American Journal of Transplantation 25 (2025) 1059–1069

Contents lists available at ScienceDirect

American Journal of Transplantation

journal homepage: www.amjtransplant.org

Original Article

Development and validation of the Neuro-Score: a specific scale to detect and monitor cognitive impairment in kidney or liver transplant recipients

Francesc Moreso [1,2,*], José Antonio Pons Miñano [3], Ana Sánchez Fructuoso [4], Carlos Jacas [1], Montserrat Alegret [5,6], Montserrat Ferrer [7,8,9], Jordi Colmenero [10], Amado Andrés Belmonte [11], Verónica López Jiménez [12], Sonia Pascual [13,14,15], Auxiliadora Mazuecos Blanca [16], Ana Paz Ventura Galiano [17], Alba Cachero [18], Antonio Rivero [19], Marta Crespo [20], Antonio Cuadrado [21], Arantxa Caballero Marcos [22], Maria Luisa Gonzalez Diéguez [23], Carolina Almohalla Alvarez [24], Naroa Maruri Kareaga [25], Jose M. Alamo Martinez [26], Giulia Pagano [10], Enriqueta Nuño Santana [11], Irina B. Torres [1], Isabel Pérez Flores [4], Juana Alonso-Titos [12], María Rodríguez-Soler [13,14], Laura Martinez Alarcón [3,27], Teresa María García Álvarez [16], Isabel Beneyto Castelló [17], Emma Gonzalez-Vilatarsana [18], Francesc Miras [28], Miguel Angel Gómez Bravo [26,29]

[1] *Hospital Universitari Vall d'Hebrón, Barcelona, Spain*
[2] *Universitat Autònoma de Barcelona, Spain*
[3] *Hospital Universitario Virgen de la Arrixaca, Murcia, Spain*
[4] *Hospital Clínico San Carlos, Madrid, Spain*
[5] *Ace Alzheimer Center Barcelona, Universitat Internacional de Catalunya, Barcelona, Spain*
[6] *Networking Research Center on Neurodegenerative Diseases (CIBERNED), Instituto de Salud Carlos III, Madrid, Spain*
[7] *Hospital del Mar Research Institute, Barcelona, Spain*
[8] *CIBERESP ISCIII, Spain*
[9] *Universitat Pompeu Fabra, Barcelona, Spain*
[10] *Liver Unit, Hospital Clínic, IDIBAPS, CIBERehd, University of Barcelona, Barcelona, Spain*
[11] *Hospital Universitario 12 de Octubre, Madrid, Spain*
[12] *Nephrology Department, Hospital Regional Universitario de Málaga, National Network for Kidney Research RICORS2040 RD21/0005/0012, Instituto Biomédico de Investigación de Málaga (IBIMA), and Universidad de Málaga, Málaga, Spain*
[13] *Liver Unit, Hospital General Universitario Dr. Balmis, Alicante, Spain*
[14] *ISABIAL, Alicante, Spain*
[15] *CIBERehd, Madrid, Spain*

Abbreviations: KMO, Kaiser-Meyer-Olkin; MMSE, mini-mental state examination; MoCA, Montreal Cognitive Assessment.

* Corresponding author. Hospital Universitari Vall dHebŕon, Barcelona, Spain, Pg. de la Vall d'Hebrón, 119, Horta-Guinardó, 08035 Barcelona, Spain.
E-mail address: francescjosep.moreso@vallhebron.cat (F. Moreso).

https://doi.org/10.1016/j.ajt.2025.01.031
Received 28 July 2024; Received in revised form 17 January 2025; Accepted 18 January 2025
Available online 28 January 2025

[16] Hospital Universitario Puerta del Mar, Cádiz, Spain
[17] Hospital Universitari i Politècnic La Fe, Valencia, Spain
[18] Hospital Universitari de Bellvitge, Barcelona, Spain
[19] Hospital Universitario Ntra. Sra. de Candelaria, Santa Cruz de Tenerife, Spain
[20] Hospital del Mar, Barcelona, Spain
[21] Gastroenterology and Hepatology Department, Clinical and Translational Research in Digestive Diseases, Valdecilla Research Institute (IDIVAL), Marqués de Valdecilla University Hospital, Santander, Spain
[22] Hospital General Universitario Gregorio Marañón, Madrid, Spain
[23] Hospital Universitario Central de Asturias, Asturias, Spain
[24] Hospital del Río Hortega, Valladolid, Spain
[25] Hospital Universitario de Cruces, Barakaldo, Spain
[26] Hospital universitario Virgen del Rocío
[27] Liver Transplant Unit, IMIB, Murcia, Spain
[28] Trialance SCCL, Barcelona, Spain
[29] Universidad de Sevilla, IBIS, Sevilla, Spain

ARTICLE INFO

Keywords:
cognitive impairment
kidney transplant
liver transplant
scale

ABSTRACT

We created and validated the Neuro-Score, a specific scale to detect and monitor cognitive impairment, including mild stages, in kidney or liver transplant recipients. A qualitative study was conducted to define a preliminary set of 62 items. Item reduction was performed using exploratory factor analysis. Confirmatory factor analysis assessed the adequacy of the factorial solution. The total scores of the Neuro-Score and mini-mental state examination were compared. Responsiveness to change was evaluated from visit 1 (baseline) to 2A (18 months later) and temporal stability from visit 2A to 2B (1-2 weeks later). Factor analysis showed 11 factors with an eigenvalue of >1. Confirmatory factor analysis yielded a logical solution with 1 factor and 11 items that explained 27.9% of the variance. The final model showed satisfactory internal consistency (Cronbach $\alpha = 0.82$). A weak negative correlation was found between Neuro-Score and mini-mental state examination total scores (Pearson $r = -0.12$; $P = .0095$). The Neuro-Score responsiveness to change was demonstrated ($P = .022$). No significant differences in the total score were observed between visits 2A and 2B, supporting the Neuro-Score temporal stability. The Neuro-Score scale is a simple, reliable, self-administered, easy-to-interpret, and consistent 11-item scale to detect and monitor cognitive impairment in kidney and liver transplant recipients.

1. Introduction

Cognitive impairment is prevalent among patients with end-stage renal disease[1] and end-stage liver disease, particularly among older individuals.[2] These deficits are associated with reduced quality of life, increased risk of hospitalization, morbidity, mortality, and longer waitlists for organ transplantation.[3-5] The etiology of cognitive impairment in these populations is multifactorial and commonly affects executive functions, orientation, attention, and memory.[1]

Kidney and liver transplant recipients show better cognitive performance after transplant, although still below that of age-matched control groups.[6-10] Posttransplant cognitive improvement appears highly variable, with postoperative complications, comorbid medical conditions, and exposure to immunosuppressants being the leading causes of residual and long-term cognitive impairment.[5,11–13]

Data on the prevalence of cognitive impairment in kidney and liver transplant recipients are limited. Moreover, prevalence rates vary widely among studies partly due to the heterogeneity in screening tests, follow-up durations, and the lack of cutoff scores for these populations.[5,9,11,14] Early detection of cognitive impairment is crucial for preventing the progression to dementia and minimizing its impact on daily living activities. However, identifying cognitive impairment early can be challenging in clinical practice, mainly because initial symptoms often go unnoticed and commonly used instruments lack the sensitivity to detect mild stages.[15] Despite its high prevalence in transplantation, cognitive impairment remains a relatively overlooked issue in this setting. Routine testing is not typically performed in clinical practice, and no specific instrument to assess cognition has been developed for these patients.[16]

There are several screening tests to detect cognitive impairment that cover different cognitive domains.[12] However, there is an unmet

need for a simple scale specifically designed to detect cognitive impairment in organ transplant recipients, particularly in its early stages. Such a scale should be easy to administer and interpret, allowing for wide adoption in clinical practice. To address this issue, we developed and validated the Neuro-Score, a user-friendly and specific patient-reported outcome measure to detect and monitor cognitive impairment, including mild stages, in kidney and liver transplant recipients receiving immunosuppression.

2. Materials and methods

2.1. Study design

The development and validation of the Neuro-Score scale comprised 2 phases: a cross-sectional qualitative study and a prospective observational study (Fig. 1). The cross-sectional qualitative study aimed to define a preliminary set of items representing cognitive functions to ensure content validity. For this purpose, kidney and liver transplant recipients, as well as a family member, from 2 centers in Spain were interviewed.

To develop and validate the Neuro-Score scale, a multicenter, prospective observational study was conducted at 18 sites in Spain after approval by the Independent Ethics Committee of Hospital Universitari Vall d'Hebrón (Barcelona, Spain). The study was scheduled across 3 visits: visit 1 (baseline), visit 2A (18 ± 6 months after visit 1), and visit 2B (1-2 weeks after visit 2A). All eligible participants attended visit 1; data from two-thirds served to develop the scale (factor analysis) and from the other third to validate the scale (internal consistency and construct validity). Participants were assigned to the scale creation or validation groups using random lists, with information stratified for each center. Stratification by center was only implemented in the randomization of patients into the creation and validation groups to ensure that no single center disproportionately contributed to each phase of the study. As these 2 phases of the study were analyzed separately, accounting for stratification was not needed. At each center, a randomly selected subset of 20% of the patients attended visits 2A and 2B to assess the scale's responsiveness to change and temporal stability (Fig. 1).

At visit 1, patients completed the set of items obtained from the qualitative study and the mini-mental state examination (MMSE; gold standard) in a paper-based format. At visit 2A, patients completed the Neuro-Score scale in electronic format to assess the scale responsiveness to change. At visit 2B, the Neuro-Score scale was completed in electronic format to determine temporal stability (test-retest reliability). The preliminary

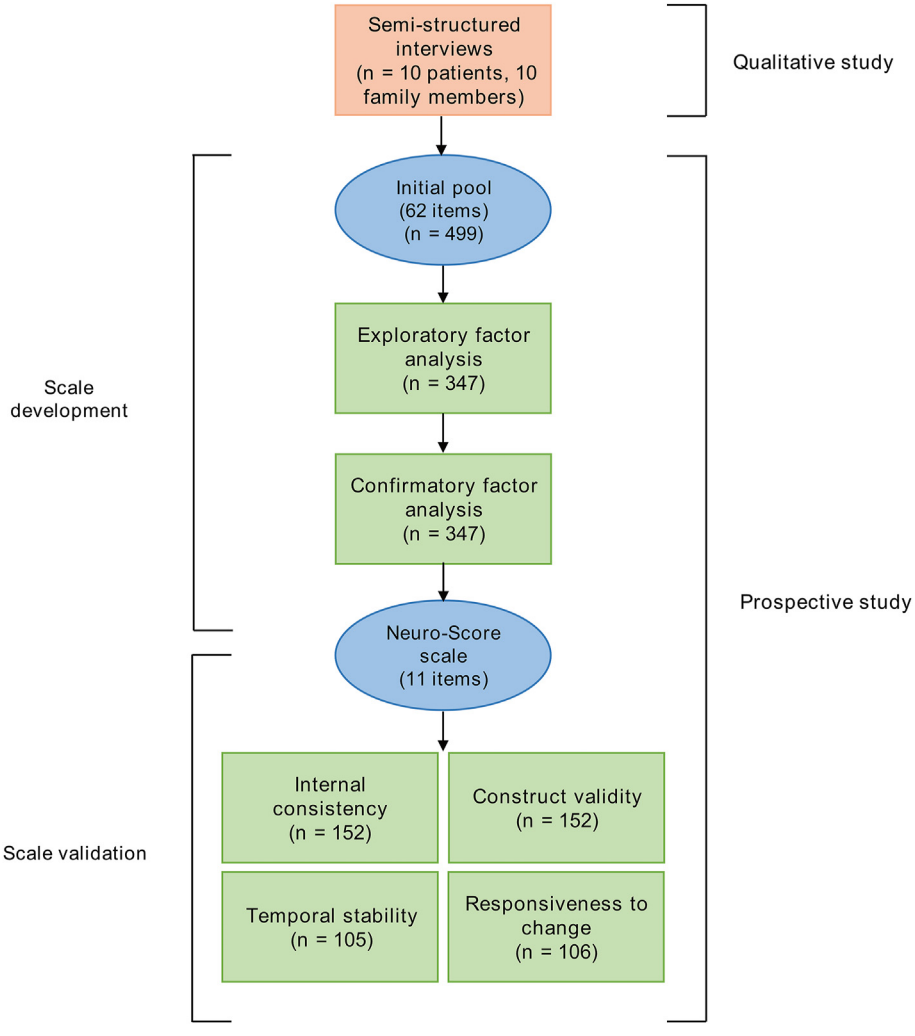

Figure 1. Flowchart showing the study design. The development and validation of the Neuro-Score scale comprised 2 phases: a cross-sectional qualitative study and a prospective observational study. The qualitative study involved 10 participants (5 liver recipients and 5 kidney recipients) and 10 family members. From this qualitative study, the initial pool of items was obtained. Subsequently, 499 patients were involved in the prospective study. Data from two-thirds of them served to develop the scale (factor analysis) and from the other third to validate the scale (internal consistency and construct validity).

pool of items and the MMSE were administered by professionals from each center who were trained for this purpose.

2.2. Participants

2.2.1. Qualitative study

The inclusion criterion for the qualitative study was kidney or liver transplantation within the previous 12 months. Exclusion criteria comprised having any condition that could challenge study assessments, such as psychiatric disorders or language comprehension limitations. Investigators aimed to include participants with diverse levels of formal education and cognitive impairment to ensure a representative and varied sample. Family members of eligible patients were also included.

2.2.2. Prospective study

For the prospective observational study, eligible participants were 60 years or older; who underwent kidney or liver transplantation at least 12 months before the inclusion in the study; with a stable kidney or liver function during the last 3 months; able to read and write; proficient in Spanish (according to the investigator); able to make a videoconference and answer an online questionnaire; and who provided written informed consent. Patients excluded comprised those diagnosed with a neurologic or psychiatric disease (except alcoholism, anxiety, or depression) or another systemic disease other than the reason for the study, which causes cognitive impairment; who were recipients of a double organ transplantation; had an active posttransplant neoplasm; had a recent ($\leq$3 months) posttransplant cardiovascular event; had an MMSE score of $<$10; diagnosed with sensory, visual, hearing, or locomotor deficits that, according to the investigator, may interfere with study procedures or any serious systemic disease, and who were not able to complete the procedures of the study.

2.3. Initial pool of items

A semistructured interview guide was developed based on study objectives and previous literature (Table 1).[17] Semistructured interviews were administered by 2 psychologists (C.S., V.A.) and 1 neuropsychologist (E.L.) with experience in qualitative research. Each interview was conducted via videoconference and lasted around 60 minutes. In the first part of the interview, only the patient was present. The second part was conducted with the patient's family member. All interviews were audio-recorded and fully transcribed to identify a preliminary set of items that were representative of cognitive impairment perceptions. Additionally, an expert committee of 4 investigators (2 on kidney transplant and 2 on liver transplant) selected a group of relevant items based on published scales used in other clinical populations. Data were examined using interpretative phenomenological analysis.[18] The first part of the analysis used the patient's own words to identify themes. Subsequently, themes were connected deductively to develop categories of cognitive complaints, described with textual examples. Repeated reading, grouping, and summarizing of themes integrated participants' shared experiences, with data collection ceasing once no new information emerged, indicating data saturation. The initial pool of items was derived from the semistructured interviews with patients and family members and a literature review. Subsequently, the items were reviewed by experts in cognitive impairment and kidney and liver transplantation.

Table 1
Semistructured interview guide.

Area	Description
Cognitive functioning and perceived impact	Participants were asked to describe the cognitive function they perceived as most affected and its impact on activities of daily living based on their experience
Cognitive functioning and perceived impact	Participants were asked to describe other affected cognitive functions and their impact on activities of daily living based on their experience[a]
Maintained or improved performance on cognitive domains	Participants were invited to identify cognitive domains they perceived as maintained or improved after the transplant
Cognitive complaints	Cognitive complaints were assessed based on the Cognitive Complaint Interview (Thomas-Anterion et al,[17] 2006)
Emotional impact of the transplant	Participants were asked to report changes in mood related to the transplant
Additional comments	Participants were encouraged to share any additional insights or comments not covered by the previous areas

[a] This question was asked repeatedly until no additional cognitive difficulties were reported.

2.4. Neuro-Score development

Item performance of the initial pool of items was evaluated through item-item correlations and by calculating its mean, median, and response distribution. An exploratory factor analysis was used to reduce them while retaining the most relevant information. To assess conceptual and measurement model, factor analysis with Varimax rotation was performed. Eigenvalues were used to determine the number of underlying dimensions, and factor loadings of at least 0.6 were set to identify items to be retained. A significant Bartlett test of sphericity and a Kaiser-Meyer-Olkin (KMO) of $>$0.7 were set to confirm that the data matrix was suitable for factor analysis.

Data were factorized to include a minimum number of factors with a satisfactory model fit. Confirmatory factor analysis was

used to assess the adequacy of the factor solution. The following cutoffs for model fit statistics were considered satisfactory: a comparative fit index and a Tucker and Lewis index of >0.90, a χ^2 of <0.3, and a root mean square error of approximation of <0.08.

2.5. Neuro-Score validation

The Neuro-Score scale was validated by assessing the following psychometric properties: reliability based on internal consistency and temporal stability, construct validity, and responsiveness to change. Internal consistency reliability measures the extent of correlation among items within a scale by assessing item-total correlations, and it was evaluated by Cronbach α coefficient.[19]

Construct validity measures the extent to which a scale adequately reflects the theoretical construct it is intended to measure.[20] To measure construct validity, Pearson correlation analyses were carried out between Neuro-Score and MMSE total scores. The MMSE was chosen as it is considered the gold standard for measuring cognitive impairment, being extensively used both in clinical practice and in research studies. This paper-based scale consists of 30 items, with a total score of up to 30 points and higher scores indicating better cognitive status.[21]

Responsiveness to change measures the ability of the scale to detect a change in cognitive impairment over time where a known change has occurred.[22] The mean total score of the Neuro-Score was calculated at visit 1 (baseline) and visit 2A (18 ± 6 months later), and Pearson correlation coefficients were determined. Differences between the 2 visits were analyzed using the Student test for paired data. The following anchor question was used as an external criterion of responsiveness: "Compared to visit 1, how do you currently feel? Much better, better, the same, worse, much worse". The analysis of variance procedure was used to determine whether changes in the Neuro-Score from visit 1 to visit 2A derived from differences in the cognitive status of patients measured with the anchor question.

Reproducibility measures the extent to which participant responses remain stable over time.[20] The agreement between test (visit 2A) and retest (visit 2B) scores was tested in a subsample of patients who completed the scale 1 to 2 weeks apart. Only subjects who reported no changes in cognitive status in the anchor question were included in the analysis of reproducibility (test-retest reliability), which was assessed by estimating the intraclass correlation coefficient.

Criterion validity of the Neuro-Score was assessed by receiver operating characteristic curves, with the aim to identify an optimal cutoff point for discriminating between patients with or without cognitive impairment. For this purpose, a cutoff of 24 points on the MMSE was used as the gold standard. This cutoff score has been largely used to identify patients with suspected cognitive impairment or dementia and has been validated in the Spanish population.[23,24]

2.6. Statistical analyses

The sample size was calculated to select a subsample of patients representing 66.6% of the population for the development and 33.3% for the validation phases. For the development phase, 150 patients per group (kidney and liver transplant) were needed, resulting in 300 patients. For the assessment of reproducibility (test-retest reliability), data from 100 randomized patients included at baseline were needed. A larger sample size to compensate for follow-up losses was unnecessary because patient recruitment for developing and validating the scale was competitive.

Continuous variables were described by mean and SD, median and IQR, and categorical variables by numbers and percentages. The level of statistical significance was set at $P < .05$ for all analyses. Statistical analyses were performed using the SAS software (SAS Institute) for Windows, version 9.4.

3. Results

3.1. Participants

The qualitative study included 10 patients (6 men and 4 women, mean age =70.9 [SD =5.4] years) and 10 family members. Five of them underwent a liver transplant and 5 a kidney transplant. Patients had varied levels of formal education and cognitive impairment. Educational levels ranged from basic literacy skills (ability to read and write) to high school education. Cognitive impairments observed among participants encompassed various domains, including language and memory.

The prospective study consisted of 499 patients from 18 Spanish centers. Of them, 354 (71.1%) were men. The mean age in the overall population was 67.4 (SD =5.4) years. The most frequent comorbidities were hypertension (329 patients, 66.2%), hypercholesterolemia (197 patients, 39.6%), and diabetes mellitus (189 patients, 38.0%). The mean MMSE score in the overall population at baseline was 28.4 (SD =1.8). Of the patients included, 254 (51.1%) underwent a liver transplant and 243 (48.9%) a kidney transplant. Seven (1.4%) patients had a rejection episode within the previous 12 months (Table 2).

3.2. Neuro-Score development

The qualitative study identified an initial pool of 62 items. Questions could be rated on a 5-point Likert scale with the following response options: never, rarely, occasionally, frequently, and almost always. A total of 499 patients completed this set of questions in a paper-based format.

Exploratory factor analysis (n = 347) showed 13 factors with an eigenvalue of >1 (Fig. 2). Two items were removed because they were redundant questions. The 11 factors represented 65.8% of the variance. The KMO of 0.947 and the Bartlett test of sphericity of <0.0001 indicated sampling adequacy for factor analysis.

To determine factor structure, data were factorized as follows: a solution without fixed factors, and solutions with 1 or 2 factors retained. All models showed satisfactory explanatory power in the confirmatory factor analysis, but a single-factor solution was selected because of its greater construction simplicity. The final model was a scale with 11 items grouped into 1 dimension with a KMO of 0.869 and a Barlett test of sphericity of <0.0001. This 11-item model explained 27.9% of the variance, with items loadings

Table 2
Demographic and clinical characteristics of study participants.

	Total N = 499	Development cohort (n = 347)	Validation cohort (n = 152)
Age (y), mean (SD)	67.4 (5.4)	67.3 (5.4)	67.7 (5.2)
Median (IQR)	66.8 (63.7-70.4)	66.5 (63.7; 70.4)	67.7 (63.2; 70.7)
Sex (men), n (%) (n = 498)	354 (71.1)	247 (71.4)	107 (70.4)
Ethnic group (White), n (%) (n = 497)	492 (99.0)	341 (98.8)	151 (99.3)
Type of transplant, n (%)			
Liver	254 (50.9)	176 (50.7)	78 (51.3)
Kidney	245 (49.1)	171 (49.3)	74 (48.7)
MMSE score, mean (SD)	28.4 (1.8)	28.36 (1.75)	28.42 (1.85)
Comorbidities, n (%) (n = 497)	417 (83.9)	288 (83.2)	129 (85.4)
Hypertension	329 (66.2)	227 (65.4)	102 (67.1)
Hypercholesterolemia	197 (39.6)	133 (38.3)	64 (42.1)
Diabetes mellitus	189 (38.0)	127 (36.6)	62 (40.8)
Hypertriglyceridemia	74 (14.9)	53 (15.3)	21 (13.8)
Other	221 (44.5)	163 (47.0)	58 (38.2)
Glomerular filtration rate (CKD-EPI, mL/min/1.73 m^2), mean (SD)	59.4 (20.7)	58.43 (20.9)	61.46 (20.1)
Immunosuppression trough levels, mean (SD)			
Tacrolimus (ng/mL) (n = 416)	5.8 (2.6)	5.91 (2.7)	5.46 (2.2)
Liver (n = 201)	5.0 (2.8)	5.2 (3.0)	4.7 (2.2)
Kidney (n = 215)	6.5 (2.1)	6.6 (2.2)	6.2 (1.8)
Mycophenolate (μg/mL) (n = 47)	2.9 (2.1)	2.8 (2.1)	3.52 (2.1)
Liver (n = 18)	4.2 (2.2)	3.8 (2.3)	5.1 (2.0)
Kidney (n = 29)	2.2 (1.7)	2.2 (1.8)	2.2 (1.0)
Everolimus (ng/mL) (n = 52)	4.6 (1.7)	4.8 (1.7)	4.3 (1.6)
Liver (n = 16)	3.58 (1.9)	3.8 (2.1)	2.9 (1.0)
Kidney (n = 36)	5.1 (1.4)	5.4 (1.2)	4.6 (1.6)
Sirolimus (ng/mL) (n = 23)	6.3 (2.1)	6.1 (2.0)	6.5 (2.2)
Liver (n = 4)	5. 5 (1.4)	5.5 (1.7)	5.3 (0)
Kidney (n = 19)	6.5 (2.2)	6.3 (2.2)	6.7 (2.3)

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; MMSE, mini-mental state examination.

ranging from 0.41 to 0.63 (Table 3). Confirmatory factor analysis showed a satisfactory fit of the final model, as evidenced by a comparative fit index of 0.88, a Tucker and Lewis index of 0.92, a χ^2 of 2.88 ($P < .0001$), and an root mean square error of approximation of 0.06.

The final Neuro-Score scale is presented in Table 4. The total score, ranging from 0 to 44, is derived from the direct sum of scores from the 11 questions, with higher scores indicating worse cognitive status. In our population, the mean total score at baseline (n = 491) was 10.8 (SD =6.5) and ranged from 0 to 32 points. The total score distribution was homogeneous across all score ranges, without concentrating on any specific point (Fig. 3).

The mean completion time of the scale was 3.7 minutes at visit 2A (n = 108) and 2.5 minutes at visit 2B (n = 109).

3.3. Neuro-Score validation

The Neuro-Score internal consistency (n = 152) was satisfactory, with a Cronbach α of 0.82 for the 11-item scale and item-total correlations ranging from 0.38 to 0.67 (Table 5). Construct validity of the Neuro-Score was confirmed in a subsample of 152 patients by the correlation with the MMSE ($r = -0.12$; $P = .0095$). The Neuro-Score responsiveness to change was demonstrated (n = 106), with a significant increase from 11.3 at visit 1 to 13.3 at

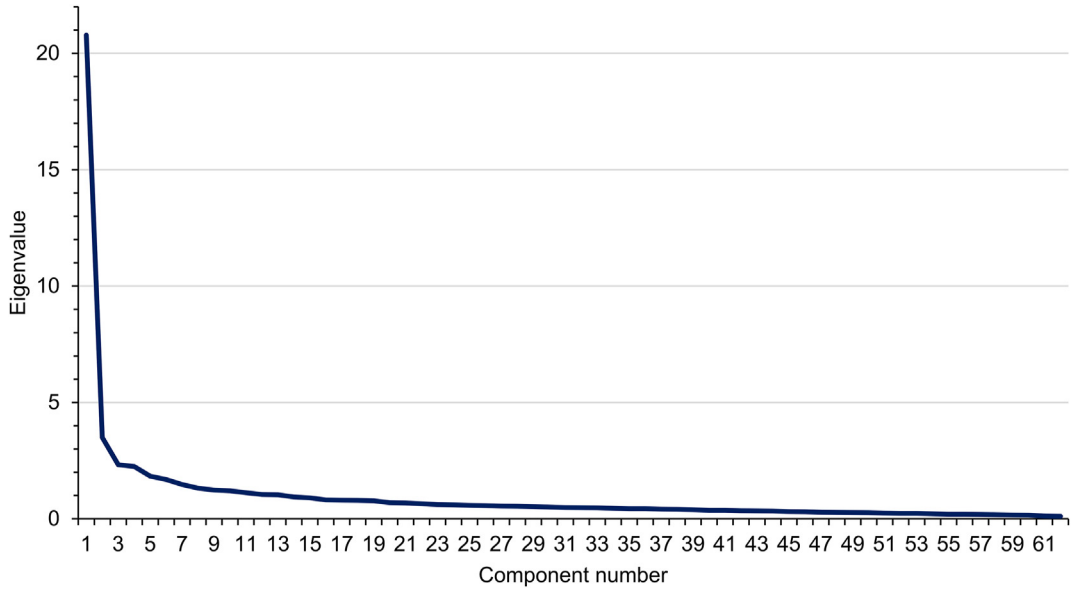

Figure 2. Scree plot of eigenvalues of components from factor analysis.

Table 3
Factor loadings of items in the confirmatory factor analysis.

Item performance	Factor 1
Item 1	0.41
Item 2	0.43
Item 3	0.43
Item 4	0.48
Item 5	0.56
Item 6	0.63
Item 7	0.56
Item 8	0.50
Item 9	0.61
Item 10	0.55
Item 11	0.58

visit 2A ($P = .022$). The correlation between changes in the Neuro-Score and changes in the anchor question was statistically significant ($P = .0430$). Conversely, no significant differences in the total score were observed between visits 2A and 2B (n = 105; $P = 0.6454$), with a high correlation between both assessments ($r = -0.87$; $P < .0001$). The mean total score was 13.3 at the test and 13.0 at the retest, indicating satisfactory temporal stability. The intraclass correlation coefficient was 0.83.

Figure 4 shows the receiver operating characteristic curve and the area under the curve value for the Neuro-Score. A cutoff of 24 points on the MMSE was used as the gold standard. The optimal Neuro-Score cutoff point to identify subjects with cognitive impairment was 17 (sensitivity =85.8%, specificity =71.4%). The Neuro-Score potential to discriminate between patients with or without cognitive impairment was good, with an area under the curve of 0.73.

4. Discussion

We developed and validated the Neuro-Score, an 11-item self-administered scale to detect cognitive impairment specifically designed for kidney and liver transplant recipients who receive immunosuppression. The Neuro-Score scale demonstrated good internal consistency, temporal stability, construct validity, and responsiveness to change.

Despite the high prevalence of cognitive impairment among organ transplant recipients, there is no specific screening tool tailored to detect cognitive impairment in this population. While current recommendations emphasize the importance of incorporating patient perspectives into health care outcomes in transplantation,[25–28], cognitive deficits are frequently overlooked in clinical practice.[16] Thus, developing a specific and practical instrument to identify and monitor cognitive impairment in organ transplant patients is essential.

Several neuropsychological tests are available to screen for cognitive impairment, but most of them were developed to assess cognitive decline associated with aging and Alzheimer disease.[12] Additionally, some tests may not be optimal for measuring cognition in kidney disease, where vascular factors are believed to play a significant role.[12] Among these scales, the MMSE is one of the most widely used worldwide. This paper-based instrument comprises 30 questions, takes 5 to 10 minutes to complete, and should be administered by trained health care providers.[21] A systematic review found little evidence supporting the MMSE as a reliable standalone test for identifying patients with mild cognitive impairment who could progress to dementia.[29] The Montreal Cognitive Assessment (MoCA) is another frequently used screening test gaining popularity for assessing global cognition in kidney disease.[30] The MoCA requires a mean completion time of 10 minutes, mandatory training, and certification for its administration. Therefore, there exists an unmet need for a brief cognitive function test specifically validated in kidney and liver transplant populations.

Table 4
The Neuro-Score scale.

Item—Spanish (validated)
Con qué frecuencia… (Nunca, Rara vez, Ocasionalmente, Frecuentemente, Casi siempre)
1. le cuesta recordar nombres de personas?
2. se traba al decir algunas palabras?
3. le cuesta recordar cosas que sucedieron hace tiempo?
4. le cuesta hacer sumas y restas sin calculadora?
5. si le interrumpen, tiene dificultades para acordarse de lo que estaba haciendo o diciendo?
6. le cuesta reaccionar ante situaciones imprevistas?
7. se pone nervioso cuando se sale de la rutina de su vida cotidiana?
8. el dolor repercute en su capacidad de atención?
9. siente que tiene cambios de humor?
10. se siente apático?
11 le cuesta orientarse en lugares nuevos?
Item—English (not validated)
How often….. (Never, Rarely, Occasionally, Frequently, Almost always)
1. do you have difficulty remembering people's names?
2. do you stumble over some words when speaking?
3. do you have difficulty remembering things that happened a long time ago?
4. do you struggle to do addition and subtraction without using a calculator?
5. do you have difficulty remembering what you were doing or saying if interrupted?
6. do you have difficulty reacting to unexpected situations?
7. do you get nervous when your daily routine is disrupted?
8. does pain affect your ability to concentrate?
9. do you feel that you have mood swings?
10. do you feel apathetic?
11. do you have difficulty orienting yourself in new places?

To address this need, we developed and validated the Neuro-Score, a specific instrument to detect cognitive impairment in organ transplant recipients. Its development involved data from a large cohort of 499 liver or kidney transplant recipients receiving immunosuppression across 18 sites in Spain. We focused on stable liver and kidney transplant recipients on immunosuppressive therapy to better assess changes in cognitive function over time and examine associations with specific factors, minimizing the variability seen in the pre-transplan period. Our population also comprised language-proficient Spanish speakers to facilitate the self-administration of the scale. We included patients aged 60 years or older, excluding those with an MMSE score of <10. This approach allowed us to focus on individuals more likely to have mild to moderate cognitive impairment, a population often overlooked by current screening tests. Early detection of mild to moderate cognitive impairment may allow the implementation of preventive actions for preserving cognitive function, reducing its impact on quality of life.

The final scale, Neuro-Score, is a self-administered instrument comprising 11 items grouped into a single dimension, enabling its completion in approximately 3 minutes. The Neuro-Score requires no complex instructions, with the same response options provided for all questions. Although the scale relies on patient self-assessments without objectively evaluating cognitive domains, it is intended as a screening and monitoring tool to identify individuals who may need further evaluation with a complete neuropsychological battery. Of paramount importance is its rapid completion time, which can reduce patient burden, optimize health care resource allocation, and facilitate early detection of cognitive impairment. Notably, completion times for kidney transplantation-specific quality-of-life patient-reported outcome measures typically range from 10 to 15 minutes.[25] The Neuro-Score supports unassisted self-reporting and online completion, which can substantially reduce the need for administrative support during completion.[26]

An important finding is that the user-friendly design of the Neuro-Score does not compromise its psychometric properties. The homogeneous distribution of the Neuro-Score across all score ranges in a population with no severe cognitive impairment suggests that the scale can detect slight differences in cognitive impairment and monitor individuals without cognitive impairment. This property is particularly valuable for identifying different degrees of cognitive decline, including mild stages, contrasting with the MMSE, which is more suited for advanced stages with a significant functional impairment.[31] This homogeneous distribution also highlights that, despite the statistically significant correlation between MMSE and Neuro-Score total scores indicating that both scales measure the same construct, the weak correlation between both instruments could suggest that each scale addresses specific stages of the cognitive impairment spectrum. In this context, future studies are needed to assess the correlation between the Neuro-Score and other neuropsychological measures able to detect mild cognitive impairment, such as the MoCA.

The Neuro-Score responsiveness to change is also key, as this psychometric property enables the evaluative use of instruments to monitor changes over time or assess interventions' effectiveness.[28] Taken together, its psychometric properties suggest the suitability of the Neuro-Score for identifying patients with cognitive impairment and monitoring their progression. However, external validation with other populations is required before it can be adopted into clinical practice.

It is important to emphasize that the Neuro-Score is not intended to be a standalone diagnostic tool, but rather an adjunct to clinical evaluations. By identifying patients who may require further neuropsychological assessment, the Neuro-Score can assist clinicians in making timely referrals for additional testing or interventions. This is particularly important in the context of transplantation, where a significant proportion of recipients are

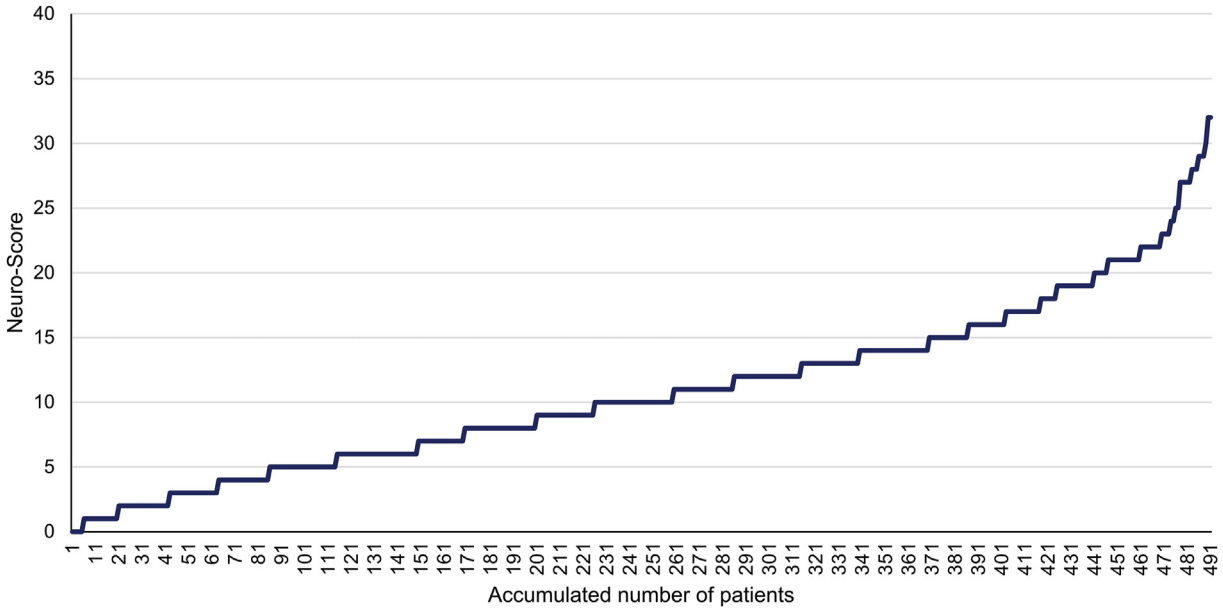

Figure 3. Neuro-Score distribution.

Table 5
Item performance of the Neuro-Score scale.

Item performance	Corrected item-total correlation	Cronbach α if item deleted
Item 1	0.45	0.81
Item 2	0.53	0.80
Item 3	0.45	0.81
Item 4	0.38	0.82
Item 5	0.48	0.81
Item 6	0.44	0.81
Item 7	0.67	0.79
Item 8	0.56	0.80
Item 9	0.45	0.81
Item 10	0.48	0.81
Item 11	0.48	0.81
Neuro-Score (total)		0.82

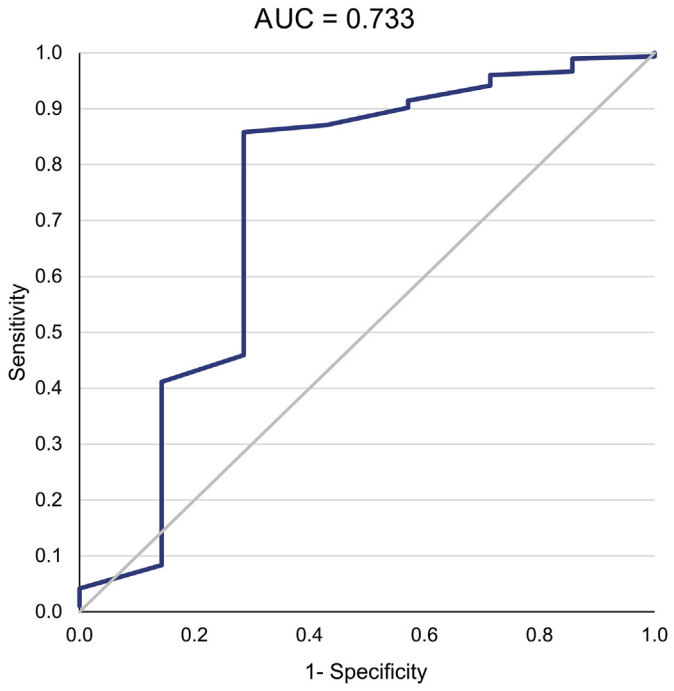

Figure 4. ROC curve and corresponding area under the ROC curve of the Neuro-Score. A cutoff point of 24 on the mini-mental state examination as the gold standard was used to identify patients with cognitive impairment. AUC, Area under the ROC curve; ROC, receiver operating characteristic.

aged 60 years or older, and cognitive impairment is prevalent.[3] Given the high demand on health care services, it is not feasible for specialists to refer all patients with suspected cognitive decline to a neurology unit. With external validation, the Neuro-Score can address this gap by providing an instrument to detect cognitive impairment at early stages. Moreover, the simplicity of the tool could lead to a more efficient use of health care resources.

The next steps for this tool include external validation with other populations, validation in English-speaking populations, comparisons of cognitive status across diverse patient and demographic groups—with a particular focus on comparing kidney and liver transplant recipients—and determining whether specific treatment changes or other factors are associated with cognitive impairment in these populations.

This study presents some limitations that are worth considering. First, the development and validation of the Neuro-Score was based on a population of liver and kidney transplant recipients, limiting its generalizability to recipients of other organs until further validation is conducted. Second, the Neuro-Score is

based on patient's self-assessments without incorporating input from caregivers. This is because incorporating caregiver assessments would have restricted the applicability of the scale to patients who have family members available and willing to provide such input during clinical visits. Third, the exclusion of patients with severe cognitive impairment following the selection criteria limits the use of the Neuro-Score to detect severe cognitive impairment and could also explain its weak correlation with MMSE scores. Fourth, the comparison of the Neuro-Score with the MMSE is limited by its cross-sectional nature. Further studies are needed comparing the longitudinal evolution of the Neuro-Score with changes in the MMSE. Finally, the scale was developed in Spanish, requiring crosscultural adaptation and validation for use in other languages and populations.

Despite these limitations, we developed and validated a brief, reliable, and consistent scale, including data from one of the largest series assessing cognitive impairment in organ transplant patients. Another strength of the study is that the initial item selection was based on semistructured interviews combined with the experience of an expert committee and did not rely only on previous literature, enhancing the ecological validity of the scale.

5. Conclusion

The Neuro-Score scale is a brief, reliable, and consistent 11-item self-administered scale to detect and monitor cognitive impairment, specifically designed for kidney and liver transplant recipients. Its psychometric properties and short completion time are expected to facilitate the implementation of the Neuro-Score scale in clinical practice as a screening tool to detect and monitor cognitive impairment in kidney and liver transplant recipients.

Acknowledgements

The authors thank Carla Granados from Trialance SCCL for providing Medical Writing assistance. JC has been supported by Departament de Recerca i Universitats de la Generalitat de Catalunya (2021-SGR-01331).

Funding

This work was supported by Chiesi España S.A.U.

Declaration of competing interest

The authors of this manuscript have conflicts of interest to disclose as described by *American Journal of Transplantation*. J.C.A. has been a speaker for and received travel grants from Chiesi and Astellas. S.P. has been a speaker for and participated in congresses of Chiesi; participated in congresses and was advisor for Nordic; and speaker for Astellas. A.M.B. has received funding and honorary from Chiesi, GSK, Sandoz, Astellas, Sanofi, Otsuka, and AstraZeneca. G.P. has been speaker for Astella and received travel grants from Chiesi. The remaining authors have no conflict of interest to disclose.

Data availability

Data are available upon request.

ORCiD

Francesc Moreso https://orcid.org/0000-0002-7267-3963
José Antonio Pons Miñano https://orcid.org/0000-0001-5017-7240
Ana Sánchez Fructuoso https://orcid.org/0000-0001-7017-9729
Carlos Jacas https://orcid.org/0000-0002-7023-3657
Montserrat Alegret https://orcid.org/0000-0002-8164-9500
Montserrat Ferrer https://orcid.org/0000-0001-9867-7391
Jordi Colmenero https://orcid.org/0000-0001-6024-8479
Amado Andrés Belmonte https://orcid.org/0000-0003-0238-1364
Verónica López Jiménez https://orcid.org/0000-0002-1793-7065
Sonia Pascual https://orcid.org/0000-0002-4265-5019
Auxiliadora Mazuecos Blanca https://orcid.org/0000-0002-5860-2309
Ana Paz Ventura Galiano https://orcid.org/0000-0002-5105-8726
Alba Cachero https://orcid.org/0000-0002-0010-4534
Antonio Rivero https://orcid.org/0009-0001-9524-0255
Marta Crespo https://orcid.org/0000-0002-1852-2259
Antonio Cuadrado https://orcid.org/0000-0002-1363-864X
Maria Luisa Gonzalez Diéguez https://orcid.org/0000-0003-1098-3891
Carolina Almohalla Alvarez https://orcid.org/0000-0002-7295-0027
Naroa Maruri Kareaga https://orcid.org/0000-0002-2396-3294
Jose M. Alamo Martinez https://orcid.org/0000-0002-4425-7938
Giulia Pagano https://orcid.org/0000-0003-2395-4731
Enriqueta Nuño Santana https://orcid.org/0000-0001-6939-9513
Irina B. Torres https://orcid.org/0000-0003-3304-0810
Isabel Pérez Flores https://orcid.org/0000-0003-4644-1277
Juana Alonso-Titos https://orcid.org/0009-0001-7795-342X
María Rodríguez-Soler https://orcid.org/0000-0001-5555-6418
Laura Martinez Alarcón https://orcid.org/0000-0001-7497-6709
Isabel Beneyto Castelló https://orcid.org/0000-0002-8433-3448
Emma Gonzalez-Vilatarsana https://orcid.org/0000-0003-2092-8714
Miguel Angel Gómez Bravo https://orcid.org/0000-0002-5155-3508

References

1. O'Lone E, Connors M, Masson P, et al. Cognition in people with end-stage kidney disease treated with hemodialysis: a systematic review and meta-analysis. *Am J Kidney Dis*. 2016;67(6):925–935. https://doi.org/10.1053/J.AJKD.2015.12.028.
2. Sorrell JH, Zolnikov BJ, Sharma A, Jinnai I. Cognitive impairment in people diagnosed with end-stage liver disease evaluated for liver transplantation. *Psychiatry Clin Neurosci*. 2006;60(2):174–181. https://doi.org/10.1111/j.1440-1819.2006.01483.x.
3. Murray AM, Knopman DS. Cognitive impairment in CKD: no longer an occult burden. *Am J Kidney Dis*. 2010;56(4):615–618. https://doi.org/10.1053/j.ajkd.2010.08.003.
4. Watanabe K, Watanabe T, Nakayama M. Cerebro-renal interactions: impact of uremic toxins on cognitive function. *Neurotoxicology*. 2014;44:184–193. https://doi.org/10.1016/J.NEURO.2014.06.014.
5. Siddiqui OM, Baskaran AB, Lin KA, et al. Cognitive impairment in liver transplant recipients with a history of cirrhosis: a systematic review. *Transplant Direct*. 2023;9(5):e1479. https://doi.org/10.1097/TXD.0000000000001479.
6. Ozcan H, Yucel A, Avşar UZ, et al. Kidney transplantation is superior to hemodialysis and peritoneal dialysis in terms of cognitive function, anxiety, and depression symptoms in chronic kidney disease. *Transplant Proc*. 2015;47(5):1348–1351. https://doi.org/10.1016/j.transproceed.2015.04.032.
7. Thomas AG, Ruck JM, Shaffer AA, et al. Kidney transplant outcomes in recipients with cognitive impairment: a national registry and prospective

cohort study. *Transplantation*. 2019;103(7):1504–1513. https://doi.org/10.1097/TP.0000000000002431.
8. Campagna F, Montagnese S, Schiff S, et al. Cognitive impairment and electroencephalographic alterations before and after liver transplantation: what is reversible? *Liver Transpl*. 2014;20(8):977–986. https://doi.org/10.1002/lt.23909.
9. Gupta A, Mahnken JD, Johnson DK, et al. Prevalence and correlates of cognitive impairment in kidney transplant recipients. *BMC Nephrol*. 2017;18(1):158. https://doi.org/10.1186/s12882-017-0570-1.
10. Van Sandwijk MS, Ten Berge IJM, Majoie CBLM, et al. Cognitive changes in chronic kidney disease and after transplantation. *Transplantation*. 2016;100(4):734–742. https://doi.org/10.1097/TP.0000000000000968.
11. Nöhre M, Bauer-Hohmann M, Klewitz F, et al. Prevalence and correlates of cognitive impairment in kidney transplant patients using the demtect—results of a KTx360 substudy. *Front Psychiatry*. 2019;10:791. https://doi.org/10.3389/fpsyt.2019.00791.
12. Jurgensen A, Qannus AA, Gupta A. Cognitive function in kidney transplantation. *Curr Transplant Reports*. 2020;7(3):145–153. https://doi.org/10.1007/s40472-020-00284-0.
13. Faravelli I, Velardo D, Podestà MA, Ponticelli C. Immunosuppression-related neurological disorders in kidney transplantation. *J Nephrol*. 2021;34(2):539–555. https://doi.org/10.1007/s40620-020-00956-1.
14. Karakizlis H, Doerr JM, Becker A, et al. Neuropsychological Assessment of Cognitive Impairment in Kidney Transplantation (NAsKiT) and its related risk factors: a study protocol. *J Nephrol*. 2022;35(7):1933–1941. https://doi.org/10.1007/s40620-022-01376-z.
15. Stewart R. Mild cognitive impairment—the continuing challenge of its "real-world" detection and diagnosis. *Arch Med Res*. 2012;43(8):609–614. https://doi.org/10.1016/j.arcmed.2012.10.011.
16. Golenia A, Malyszko JS, Malyszko J. Cognitive impairment and kidney transplantation: underestimated, underrecognized but clinically relevant problem. *Kidney Blood Press Res*. 2022;47(7):459–466. https://doi.org/10.1159/000521907.
17. Thomas-Antérion C, Honoré-Masson S, Laurent B. The cognitive complaint interview (CCI). *Psychogeriatrics*. 2006;6(Suppl 1):S18–S22. https://doi.org/10.1111/j.1479-8301.2006.00129.x.
18. Smith Flowers P, Larkin MJ. *Interpretative phenomenological analysis: theory, method and research*. Sage Publications; 2009:225. https://www.researchgate.net/publication/221670349_Interpretative_Phenomenological_Analysis_Theory_Method_and_Research. Accessed April 3, 2024.
19. Bull C, Byrnes J, Hettiarachchi R, Downes M. A systematic review of the validity and reliability of patient-reported experience measures. *Health Serv Res*. 2019;54(5):1023. https://doi.org/10.1111/1475-6773.13187.
20. The practice of social research, 15th edition. 9780357360767, Cengage. Accessed April 3, 2024. https://www.cengage.com/c/the-practice-of-social-research-15e-babbie/9780357360767/.
21. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189–198. https://doi.org/10.1016/0022-3956(75)90026-6.
22. Revicki DA, Cella D, Hays RD, Sloan JA, Lenderking WR, Aaronson NK. Responsiveness and minimal important differences for patient reported outcomes. *Health Qual Life Outcomes*. 2006;4:70. https://doi.org/10.1186/1477-7525-4-70.
23. Blesa R, Pujol M, Aguilar M, et al. Clinical validity of the "mini-mental state" for Spanish speaking communities. *Neuropsychologia*. 2001;39(11):1150–1157. https://doi.org/10.1016/S0028-3932(01)00055-0.
24. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc*. 1992;40(9):922–935. https://doi.org/10.1111/J.1532-5415.1992.TB01992.X.
25. Wang Y, Snoep JD, Hemmelder MH, et al. Outcomes after kidney transplantation, let's focus on the patients' perspectives. *Clin Kidney J*. 2021;14(6):1504–1513. https://doi.org/10.1093/ckj/sfab008.
26. Breckenridge K, Bekker HL, Gibbons E, et al. How to routinely collect data on patient-reported outcome and experience measures in renal registries in Europe: an expert consensus meeting. *Nephrol Dial Transplant*. 2015;30(10):1605–1614. https://doi.org/10.1093/ndt/gfv209.
27. Hawkins J, Wellsted D, Corps C, et al. Measuring patients' experience with renal services in the UK: development and validation of the Kidney PREM. *Nephrol Dial Transplant*. 2022;37(8):1507–1519. https://doi.org/10.1093/ndt/gfac030.
28. Bull C, Teede H, Watson D, Callander EJ. Selecting and implementing patient-reported outcome and experience measures to assess health system performance. *JAMA Health Forum*. 2022;3(4):e220326. https://doi.org/10.1001/jamahealthforum.2022.0326.
29. Arevalo-Rodriguez I, Smailagic N, Roqué-Figuls M, et al. Mini-Mental State Examination (MMSE) for the early detection of dementia in people with mild cognitive impairment (MCI). *Cochrane Database Syst Rev*. 2021;2021(7):CD010783. https://doi.org/10.1002/14651858.CD010783.pub3.
30. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x.
31. Sewell MC, Luo X, Neugroschl J, Sano M. Detection of mild cognitive impairment and early stage dementia with an audio-recorded cognitive scale. *Int Psychogeriatr*. 2013;25(8):1325–1333. https://doi.org/10.1017/S1041610213000598.