Validation of the New Interpretive Guidelines for the Clinical Dementia Rating Scale Sum of Boxes Score in the National Alzheimer’s Coordinating Center Database

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Background: It was recently demonstrated that the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) score can be used to accurately stage severity of Alzheimer dementia and mild cognitive impairment (MCI). However, to our knowledge, the utility of those interpretive guidelines has not been cross-validated or applied to a heterogeneous sample of dementia cases.

Objective: To cross-validate the staging guidelines proposed in a previous study using the National Alzheimer’s Coordinating Center (NACC) database.

Design: The previously published cut scores were applied to the NACC sample and diagnostic accuracy estimates obtained. Next, analyses were restricted to NACC participants with a CDR global score (CDR-GS) of 0.5 and receiver operating characteristic curves generated to determine optimal CDR-SB cut scores for distinguishing MCI from very early dementia.

Setting: The 2008 NACC uniform data set.

Participants: There were 12,462 participants (5,115 controls; 2,551 patients with MCI; 4,796 patients with dementia, all etiologies) in the NACC data set used for the current analysis.

Main Outcome Measure: Accurate prediction of diagnoses (MCI or dementia) using the CDR-SB score.

Results: The previously proposed CDR-SB ranges successfully classified the vast majority of patients across all impairment ranges with a k of 0.91 and 94% overall correct classification rate. Additionally, the CDR-SB score discriminated between patients diagnosed with MCI and dementia when CDR-GS was restricted to 0.5 (overall area under the curve = 0.83).

Conclusions: These findings cross-validate the previously published CDR-SB interpretive guidelines for staging dementia severity and extend those findings to a large heterogeneous sample of patients with dementia. Additionally, the CDR-SB scores distinguished MCI from dementia in patients with reasonable accuracy when CDR-GS was restricted to 0.5.

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Tagging dementia severity via global assessment measures is commonplace in both clinical and research settings. Staging dementia severity is also critical for clinical trials as outlined by the US Food and Drug Administration’s Guidelines for the Clinical Evaluation of Antidementia Drugs. The Washington University Clinical Dementia Rating (CDR) scale is frequently used to stage dementia severity and yields both a global (CDR-GS) and sum of boxes (CDR-SB) score. While the CDR-GS is typically used for staging purposes, the CDR-SB score is a more detailed quantitative general index than the CDR-GS and it provides more information than the CDR total score in cases of mild dementia.

O’Bryant and colleagues, examining data from 1577 participants of the Texas Alzheimer’s Research Consortium minimum data set, recently demonstrated that the CDR-SB scores could be used to stage dementia severity in a sample of controls (n = 110) and patients diagnosed with mild cognitive impairment (MCI) (n = 202) and Alzheimer disease (n = 1265) and new interpretive guidelines were presented. Additionally, the CDR-SB scores reliably discriminated between MCI and very early Alzheimer disease when CDR-GS was restricted to 0.5 (n = 232). However, to our knowledge, those guidelines have not been cross-validated nor have they been applied to a heterogeneous sample of dementia cases. The current investigation was designed to cross-validate and extend the
previous findings through analysis of the NACC database. It was hypothesized that the previously published CDR-SB cut scores would correctly stage the vast majority of participants. Additionally, the current study evaluated the utility of the CDR-SB scores in distinguishing between patients diagnosed with MCI and very early forms of dementia (all types) when CDR-GS was restricted to 0.5. It was hypothesized that CDR-SB scores would accurately predict diagnoses (MCI or dementia) when CDR-GS was restricted to 0.5.

### METHODS

#### PARTICIPANTS

Data were taken from the 2008 NACC uniform data set. This information contains data from all National Institute on Aging–funded Alzheimer’s Disease Centers. Inclusion criteria were (1) age 55 years and older and (2) available data on the CDR. All participants were evaluated according to standardized protocols and consensus diagnosis according to published guidelines. To remove extreme outliers, Mini-Mental State Examination (MMSE) cut scores of 24 and higher and 20 and higher were included for inclusion of controls and patients with MCI, respectively. A total of 263 participants (185 controls; 78 patients with MCI) were excluded from analyses based on these MMSE cut scores. Of the entire NACC sample, 12,462 participants met inclusion criteria and were used for the current project. The NACC protocols at each participating center are conducted under institutional review board approval.

#### MEASURES

The CDR is obtained through a semi-structured interview of patients and informants, and the subject’s cognitive status is rated in 6 domains of functioning including memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The CDR-GS is computed via an algorithm and the CDR-SB score is obtained by summing each of the domain box scores, with scores ranging from 0 to 18.

### RESULTS

Demographic characteristics of the study population are provided in Table 1 and Table 2. Subjects with dementia were significantly older and control participants significantly younger than patients with MCI. The dementia group had significantly fewer years of education than the MCI group, who had significantly fewer years of education than the control group. As expected, there were more women than men across all groups. Also as expected, the control group performed significantly better on the MMSE than patients with MCI, who scored significantly better than the dementia sample. Mean...
CDR-SB scores were highest in the dementia group, followed by the MCI and control groups (Table 1). Table 2 presents demographic data broken down by all dementia diagnostic groups.

To cross-validate the previously published CDR-SB interpretive guidelines, the CDR-SB ranges5 were applied to the entire NACC sample. The CDR-SB ranges correctly classified 94% of the entire sample with an overall \( \kappa \) of 0.91 (Table 3).

Next, the sample was restricted to only those with a CDR-GS of 0.5. Using receiver operating characteristic curve analyses, a CDR-SB cut score of 2.5 or higher yielded a sensitivity of 0.71 and specificity of 0.81 with an area under the curve of 0.83 for the all dementia group (n=1211) vs the MCI group (n=2132). Detailed information regarding optimal cut scores for each diagnostic group is presented in Table 4. In a logistic regression analysis, after adjustment for age, sex, and education and MMSE scores, an odds ratio of 2.89 (95% confidence interval, 2.64-3.16) was obtained for the CDR-SB score, indicating that for each 1-point increment in CDR-SB score, there was approximately a 3-fold increased likelihood of being diagnosed with dementia.

In the current study, the new interpretive CDR-SB guidelines correctly classified 94% of the 12,462 participants available from the NACC database, cross-validating the new CDR-SB interpretive guidelines proposed by O’Bryant and colleagues5 (Table 5) and extending those guidelines to a heterogeneous sample of dementia cases.

There are several advantages to the current CDR-GS guidelines. First, they offer greater precision for tracking which is not possible with the CDR-GS. From a research perspective, this will allow for a more refined approach...
Table 5. Dementia Severity Categories Based on CDR-SB Scores

<table>
<thead>
<tr>
<th>CDR-SB Range</th>
<th>Staging Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>0.5-4.0</td>
<td>Questionable cognitive impairment</td>
</tr>
<tr>
<td>0.5-2.0</td>
<td>Questionable impairment</td>
</tr>
<tr>
<td>2.5-4.0</td>
<td>Very mild dementia</td>
</tr>
<tr>
<td>4.5-9.0</td>
<td>Mild dementia</td>
</tr>
<tr>
<td>9.5-15.5</td>
<td>Moderate dementia</td>
</tr>
<tr>
<td>16.0-18.0</td>
<td>Severe dementia</td>
</tr>
</tbody>
</table>

Abbreviation: CDR-SB, Clinical Dementia Rating Scale Sum of Boxes score.

to evaluating the utility of therapeutic interventions in slowing the progression of the disease as well as provide opportunity to better statistically model factors that impact progression of these diseases. Given the data on the reliability of the CDR with published training modules, these data may also prove useful in training new health care providers across a range of disciplines with a tool for identifying early stages of dementia disorders, which is of critical importance in light of the advancing age of the population, and the literature documenting the inability of nonspecialists to detect these conditions.

Additionally, the present study demonstrated the utility of CDR-SB scores in predicting diagnosis (MCI vs dementia) when CDR-GS was restricted to 0.5 (questionable dementia); the nature of the CDR-GS does not allow for making this important distinction. Applying the CDR-SB range for questionable cognitive impairment (CDR-SB=0.5-4.0) (Table 5) produced the ability to discriminate these groups with reasonable accuracy, though the estimates of diagnostic accuracy varied between diagnostic groups. As an example, the good specificity estimates found for probable Alzheimer disease and frontotemporal dementia (0.81 and 0.80, respectively) would yield better correct diagnoses of disease presence (ie, positive predictive power, “specificity rules in” a diagnosis) while the sensitivity of possible Alzheimer disease (0.80) would yield better estimates of disease absence (ie, negative predictive power, “sensitivity rules out” a diagnosis). Moreover, the finding of more than a 3-fold increase (odds ratio, 3.32) in the likelihood of being diagnosed with some form of dementia for every 1-point increase in CDR-SB score supports the use of CDR-SB as an important tool in distinguishing MCI from early dementia as well as its utility in tracking progression from MCI to dementia. As mentioned previously, the CDR-SB may provide a good tool for training new health care providers to increase detection of syndromes of cognitive deterioration early during the course and it is likely that the combination of CDR-SB along with a cognitive screening instrument (eg, MMSE) will improve diagnostic accuracy estimates and should be tested. The present research supports the validity of these new CDR interpretive guidelines and provides researchers and clinicians a means for greatly enhancing the utility of this instrument.

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REFERENCES