Validity of the Clinical Dementia Rating Scale for the Detection and Staging of Dementia in Brazilian Patients

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Abstract: The aim of this study was to determine the diagnostic value and agreement analyses between Clinical Dementia Rating (CDR) and dementia diagnostic criteria (gold standard), Blessed Dementia Rating scale (BDRS), and Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised (DSM III-R) criteria for severity. In a sample of 343 Southern Brazilian participants, CDR was consecutively assessed in 295 dementia patients (Alzheimer disease, vascular dementia, and questionable) and 48 healthy elderly. The National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable Alzheimer disease and the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN) for probable vascular dementia were the gold standard. A battery of cognitive tests and the Mini Mental State Examination (as a screening test at study entry) were also applied. Sensitivity and specificity were obtained through contingency tables. Validity and reliability were measured through κ coefficient, Kendall b, and percent agreement. CDR agreement among raters was demonstrated by percent agreement. Agreement to gold standard was good ($\kappa = 0.75$), as well as to the Blessed scale ($\kappa = 0.73$), and excellent to the DSM III-R ($\kappa = 0.78$). CDR detection of dementia among healthy elderly or questionable dementia was 86% and 80% sensitive, respectively, and 100% specific for both settings. In conclusion, agreement of CDR global score with the gold standard was good, and diagnostic values were high.

Key Words: dementia, Clinical Dementia Rating Scale, agreement analysis, MMSE, DSM III-R, Blessed Dementia Scale, Brazil

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The Clinical Dementia Rating (CDR) scale, a global dementia staging instrument, developed by the Memory and Aging Project at the Washington University School of Medicine (St Louis, MO)[1] was conceived primarily for use in persons with dementia of the Alzheimer type, or the equivalent probable Alzheimer disease (AD). It has been used to stage other dementing illnesses as well.[2–4]

The CDR score is derived from a standard set of information collected in a clinical instrument that uses other well-known scales for some of its foundation. For example, the collateral source or informant interview incorporates much of the dementia scale of Blessed and colleagues.[5] The clinical protocol incorporates semistructured interviews, of the patient and informant to obtain information sufficient to rate the subject's cognitive performance in 6 domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Without reference to psychometric performance, each domain is rated on 5 levels of impairment: 0 (none), 0.5 (questionable), 1 (mild), 2 (moderate), and 3 (severe). An exception is that personal care is rated on only a 4-point scale: 0 to 3. Using all of the information from the clinical protocol to evaluate decline from the patient's premorbid level of performance, clinical judgment determines the best rating for each domain. The CDR rates only impairment caused by cognitive loss rather than by physical disability or other noncognitive factors. The global CDR is derived from a synthesis of the individual ratings in each of the 6 domains in accordance with established scoring rules.[6] Computer algorithms for these scoring rules have been developed.[7] The global CDR represents a 5-point ordinal scale, where CDR 0 indicates no dementia, and CDR 0.5, 1, 2, and 3 indicate questionable, mild, moderate, and severe dementia. The CDR is thus dichotomous for the presence or absence of dementia (ie, CDR of 0 vs. CDR of 0.5 or greater). A standardized training and reliability protocol also has been developed using videotaped assessments of patients with AD representing each CDR stage (CDR 0 to 3) for the multicenter antidementia drug trials sponsored by the Alzheimer's Disease Cooperative Study.[7]

The CDR scale has been shown to be effectively and reliably applied by nonmedical personnel to identify and

stage dementia.[8] The scale has been widely adapted for clinical research around the world and as a criterion standard in multicenter clinical trials in Alzheimer disease.[9] As the population ages world-wide it will be increasingly important to be able to apply standardized instruments for dementia research in these important emerging populations.

Brazil has the largest population in South America and the largest number of elderly (around 15 million) with an expected increase of over 100% during the next 20 years.[10] Thus application of standard instruments to this population is important for research not only within the context of the emerging elderly of South America, but to compare with other groups around the world.

In this study, we evaluated the accuracy of the CDR for determining and staging dementia (vascular and Alzheimer disease) in relation to diagnostic criteria [gold standards: National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN) and National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)]. As a measure of our Brazilian CDRs validity and reliability we compared it to the diagnostic agreement obtained when patients were independently assigned to a dementia status using NINDS-AIREN and NINCDS-ADRDA criteria. We also examined interrater agreement of CDR assignments and the ability of our CDR ratings to match up to other measures of global dementia severity (eg, mild, moderate, and severe levels) using the Blessed Dementia rating scale (BDRS) and Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised (DSM III-R). We also compared Mini Mental State Examination (MMSE) and other cognitive measures among CDR global scores for convergent validity.

METHODS

Patients from the Alzheimer's Disease Center and Neurogeriatric Clinic from Hospital de Clinicas de Porto Alegre (Brazil) with AD, vascular dementia (VD), and questionable dementia were consecutively evaluated for the study during a 3-year period. We applied the DSM-IV criteria for dementia,[11] the NINCDS-ADRDA[12] for probable AD, and the NINDS-AIREN[13] for probable VD. The diagnostic criteria, auxiliary tests, and neuropsychologic tests have been all appropriately translated and adapted to the Brazilian cultural needs.[14–16] The diagnosis of dementia was based on clinical history of cognitive and functional impairments and neurologic examination. Impairments in cognitive function were documented using standardized psychometric tests. Cognitive impairment (memory impairment—impaired ability to learn new information or to recall previously learned—and one, or more, of the following: aphasia, apraxia, agnosia, executive dysfunction) was assessed with this battery to fulfill DSM-IV criteria for dementia. The battery was given by one member of the team unaware of the clinical information. The file with the cognitive results was added to the patient's protocol for the next appointment when dementia diagnosis was defined. During this second interview routine investigation and neuroimaging (computed tomography) were requested. Subsequently criteria for AD or VD were fulfilled by integrating the clinical and laboratory data. This diagnosis was considered the clinical gold standard for comparison to the CDR results. Lewy body dementia, frontotemporal, and other rare causes of dementia were also excluded according to standardized criteria.[17,18]

The clinical criteria for questionable dementia were MMSE below education-adjusted cutoffs and not fulfilling AD or VD criteria.[19,20] Most of the questionable dementia cases diagnosed clinically may be considered as patients with mild cognitive impairment (MCI).

The CDR scale is an adapted version for the Brazilian Portuguese from the official English version available at the Washington University (St Louis, MO) CDR website.[21] As stated in a previous validation study, translation and back translation is not necessary when using an instrument such as this, because it did not consist of questions that require application in exactly the same manner.[22]

CDR interviews and Blessed scales were applied independently of the cognitive testing. Those who administered the CDR were not aware of the final gold standard clinical diagnosis or the Blessed scale result. For the BDRS, we divided the full range of the scale into thirds and called them mild, moderate, and severe (Table 1). We further analyzed its validity for severity against DSM III-R criteria.

TABLE 1. Demographic and Clinical Characteristics of Diagnostic Groups

	Diagnostic Groups			
Variables	**Healthy Elderly (N = 48)**	**Question-able (N = 61)**	**Dementia (N = 234)**	***P***
Sex*				
Male [N (%)]	14 (29%)	27 (44%)	101 (43%)	0.177
Age†				
Mean ± SD	74.5 ± 6.82	67.47 ± 10.22	71.2 ± 9.99	0.001
Education†				
Mean ± SD	3.65 ± 2.65	4.57 ± 2.70	4.90 ± 4.00	0.093
MMSE†				
Mean ± SD	23.15 ± 4.85	22.02 ± 3.65	13.76 ± 7.50	0.0001
Blessed†				
Mean ± SD	0.00 ± 0.00	3.58 ± 2.24	13.53 ± 6.90	0.0001
CDR [N (%)]‡				0.0001
0.0	48 (100%)	0	0	
0.5	—	47 (77%)	32 (14%)	
1.0	—	10 (16%)	61 (26%)	
2.0	—	1 (2%)	84 (36%)	
3.0	—	1 (2%)	50 (21%)	
Missing	0	0	7 (3%)	

*$\chi^2 = 3.467$.
†ANOVA followed by Bonferroni post-hoc test.
‡$\chi^2 = 456.90$.

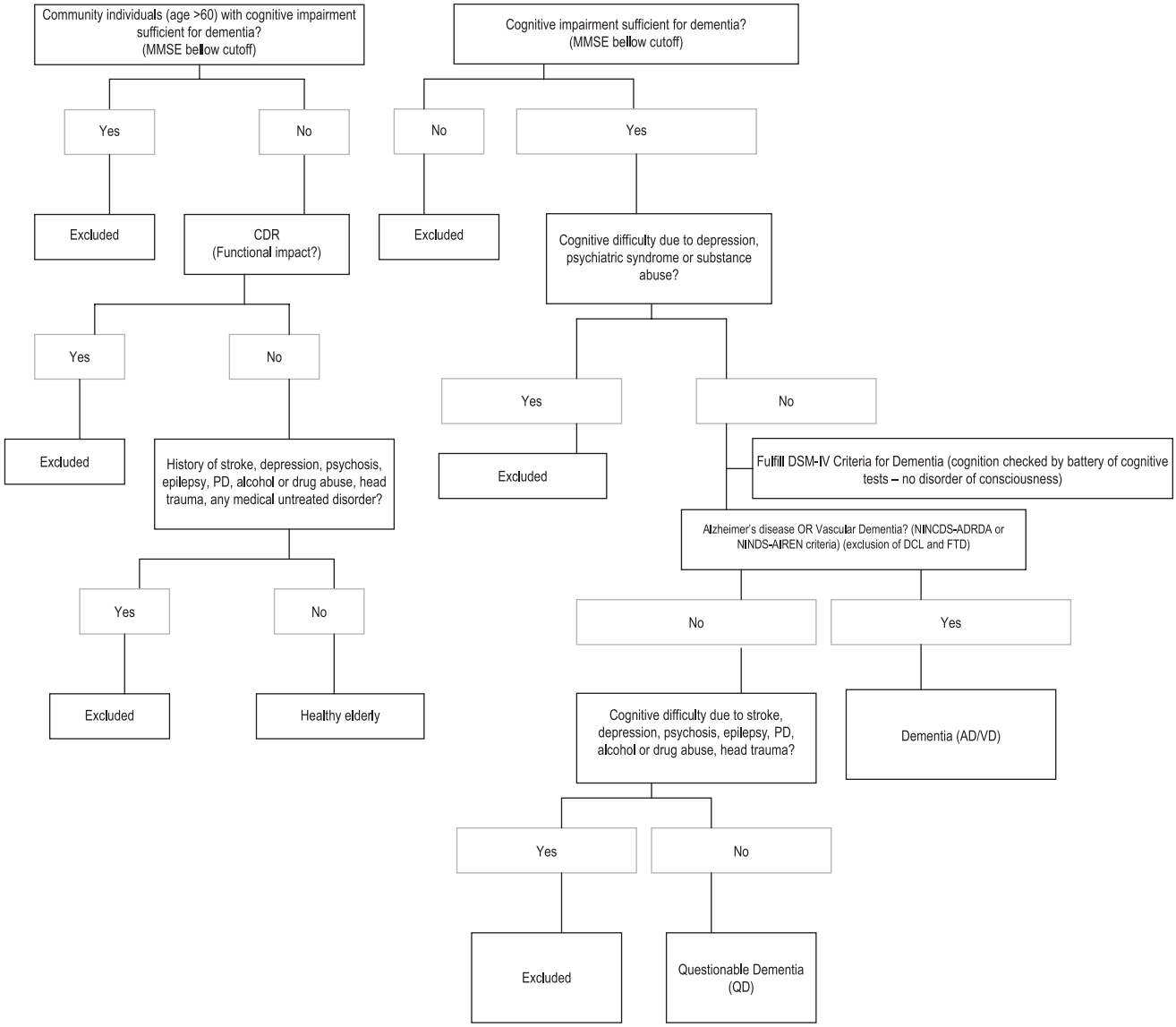

FIGURE 1. Participant selection process.

One member of the assessment team (M.L.F.C.) was previously trained at the NIA-Layton Aging and Alzheimer's Disease Center at the Oregon Health and Science University, Portland, OR. This member trained the rest of the research team when back home in Brazil.

The sample was composed of 343 participants (AD = 121, 35%; VD = 113, 33%; questionable dementia = 61, 18%; healthy elderly = 48, 14%). A flowchart illustrates the participant selection process (Fig. 1). This sample size was sufficient to detect disagreement of at least 20% between CDR and gold standard, considering the significance of κ coefficient. An excellent agreement is achieved by $\kappa \geq 0.75$; therefore, a level of agreement of 80% would be excellent.[23] Disagreement of 20% (complement for agreement of 80%) was used in the equation applied for the prevalence of dementia observed in Brazilian studies (7.1%).[24] The fixed parameters were β and α error of 20% and 5%, respectively.

The study was approved by the Ethics Committee for Medical Research of Hospital de Clínicas de Porto Alegre. All participants and/or their proxies signed an informed consent before being enrolled into the study.

Instruments

In addition to the CDR and Blessed scales, a battery of cognitive tests were also administered: digit span, span, visual recognition span, Wechsler Logical Memory I and II, clock drawing, house drawing, abstraction tests, calculation, famous faces, and praxis.[25] The MMSE[25,26] was first applied to all participants as a screening test, as this information was present for all cases we also analyzed its distribution among CDR global scores.

Analyses

Descriptive statistics are presented as means ± SD for parametric variables and frequency (%) for categorical ones. We analyzed parametric data with student *t* test or 1-way analysis of variance (ANOVA). Nonparametric tests (Mann-Whitney or Kruskall-Wallis, Spearman rank correlation) were used for ordinal data and those without normal distribution. Categorical variables were analyzed with association tests (χ^2 with Yates or Fisher correction as appropriate). Diagnostic values (sensitivity and specificity) were obtained through contingency tables. CDR interrater reliability (agreement among raters) was demonstrated by percent agreement. A group of 4 interviewers participated in the interrater agreement with 90 participants (20 healthy elderly, 20 questionable, and 50 dementia patients). They rated subjects in pairs. Each pair of interviewers rated 15 participants.

Validity and severity rating reliability were demonstrated with measures of agreement of CDR with the gold standard or other tests (percent agreement, Kendall τ, and κ). Agreement between CDR and BDRS, DSM III-R, or gold standard (AD/VD diagnostic criteria), was obtained from all participants. The weighted κ statistic with 95% confidence interval was calculated for all categories. κ greater than 0.75 was taken as an excellent agreement, between 0.75 and 0.40 intermediate to good agreement, and below 0.40, poor agreement.[23] To carry out agreement analysis, both scales needed an identical number of categories. In the case of CDR and DSM III-R, we show 2 strategies. First, excluding CDR 0.5 from the analysis; and second, collapsing CDR into 3 global scores by combining CDR 0.5 and 1 into a single score to compare with the mild stage of DSM III-R criteria.[27,28] For severity analyses with the CDR, the BDRS range of scores was divided into thirds.

RESULTS

Validity and Interrater Reliability

Interrater reliability for the CDR global score was 85% agreement (Table 2). Percentage of agreement with the gold standard (all dementias) was 87% overall and κ coefficient was 0.75. The stage-based (severity) agreement (DSM III-R) was 86%, κ = 0.78 (all stages); mild versus moderate was 82%, κ = 0.77 (0.69 to 0.81); and moderate versus severe, 88%, κ = 0.85 (0.80 to 0.91). The Blessed scale (in thirds) stage agreement was 85%, κ = 0.73 (all stages); mild versus moderate was 82%, κ = 0.77 (0.69 to 0.80); and moderate versus severe, 86%, κ = 0.80 (0.73 to 0.85). Excluding CDR 0.5 from the analysis, the severity agreement (DSM III-R) was 86%, κ = 0.78 (all stages), and mild versus moderate was 82%, κ = 0.76 (0.69 to 80).

Sensitivity and Specificity of Dementia Diagnosis and Rating Severity

The CDR identified 79 questionable dementia cases and 207 dementia cases (CDR > 0.5). CDR dementia severity ratings were mild 68 (34%); moderate 83 (42%); and severe 45 (22%). Dementia severities according to DSM III-R criteria were 75 mild, 91 moderate, and 54 severe cases. The healthy elderly subjects were not classified by these criteria and received a code for missing. Severity ratings obtained with the Blessed scale were mild 122 (45%); moderate 90 (34%); and severe 57 (21%). Figure 2 summarizes these data.

TABLE 2. Agreement on CDR Global Score Versus Gold Standard Clinical Diagnosis of Dementia and Among Raters (95% Confidence Interval)

	% Agreement With Gold Standard (N = 336)	Kendall τ (N = 336)	κ (N = 336)	% Agreement Among Raters* (N = 90)
Global CDR	87 (78, 95)	0.79 (0.70 0.85)	0.75 (0.67 0.82)	85 (75, 95)

*Percent agreement was calculated from observation of 4 raters in pairs from 90 interviews.

Sensitivity for detection of questionable and dementia cases was 86%, and specificity was 80% in relation to gold standard (diagnostic criteria). Detection between healthy elderly and dementia showed sensitivity of 86% and specificity of 100%. Whereas between questionable cases and healthy elderly sensitivity was 80% and specificity was 100%.

The ability of the BDRS (divided into 3 severity categories) to stage dementia in relation to DSM III-R criteria was 100% sensitive (comparing moderate and severe categories) and 97% specific. For categories mild and moderate, the Blessed scale showed 100% sensibility and 100% specificity to DSM III-R (Table 3).

CDR Global Scores

Collapsing CDR 0.5 Into Score 1. Sensitivity for staging dementia was 79% and specificity was 100% for either mild/moderate or moderate/severe categories of the Blessed dementia scale in thirds (Table 4). Sensitivity of CDR (global scores 2 and 3) compared with DSM III-R moderate and severe was 84% and specificity was 100%, however, with global scores 1 and 2 to DSM III-R mild to moderate, sensitivity was 80% and specificity, 98% (Table 5).

Without CDR 0.5. Staging dementia with CDR (global scores 1 and 2) for DSM III-R mild and moderate, sensitivity was 98% and specificity was 80%. For moderate and severe, sensitivity was 100% and specificity was 84%. For the Blessed Dementia scale in thirds, sensitivity was 100% and specificity 79%.

Correlations

The CDR was not correlated with education (Spearman $r = 0.07$; $P = 0.204$) or age (Spearman $r = 0.04$; $P = 0.47$). The CDR was correlated with MMSE (Spearman $r = -0.77$; $P = 0.0001$) and Blessed

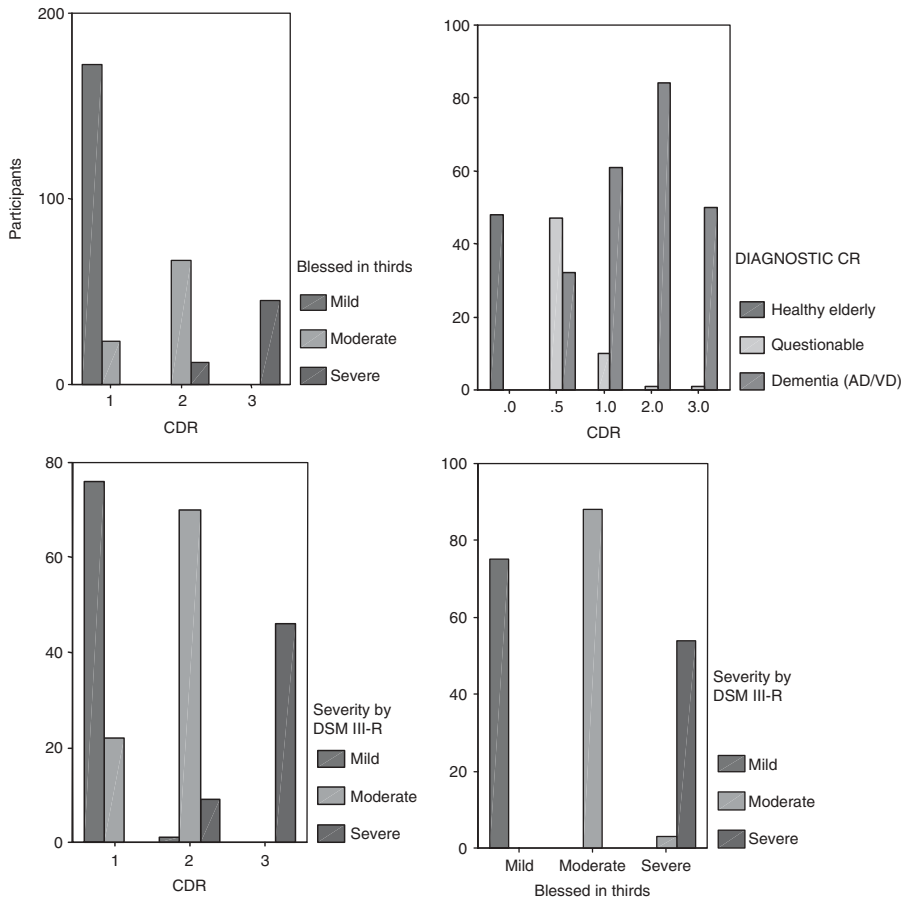

FIGURE 2. Distribution of dementia ratings with CDR, diagnostic criteria, DSM III-R criteria for severity, and BDRS.

Dementia scale (Spearman $r = 0.98$; $P = 0.0001$). The BDRS was correlated with MMSE (Spearman $r = -0.82$; $P = 0.001$), but was not correlated with age (Spearman $r = 0.07$; $P = 0.211$) and education (Spearman $r = 0.02$; $P = 0.689$).

Cognitive Tests and MMSE

The MMSE was significantly different between all categories of CDR (1-way ANOVA, $F = 135.11$; $P = 0.0001$; Tukey test post-hoc). Figure 3 shows box plots of the MMSE means ± 2 SE across CDR global scores, demonstrating the range of performances from participants classified according to CDR score. The cognitive testing identified significant differences among CDR global scores (Kruskal-Wallis ANOVA) (Table 6). There was a clear decrease in mean cognitive test scores with increasing CDR global scores indicating convergent validity.

DISCUSSION

We report the performance characteristics of a Brazilian Portuguese version of the CDR in a group of dementia patients representing an urban elderly group of generally low educational level. We found that there was high reliability, and interrater agreement, similar to studies reported in more highly educated English-speaking cohorts. The validity of this assessment compared

TABLE 3. Severity of Dementia: DSM III-R Versus Blessed Dementia Scale (in 3 Categories)

	DSM III-R: Severity of Dementia			
Blessed	Not Classified	Mild	Moderate	Severe
Severe	—	—	3 (3%)	54 (100%)
Moderate	—	—	88 (97%)	—
Mild	48 (100%)	75 (100%)	—	—

$\chi^2 = 421.55$; $P = 0.0001$.

TABLE 4. Severity of Dementia: Blessed Scale (in 3 Categories) Versus CDR

	Blessed: Severity of Dementia		
CDR	Mild	Moderate	Severe
0.5	71 (100%)	—	—
1	51 (73%)	19 (27%)	—
2	—	71 (85.5%)	12 (14.5%)
3	—	—	45 (100%)

$\chi^2 = 389.4$; $P = 0.0001$.

TABLE 5. Severity of Dementia: DSM III-R Versus CDR

	DSM III-R: Severity of Dementia			
CDR	Not Classified	Mild	Moderate	Severe
0	48 (96%)	—	—	—
0.5	2 (4%)	30 (40%)	—	—
1	—	44 (57%)	18 (20%)	—
2	—	1 (1%)	74 (80%)	9 (16%)
3	—	—	—	46 (84%)

$\chi^2 = 322.68$; $P = 0.0001$.

with several widely used assessment methods showed good diagnostic concordance (sensitivity 86%, and specificity 100%) with standard diagnostic criteria. Very good CDR global score agreement among raters (85%) and with gold standard clinical diagnostic categorization (κ coefficient = 0.75). The CDR global scores attained in this study mapped well to the MMSE and most cognitive tests in terms of differentiating among severities of dementia. We also observed high correlations between CDR and Blessed scales for rating severity of dementia. Both scales did not correlate with age, or to education in this population that was of a lower mean educational level than most North American or European reports. The expected correlation of the CDR and Blessed with the MMSE was observed.

The rate of classification of questionable dementia with CDR was higher than with the clinical criteria. Sensitivity was 86% and specificity was 80%. The CDR detection of dementia patients among healthy elderly showed a sensitivity of 86% and specificity of 100%.

The BDRS with the cutoffs categorized into tertiles of severity had a sensitivity of 100% and specificity 97% to 100% for staging dementia with DSM III-R as the standard. CDR global scores (with mild comprised of those with a score of 0.5 combined with those scoring 1) showed lower sensitivity (79%) and similar specificity (100%) for staging dementia using the BDRS as the gold standard; lower sensitivity (80% to 84%) and similar specificity (98% to 100%) (comparing moderate to severe and mild to moderate, respectively) using DSM III-R as the standard. Both strategies used (exclusion of CDR 0.5 and collapsing CDR 0.5 into CDR 1) to allow these analyses demonstrated similar diagnostic values for stages mild and moderate, at least in this sample.

Raters experienced the most difficulty with rating questionable and mild dementia, which has been observed by others.[29] After training, agreement with "gold standard" CDR scores was 85%. This result indicates that the training protocol is useful for establishing good levels of agreement in staging dementia severity. Inter-rater agreement in our study was also 85%. High levels of agreement on global CDR among raters and/or with a gold standard have been well documented.[8,30]

A previous validation of this scale in Brazil was carried out in a cohort of elderly with 156 individuals, from whom only 34 were identified as having dementia according to DSM-IV and NINCDS-ADRDA criteria (62 normal and 60 CDR = 0.5). Sensitivity was 91% and specificity was 100%.[22]

The CDR is increasingly used in longitudinal studies and in clinical trials for staging the severity of dementia, including several recent studies in ethnically diverse Asian populations.[31–34] However, the transcultural validity and feasibility of the CDR remains to be further substantiated. It may be anticipated that the CDR, relying on informant information is less susceptible to the educational, linguistic, and sociocultural influences that can confound interpretation of psychometric tests.[6]

There are some limitations to this study. We were not able to obtain autopsy in this patient sample. This may be problematic in some countries where cultural norms are not widely attuned to the need for this procedure. However, all patients had neuroimaging (computed tomography or magnetic resonance imaging).

In summary, we have completed a clinical validation of the CDR scale in a Brazilian population of patients and established that this Portuguese version of the CDR may be appropriately applied for research in this setting. This provides an opportunity to extend research into the growing elderly population of Brazil, a previously understudied ethnically and culturally diverse country for further clues as to potentially different risks and susceptibilities leading to dementia and its progression. In addition this study provides a basis for comparison to other CDR-based studies of dementia in other populations around the world.

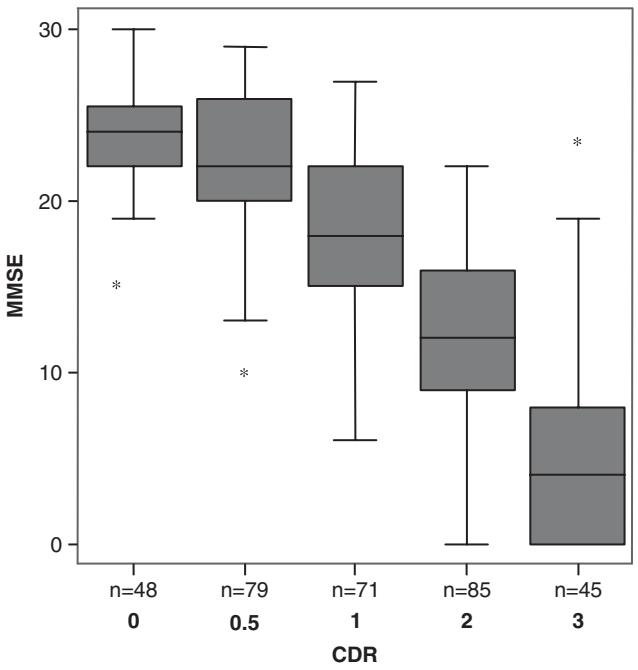

FIGURE 3. Boxplots of MMSE means ± 2SE and 95% CI of each CDR global score (* are outliners).

TABLE 6. Cognitive Tests Versus CDR (Kruskall-Wallis ANOVA)—Mean (SD)

	CDR: Staging Dementia					
Tests	**0**	**0.5**	**1.0**	**2.0**	**3.0**	***P***
Digit span	5.4 (1.43)	4.85 (1.42)	4.61 (1.71)	3.29 (2.09)	0.60 (1.34)	0.000
Word span	4.6 (1.54)	3.76 (1.65)	3.35 (1.60)	2.29 (2.09)	0.80 (1.79)	0.010
Famous faces	14.3 (2.01)	12.2 (1.34)	11.25 (6.41)	2.89 (4.23)	3.20 (7.16)	0.021
Logic I*	4.5 (1.62)	3.74 (1.28)	3.00 (2.63)	1.00 (2.00)	0.60 (0.89)	0.009
Logic D†	2.3 (1.83)	1.6 (1.25)	1.27 (2.28)	0.44 (0.88)	0.60 (1.34)	0.065
VRS	9.5 (3.81)	8.4 (3.1)	7.11 (4.4)	2.50 (4.07)	0.80 (1.79)	0.033
Calculations	4.5 (1.02)	3.9 (1.07)	1.74 (0.45)	1.93 (0.26)	2.00 (0.5)	0.18
Clock‡	3.5 (1.05)	2.00 (1.0)	1.61 (0.5)	1.20 (0.41)	1.20 (1.41)	0.01
House§	3.0 (0.83)	2.05 (0.9)	1.42 (0.48)	1.20 (0.52)	1.20 (0.4)	0.01

*Wechsler Logical Memory Immediate.
†Wechsler Logical Memory Delayed.
‡Clock drawing.
§House drawing.
Mann-Whitney *U* test:
CDR = 0 versus CDR = 0.5 were statistically different in all tests but VRS ($P = 0.083$).
CDR = 1 versus CDR = 2 were statistically different in all tests but Logic D ($P = 0.583$).
CDR = 1 versus CDR = 3 were statistically different in all tests but Logic D ($P = 0.655$).
CDR = 2 versus CDR = 3 were statistically different only in the Digit span ($P = 0.009$).
CDR = 0.5 versus CDR = 1 were not statistically different in all tests.
VRS indicates visual recognition span.

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