acute kidney disease due to post-operative infections, urologic reflux diseases, analgesic medication;

\(^{c}\) Including oral antidiabetics and insulin therapy;

\(^{d}\) Psychoactive drugs include antipsychotics, antidepressants, anticonvulsives and drugs containing L-DOPA;

\(^{e}\) p-value of nonparametric Mann-Whitney-U test for independent samples;

\(^{f}\) ACE = Angiotensin Converting Enzyme.

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\[ R^2 = 0.39, p < 0.001 \] of the variance in the MoCA and the non-executive functions composite score explained 34\% \( (R^2 = 0.34, p < 0.001) \). Together, executive and non-executive functions accounted significantly for overall performance on the MoCA \( (R^2 = 0.44, p < 0.001) \), while the covariates age \( (R^2 = 0.07, p < 0.05) \) and education \( (R^2 = 0.05, p < 0.05) \) only marginally affected variance in performance. Sleepiness and fatigue did not show a significant effect on cognitive performance, yet high scores on the depression scale had a mild effect \( (R^2 = 0.13, p < 0.001) \).

### ROC analysis and predictive values

The ROC analysis disclosed an optimal cut-off for the MoCA at \( \leq 24 \) points \( (R^2 = 0.34, p < 0.001) \). Together, executive and non-executive functions accounted significantly for overall performance on the MoCA \( (R^2 = 0.44, p < 0.001) \), while the covariates age \( (R^2 = 0.07, p < 0.05) \) and education \( (R^2 = 0.05, p < 0.05) \) only marginally affected variance in performance. Sleepiness and fatigue did not show a significant effect on cognitive performance, yet high scores on the depression scale had a mild effect \( (R^2 = 0.13, p < 0.001) \).

### Discussion

Here we demonstrate that the MoCA is a valid and well-suited screening tool for cognitive impairment in HD patients. The MoCA was capable of discriminating between HD patients with and without cognitive impairment, as defined by performance on a comprehensive neuropsychological test battery, presenting good sensitivity and specificity levels, as well as a good concurrent validity. In contrast, the MMSE revealed only a weak group discriminative power.

Our main results confirm that the MoCA is able to reliably identify cognitive impairment in CKD patients undergoing hemodialysis. We could establish an optimal cut-off of \( \leq 24 \) points out of a 30 points maximum, which is lower than the cut-off value of \( \leq 26 \) described in the original data collected in a population of patients with AD and mild cognitive impairment (MCI) [11]. Given that cut-off values are population specific [39], several other studies have determined lower values in different populations, e.g. a cut-off of 23.5 in a population with MCI [19] and of 21-22 in a population with cerebral small vessel disease [17]. With a good sensitivity (76.67) and specificity (78.57) our findings are consistent with previous research, where the MoCA’s sensitivity in detecting cognitive impairment ranged from 56\% to 100\%, while specificity varied between 29\% and 87\%, depending on the study population [11,18,40]. More specifically, in the detection of vascular cognitive impairment the MoCA presented a specificity of 68\% and lower sensitivity of 56\% in a population with silent cerebral infarction [40].
The detailed cognitive assessment showed a distinct difference in achievement between groups. This tendency was equally present in the MoCA results, whereas performance did not differ between groups for the MMSE. The prevalence of cognitive impairment of 70% in this cohort, as classified by the testing battery, corresponds to the levels of cognitive dysfunction stated in

### Table 2. Neuropsychological test results.

| Neuropsychological domain/test | Test results | Mann-Whitney-U |
|-------------------------------|--------------|---------------|
|                               | N  | Patients | N  | Controls | p     | Effect size r |
| **Screening tests**           |    |          |    |          |       |               |
| Montreal Cognitive Assessment (MoCA) | 43 | 24.0 (4.0) | 42 | 28.0 (3.0) | <.001* | –.573         |
| Mini Mental State Examination (MMSE) | 41 | 29.0 (2.0) | 41 | 29.0 (2.0) | .03   | –.247         |
| **Attention**                 |    |          |    |          |       |               |
| Test of attentional performance (TAP) | 35 | 276.0 (73.0) | 39 | 243.0 (60.0) | .03   | –.262         |
| TAP Phasic Alertness          |    |          |    |          |       |               |
| Digit span forwards           | 41 | 7.0 (2.0)  | 42 | 8.0 (4.0)  | .002  | –.338         |
| **Verbal Memory**             |    |          |    |          |       |               |
| California Verbal Learning Test (CVLT) | 37 | 50.0 (16.0) | 42 | 61.0 (15.0) | <.001* | –.415         |
| CVLT Total learned            |    |          |    |          |       |               |
| CVLT Interference             | 37 | 5.0 (4.0)  | 42 | 6.0 (3.0)  | .04   | –.232         |
| CVLT Immediate Recall         | 37 | 9.0 (6.0)  | 42 | 12.5 (6.0) | .002  | –.327         |
| CVLT Delayed Recall           | 37 | 11.0 (6.0) | 42 | 12.5 (4.0) | .002  | –.341         |
| CVLT Recognition (correct)    | 37 | 16.0 (2.0) | 42 | 16.0 (1.0) | .60   | –.095         |
| **Non-verbal Memory**         |    |          |    |          |       |               |
| Medical College of Georgia Complex Figures (MCGCF) | 36 | 17.8 (12.4) | 42 | 28.0 (13.5) | .004  | –.325         |
| MCGCF Immediate Recall        |    |          |    |          |       |               |
| MCGCF Delayed Recall          | 36 | 16.5 (12.6)| 41 | 28.0 (13.5)| .008  | –.266         |
| **Visuospatial**              |    |          |    |          |       |               |
| MCGCF Copy                    | 36 | 31.5 (8.5) | 42 | 34.0 (2.0) | .02   | –.264         |
| Visual Object Space Perception (VOSP) Incomplete letters | 40 | 20.0 (1.0) | 42 | 20.0 (1.0) | .39   | –.095         |
| **Language**                  |    |          |    |          |       |               |
| Boston Naming Test            | 39 | 15.0 (0.0) | 42 | 15.0 (0.0) | .06   | –.207         |
| **Executive**                 |    |          |    |          |       |               |
| Semantic word fluency         | 39 | 28.0 (17.0)| 42 | 39.5 (12)  | <.001*| –.409         |
| Phonemic word fluency         | 39 | 14.0 (9.0) | 42 | 21.0 (10.0)| <.001*| –.492         |
| Digit span backwards          | 41 | 6.0 (2.0)  | 42 | 6.0 (1.0)  | .25   | –.126         |
| **Stroop Test**               |    |          |    |          |       |               |
| Colour reading                | 33 | 35.0 (14.0)| 41 | 32.0 (6.0) | .01   | –.288         |
| Colour naming                 | 33 | 54.0 (17.0)| 41 | 47.0 (12.0)| .01   | –.285         |
| Interference                  | 33 | 96.0 (49.0)| 41 | 86.0 (28.0)| .02   | –.269         |
| Trail Making Test (TMT) Part A | 39 | 51.0 (38.0)| 42 | 32.5 (15.0)| <.001*| –.512         |
| Trail Making Test (TMT) Part B | 38 | 110.5 (96.0)| 42 | 73.5 (37.0)| <.001*| –.427         |
| **Depression**                |    |          |    |          |       |               |
| Hospital Anxiety and Depression Scale (HADS) | 42 | 11.0 (9.0) | 42 | 4.5 (7.0)  | <.001*| –.373         |
| Total score                   | 42 | 6.0 (5.0)  | 42 | 3.0 (5.0)  | .02   | –.266         |
| Anxiety                       | 42 | 4.5 (5.0)  | 42 | 1.0 (4.0)  | <.001*| –.428         |
| **Fatigue**                   |    |          |    |          |       |               |
| Epworth Sleepiness Scale (ESS) | 42 | 6.5 (5.0)  | 42 | 5.5 (5.0)  | .05   | –.217         |
| Fatigue                       | 21 | 5.0 (5.0)  | 34 | 2.0 (4.0)  | .02   | –.318         |

Notes. Test results presented as median (IQR). *p*-values with Bonferroni correction for multiple comparisons. Significant difference at p<.001. Effect sizes, r: small (0.10–0.29), medium (0.30–0.49), large (>0.50). doi:10.1371/journal.pone.0106700.t002
previous studies with larger cohorts of dialysis patients [5,7]. The results presented by the MMSE equally match previous characterizations of CKD patient cohorts, where the level of cognitive dysfunction was measured at 30% when only using the MMSE as a diagnostic measure [4,6]. The prevalence of cognitive dysfunction in this patient cohort appears, therefore, to be similar to previous findings and allows the assumption that it is representative for this population. Correlation analysis showed a strong relationship between MoCA results and the detailed neuropsychological testing, especially for memory and executive functions, which may suggest good diagnostic ability in these areas. There remains, nevertheless, a limitation for interpretation of correlation between tests, due to a partial overlap between tasks that may affect association analysis.

The profile of cognitive deficits found in our patient population, including significant impairment in executive functions, processing speed, word fluency and short-term verbal and non-verbal memory capacity, stands in accordance to previous findings [3,41] and similar results have been associated with vascular disease as a potential cause of cognitive impairment in HD patients [15,42]. Given the high prevalence of executive dysfunction in CKD patients and our findings that performance in the MoCA was predominantly dependent on executive ability (as has been described before [43]), we believe that this is one of the strengths of the MoCA in comparison to other generally used cognitive screening instruments. In this regard, the focus of the MoCA on executive functions is believed to be a reason why it is far superior to the MMSE in particular clinical populations, given that the MMSE lacks the assessment of such cognitive domains and has a tendency to produce ceiling effects [43,44].

This may be particularly important considering that the majority of previous studies with CKD patients have included the MMSE as the preferred cognitive screening test [42] or even the only cognitive instrument [45,46]. Methodologically, the fact that the MoCA and the MMSE subtests partially overlap may limit considerations of their differential discriminant validity, but it should be noted that the original rationale behind MoCA, through the inclusion of a wider range of cognitive domains than the MMSE, especially considering the executive functions, already entails some advantage in terms of sensitivity and specificity.

Based on our current results, and as others have suggested [8], the MMSE may be inadequate for this population and may underestimate the extent of cognitive impairment. Nevertheless, a recent study showed that the MMSE was able to detect progression of cognitive impairment in HD patients [47], but may be less suited for early detection of mild cognitive deficits in other populations [48]. In a similar fashion, another screening test, the Kidney Disease Quality of Life Cognitive Function (KDQOL-CF), was found to be inadequate for assessing cognitive function in HD patients, due particularly to the lack of executive tasks [49].

A procedural advantage of the MoCA over the MMSE may also be the availability of alternative versions [25], which enables longitudinal testing while avoiding practice effects. Longitudinal testing is especially interesting in HD patients, as fluctuations in cognitive performance during the hemodialysis cycle have been identified [20,50].

Concerning predictive clinical variables, we were able to show that high comorbidity rates were associated with lower performance on the MoCA, which opens the question of the etiological factors that may contribute to cognitive impairment in HD patients. Previous studies have reported that comorbidity, especially cardiovascular disease, is a predictor of cognitive impairment in HD patients [51,52].

The results of our study also provide evidence that the MoCA is a more sensitive measure of cognitive function compared to the MMSE, which lacks the assessment of executive functions and has a tendency to produce ceiling effects [43,44]. The MoCA, on the other hand, shows good levels of sensitivity and specificity, as well as an overall greater AUC than the MMSE, which suggests that it may be a more appropriate screening tool for detecting cognitive impairment in HD patients.

### Table 3. Criterion (cut-off) values and coordinates of the ROC curves of MoCA and MMSE.

| Screening test | Criterion | Sensitivity | 95% CI | Specificity | 95% CI |
|---------------|-----------|-------------|--------|-------------|--------|
| MoCA          | ≤22       | 46.67       | 28.3–65.7 | 78.57       | 49.2–95.3 |
|               | ≤24*      | 76.67       | 57.7–90.1 | 78.57       | 49.2–95.3 |
|               | ≤25       | 86.67       | 69.3–96.2 | 57.14       | 28.9–82.3 |
|               | ≤26       | 90.00       | 73.5–97.9 | 35.71       | 12.8–64.9 |
| MMSE          | ≤27       | 37.93       | 20.7–57.7 | 83.33       | 51.6–97.9 |
|               | ≤28*      | 55.17       | 35.7–73.6 | 75.00       | 42.8–94.5 |
|               | ≤29       | 89.66       | 72.6–97.8 | 33.33       | 9.9–65.1 |

Note: *optimal cut-off score based on maximal sensitivity and specificity using the receiver operating characteristic (ROC) analysis.

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**Figure 2. ROC curves for the cognitive screening tests Montreal Cognitive Assessment and Mini-Mental State Examination.** The receiver operating characteristics curves for the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE) illustrate the discriminative capacity of each of the screening tests, displaying their individual sensitivity, specificity and area under the curve (AUC). The MoCA shows good levels of sensitivity and specificity, as well as an overall greater AUC than the MMSE, while the MMSE presents a high specificity and relatively low sensitivity. Notes: MoCA = Montreal Cognitive Assessment; MMSE = Mini-Mental State Examination; AUC = Area under the curve. doi:10.1371/journal.pone.0106700.g002
or mediator role that different comorbidities play in cognitive impairment in such a heterogeneous group.

Other interesting findings were that although levels of fatigue and sleepiness were higher in the patient group, which is in line with statements from earlier studies that fatigue is a common problem in HD patients [5,51], we did not find fatigue or sleepiness to influence cognitive performance. It is possible that conducting the assessment on a dialysis-free day avoided post-dialytic fatigue and enabled a more objective assessment of cognitive performance. In contrast, a significant association was found between lower performance and higher levels of depressive symptoms, which supports assumptions that depression may be a relevant co-factor for poor cognitive performance and should also be screened for in CKD patients [52–54]. This is especially important when taking into account the prevalence of depression of up to 25% in HD patients [51] and the number of associated problems, including lower quality of life and higher hospitalization and mortality rates [54].

Further strengths of our study include the detailed neuropsychological testing, which enabled a comprehensive evaluation of cognition and the interpretation of concurrent validity, as well as the inclusion of a healthy control group that served as reference for cognitive performance. The MoCA has recently been suggested for cognitive screening in a small cohort of HD patients showing similar results for MoCA with an average of 24 points before dialysis [20], yet the emphasis was put on testing environment and variation in performance during the HD cycle and only the MMSE was used as a reference. This is therefore a valuable addition, as there is no precedent data on the psychometric analysis of the MoCA in comparison to detailed cognitive analysis and clinical characterization of a moderate size sample of HD patients. Limitations are, nevertheless, the relatively small sample size, which makes it difficult to generalize our findings. Although our results allow the assumption of cognitive impairment in HD patients below the cut-off value of 24 points in the MoCA, a clear distinction between MCI and dementia cannot be made in this study, due to the exclusion of patients with dementia. Equally, one must mention again the concordance of tests used in the screening tests and the detailed test battery that may influence correlation analyses in form of a positive bias. Our decision to enter education as a covariate rather than using the education correction for MoCA values, for which there is no normative data for a German population, may be seen as inadequate as there is a slight difference in educational levels between groups. Furthermore, data on subjective cognitive impairment, and clinical data were limited, the latter especially for the control sample, reducing our ability to assess variables, such as cardiovascular risk factors and hemodialysis parameters, in more detail. Further research is warranted to confirm these findings in a larger patient sample, possibly including non-dialysis CKD patients to further define indications for cognitive screening with the MoCA.

Cognitive impairment is a highly relevant clinical factor for disease progression in HD patients, possibly also affecting daily-life activities, thereby impeding adherence to therapeutic regimes and compromising quality of life. With the aims of improving individual outcome and optimizing the utilization of medical care resources, a brief cognitive screening test for HD patients is an essential addition to clinical practice. We presume that the MoCA, granted its validity and psychometric characteristics, is very suitable for this purpose, as it represents a multi-dimensional screening test that not only includes relevant tasks for the assessment of the HD population, but also offers the possibility of longitudinal measurements with available alternate versions.

In conclusion, the MoCA is an adequate screening tool for a brief bedside evaluation of global cognitive performance in HD patients and has the potential to assist in the daily clinical care of HD patients.
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