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Improving the clinical detection of Lewy body dementia with the Lewy body composite risk score

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Abstract

Introduction: Dementia with Lewy bodies (DLB) is a challenge to diagnose, particularly outside of expert centers with long delays in diagnosis leading to significant burden to patients and caregivers. Although consensus criteria have excellent specificity, there is no standardized way to assess symptoms reducing sensitivity. We developed the Lewy body composite risk score (LBCRS) from autopsy-verified cases to improve the ability to detect DLB in clinic and research populations.

Methods: The LBCRS was tested in a consecutive series of 256 patients compared with the clinical dementia rating and gold standard measures of cognition, motor symptoms, function, and behavior. Psychometric properties including floor and ceiling effects; concurrent, construct, and known-groups validity; and internal consistency of the LBCRS were determined. Receiver operator characteristic (ROC) curves assessed the ability of LBCRS to differentiate (1) DLB from Alzheimer's disease (AD), (b) DLB from all dementia, and (c) mild cognitive impairment (MCI) due to DLB from MCI due to AD. The LBCRS was completed independent of the clinical evaluation.

Results: Mean LBCRS scores were significantly different between DLB and AD (6.1 $\pm$ 2.0 vs. 2.4 $\pm$ 1.3, $P < .001$) and between MCI-DLB versus MCI-AD (3.2 $\pm$ 0.9 vs. 1.0 $\pm$ 0.8, $P < .001$). The LBCRS was able to discriminate DLB from other causes of dementia. Using a cutoff score of 3, areas under ROC for DLB versus AD = 0.93 (0.89–0.98) and for MCI-DLB versus MCI-AD = 0.96 (0.91–1.0).

Discussion: The LBCRS increases diagnostic probability that Lewy body pathology is contributing to the dementia syndrome and should improve clinical detection and enrollment for clinical trials.

Keywords: Lewy body dementia; Alzheimer's disease; Mild cognitive impairment; Clinical trials

1. Introduction

The Lewy body dementias, composed of two related disorders: dementia with Lewy bodies (DLB) [1] and Parkinson's disease dementia (PDD) [2], are a challenge to diagnose, particularly outside of expert centers [3]. One of the great challenges in differential diagnosis of neurodegenerative disorders is attributing clinical symptoms to specific pathologies to guide treatment choices and discuss prognosis and clinical course [4,5]. Although PDD provides a potentially easier route to diagnosis because the cognitive disorder begins in face of an established movement disorder [2] and criteria have defined a mild cognitive impairment (MCI) state [6], DLB is a more difficult entity to diagnose with delays in diagnosis approaching 18 months [7] leading to significant burden to patients and caregivers [8–10]. Patients with dementia are often misdiagnosed [7,11] with a neurologist finally establishing a diagnosis of DLB or PDD in 62% of cases [7]. Although consensus criteria for DLB [1] have excellent specificity (79%–100%) [12], there is no standardized way to assess or operationalize many of the cognitive and behavioral symptoms which markedly decrease sensitivity in clinical practice (range 12%–88%) [12,13].

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To address the difficulty in making DLB diagnosis and assist in the diagnosis of PDD, we developed the Lewy body composite risk score (LBCRS) [14] to improve the ability to detect DLB and PDD in clinic and research populations and increase the likelihood of determining whether Lewy bodies are contributing pathology to the cognitive diagnosis. The LBCRS was derived from clinical features in autopsy-verified cases of healthy controls, Alzheimer's disease (AD), DLB, and Parkinson's disease with and without dementia [15]. Features that predicted Lewy bodies at autopsy included extrapyramidal signs, cognitive fluctuations, hallucinations, and sleep disturbances [15]. The LBCRS was initially validated in a research sample with excellent psychometric properties demonstrating discrimination between AD and DLB cases with an area under the curve (AUC) of 96.8% (95% confidence interval [CI], 0.93–1.0) [14]. A cutoff score of 3 provided a sensitivity of 90% and a specificity of 87%. Here, we present the psychometric evaluation of the LBCRS in a well-characterized clinic sample.

2. Methods

2.1. Study participants

Participants were drawn from a consecutive series of 256 referrals to the Pearl I. Barlow Center for Memory Evaluation and Treatment, a dementia specialty practice at NYU Medical Center, from September 2013 to December 2014. Assessments were completed by a transdisciplinary team of a neurologist, geriatric nurse practitioner, social worker, and psychometrician, and all components of the assessment were part of standard of care at our center [16]. The LBCRS was completed by the author after the entire evaluation was performed. During the 75–90 minute office visit, the patient and caregiver underwent a comprehensive evaluation including the clinical dementia rating (CDR) and its sum of boxes (CDR-SB) [17], mood, neuropsychological testing, caregiver ratings of behavior and function, and caregiver burden and depression. This study was approved by the NYU Langone Medical Center Institutional Review Board.

2.2. Clinical assessment

Independent semi-structured interviews were conducted with the patient and a collateral source. The CDR [17] was used to determine the presence or absence of dementia and to stage its severity. The CDR rates cognitive function in six categories (memory, orientation, judgment and problem solving, performance in community affairs, home and hobbies, and personal care); a global CDR 0 indicates no dementia; CDR 0.5 represents MCI or very mild dementia; CDR 1, 2, or 3 corresponds to mild, moderate, or severe dementia. Diagnoses were determined using published clinical criteria for MCI due to AD [18], AD [19], DLB [1] frontotemporal degeneration (FTD) [20,21], and vascular dementia (VaD) [22]. Research criteria were used for defining MCI due to DLB [22–25]. Extrapyramidal features were assessed with the Movement Disorders Society-Unified Parkinson's Disease Rating Scale, motor subscale part III (UPDRS) and a modified Hoehn and Yahr stage was assigned [26]. The Charlson comorbidity index [27] was completed to assess the potential impact of comorbid medical conditions on the patient's cognitive status.

2.3. Caregiver evaluation

Caregivers completed evaluations to determine the presence and severity of noncognitive symptoms observed in the patient and their impact on the caregiver. The neuropsychiatric inventory (NPI) [28] assessed behavior, Mayo fluctuation questionnaire (MFQ) [29] assessed presence of cognitive fluctuations, and Epworth Sleepiness Scale (EES) [30] assessed daytime sleepiness. The Mayo sleep questionnaire (MSQ) [31] assessed the presence of parasomnias, particularly rapid eye movement sleep behavior disorder (RBD). A caregiver rating of daytime alertness was collected using a 1-10 Likert scale [31]. The functional activities questionnaire [32] was used to rate performance of activities of daily living. The Zarit burden inventory [33] evaluated caregiver burden and the personal health questionnaire [34] assessed caregiver depression.

2.4. Neuropsychological evaluation

Each patient was administered a 30-minute test battery at the time of the office visit to assess their cognitive status. The psychometrician was unaware of the diagnosis, CDR stage, or LBCRS. A brief global assessment was performed using the mini mental state examination (MMSE) [35]. The battery included measures of episodic memory (Hopkins verbal learning task) [36]; semantic memory (animal fluency) [37] and 15-item Boston naming test [38]; and working memory (letter-number sequencing) [39]. Two-timed measures addressed psychomotor and executive abilities: trail making A and trail making B [40]. Construction was assessed with the clock drawing task [41]. Mood was assessed with the hospital anxiety depression scale [42] providing subscale scores for depression (HADS-D) and anxiety (HADS-A).

2.5. Completion of the LBCRS

The LBCRS (Table 1) was not considered during the clinical assessment or diagnosis. The LBCRS was completed after all other rating scales were scored and the diagnosis presented to the patient and family. Data were taken from the patient charts to complete the LBCRS with questions 1–4 taken from the UPDRS, question 5 from the ESS, questions 6–7 from the MFQ, question 8 from the NPI, question 9 from the MSQ, and question 10 from physical findings and complaints of the patient. The operationalization of physical findings as being present for at least 6 months or symptoms occurring at least three times over the past 6 months

Table 1
Lewy body composite risk score

Please rate the following physical findings being present or absent for the past 6 mo and symptoms as being present or absent for at least 3 times over the past 6 mo. Does the patient…	Yes	No
Have slowness in initiating and maintaining movement or have frequent hesitations or pauses during movement?		
Have rigidity (with or without cogwheeling) on passive range of motion in any of the 4 extremities?		
Have a loss of postural stability (balance) with or without frequent falls?		
Have a tremor at rest in any of the 4 extremities or head?		
Have excessive daytime sleepiness and/or seem drowsy and lethargic when awake?		
Have episodes of illogical thinking or incoherent, random thoughts?		
Have frequent staring spells or periods of blank looks?		
Have visual hallucinations (see things not really there)?		
Appear to act out his/her dreams (kick, punch, thrash, shout or scream)?		
Have orthostatic hypotension or other signs of autonomic insufficiency?		
Total score		

permitted the scoring of the LBCRS by totaling the sum of signs and symptoms rated as present.

2.6. Statistical analyses

Analyses were conducted in SPSS version 21 (Armonk, NY). Descriptive statistics were used to present demographic and clinical characteristics of patients, informant ratings, LBCRS, CDR, CDR-SB, and neuropsychological testing. One-way analysis of variance (ANOVA) was used for continuous data, and chi-square analyses were used for categorical data. Concurrent validity was assessed comparing the strength of association between LBCRS scores and other clinical scales using Pearson correlation coefficients. The partial eta-squared (η^2) from the omnibus ANOVA was used to estimate effect size. To assess item variability, the item frequency distributions, range, and standard deviations were calculated. Item and scale scores were examined for floor and ceiling effects (i.e., clustering of participants at the best and worst possible scores, respectively). Principal components analyses using Varimax rotation were performed to explore the underlying factor structure of the LBCRS [43]. To determine the range of scores measured by the LBCRS and subscales, the observed score range and measures of central tendency and variability were computed. Internal consistency was examined as the proportion of the variability in the responses that is the result of differences in the respondents. Internal consistency was reported as the Cronbach α reliability coefficient. Coefficients >0.7 are good measures of internal consistency [44]. Receiver operator characteristic (ROC) curves were used to assess the discriminative ability of LBCRS to differentiate (a) DLB from AD; (b) DLB from all dementia, and (c) MCI due to DLB from MCI due to AD reported as the AUC with 95% confidence intervals. Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values, and likelihood ratios were reported. The likelihood ratio of any screening test is the probability that a positive test is found in persons with disease divided by the probability of the same finding in persons without disease [45]. Likelihood ratios range from 0 to infinity, with larger numbers providing more convincing evidence of disease; smaller numbers argue that disease is less likely [45]. Ratios close to 1 lack diagnostic value. Known-groups validity was assessed comparing the mean performance between groups (DLB vs. AD; MCI due to DLB vs. MCI due to AD) [46].

3. Results

3.1. Sample characteristics

The cohort had a mean age of 77.8 ± 8.2 years (range, 50–98 years) with a mean education of 15.5 ± 3.5 years (range, 4–24 years), and 53% female. The sample race/ethnicity was 89.8% white, non-Hispanic; 4.3% African-American, non-Hispanic; 4.7% Hispanic; and 1.2% Asian. Informants were 53.9% spouses and 46.1% nonspouse caregivers (adult children, friends, and other relatives). The mean MMSE score of the sample was 21.7 ± 6.3 (range, 0–30), and the Charlson comorbidity index [27] was 2.2 ± 1.4 (range, 0–9). Diagnoses include no cognitive impairment (n = 8), MCI (n = 71), AD (n = 100), DLB (n = 53), VaD (n = 5), FTD (n = 10), and other dementias (n = 9). Of those with MCI, 57 were thought to be due to AD [18] and 14 were thought to be due to DLB [23–25]. Sample characteristics, neuropsychological performance, ratings, and LBCRS scores by diagnosis are shown in Table 2. Table 3 demonstrates the strength of association between the LBCRS and clinical indices and tests of cognition, behavior, and function. Higher LBCRS scores were generally highly correlated with poorer performance and worse health ratings.

3.2. Reliability and scale score features of the LBCRS

Principal component analysis revealed two domains. A motor domain (Eigenvalue 3.1; 31.8% variance) consisted of the clinical signs of bradykinesia, rigidity, tremor, and postural instability. A nonmotor domain (Eigenvalue 1.3; 13.1% variance) consisted of the clinical symptoms of daytime sleepiness, illogical or incoherent thoughts, staring spells, hallucinations, RBD, and autonomic insufficiency (e.g., orthostatic hypotension, chronic constipation, sialorrhea) [47]. Table 4 demonstrates the inter-item and item-total correlations for the LBCRS as well as the factor loadings. The degree to which the LBCRS was free from random error was assessed using Cronbach α for the total score, motor factor, and nonmotor factor (Table 5). The

Table 2
Sample characteristics

	Dementia			MCI		
Characteristics	AD (n = 100)	DLB (n = 53)	*P* value	2° AD (n = 57)	2° DLB (n = 14)	*P* value
Clinical features						
Age, y	79.9 (7.6)	78.6 (7.6)	.32	76.1 (8.9)	77.6 (9.1)	.59
Gender, % male	40.0	62.3	.009	43.9	57.1	.37
Education, y	15.2 (3.9)	14.5 (3.6)	.29	15.8 (2.9)	16.1 (3.0)	.70
CDR-SB	5.8 (3.3)	8.9 (5.1)	<.001	1.8 (0.9)	2.4 (1.0)	.04
CDR	0.9 (0.5)	1.5 (0.9)	<.001	0.5 (0.1)	0.5 (0.0)	.99
Charlson comorbidity index	2.3 (1.3)	2.4 (1.5)	.63	1.9 (1.2)	2.2 (1.7)	.42
Systolic BP, sitting, mm Hg	132.8 (18.9)	125.4 (22.4)	.04	135.6 (19.0)	139.4 (25.0)	.54
Systolic BP, standing, mm Hg	132.6 (18.4)	123.5 (22.7)	.02	133.2 (18.7)	137.0 (22.1)	.35
Mini-physical performance test	9.8 (2.6)	8.4 (3.1)	.02	11.8 (2.6)	10.5 (3.5)	.14
Functional activities questionnaire	10.7 (8.7)	17.4 (10.1)	<.001	3.4 (4.0)	5.7 (5.6)	.10
UPDRS III	7.3 (8.7)	33.3 (22.3)	<.001	1.2 (2.3)	9.8 (12.4)	<.001
Hoehn and Yahr stage	0.4 (1.1)	2.7 (1.4)	<.001	0.0 (0.0)	0.7 (1.0)	<.001
Presence of Parkinsonism, %	26.0	87.0	<.001	0	35.7	<.001
Bradykinesia	57.3	91.3	<.001	14.8	57.1	.001
Rigidity	6.3	71.1	<.001	0	7.1	.05
Tremor	7.3	34.8	<.001	0	7.1	.05
Postural Instability	27.1	76.1	<.001	0	28.6	<.001
FAQ	10.7 (8.7)	17.4 (10.1)	<.001	3.4 (4.0)	5.7 (5.6)	.10
Neuropsychological features						
MMSE	19.6 (5.5)	18.0 (7.6)	.15	25.9 (3.6)	26.6 (2.9)	.46
Animal naming	8.3 (4.0)	8.8 (4.3)	.83	16.7 (5.8)	13.8 (5.6)	.09
Boston naming test	7.6 (4.2)	8.8 (4.2)	.12	11.3 (3.1)	12.5 (1.5)	.19
HTLV—total	9.9 (4.7)	9.8 (4.4)	.79	15.8 (4.3)	15.9 (4.3)	.92
HTLV—delayed	0.5 (1.3)	0.9 (1.6)	.13	2.7 (2.4)	2.8 (3.0)	.82
HTLV—cued	4.7 (3.4)	5.8 (2.9)	.09	9.1 (1.9)	9.5 (1.8)	.57
Letter-number sequencing, % impaired	66.7	95.0	.01	62.8	45.5	.29
Trail making A, s	81.8 (47.3)	101.4 (53.6)	.05	40.7 (19.9)	49.6 (26.3)	.16
Trail making B, s	168.3 (26.7)	164.8 (32.6)	.64	108.3 (41.4)	109.4 (38.3)	.93
Clock drawing, % impaired	91.7	88.9	.75	42.1	42.9	.96
Behavioral features						
HADS-anxiety	5.4 (3.4)	6.3 (3.6)	.59	6.1 (3.7)	6.5 (2.7)	.69
HADS-depression	5.7 (3.4)	7.8 (4.2)	.004	5.3 (3.6)	5.4 (2.9)	.96
NPI-Q	7.7 (5.8)	11.6 (5.7)	<.001	5.0 (4.4)	7.7 (5.6)	.06
Mayo fluctuation questionnaire	1.6 (1.1)	2.9 (0.9)	<.001	1.1 (0.9)	2.1 (1.5)	.003
Epworth sleepiness scale	6.9 (4.9)	9.7 (5.2)	.001	6.7 (4.5)	8.9 (4.7)	.12
Alertness rating	7.2 (2.0)	5.6 (1.8)	<.001	7.9 (1.6)	6.1 (2.0)	.001
Hallucinations, %	8.4	47.8	<.001	1.9	7.1	.30
Misidentifications, %	1.1	34.8	<.001	0	14.3	.005
Capgras delusions, %	1.1	17.4	<.001	0	0	—
RBD, %	5.3	41.5	<.001	3.6	35.7	<.001
Fluctuations, %	43.9	92.2	<.001	32.7	42.9	.48
Lewy body composite risk scores						
Total score	2.4 (1.3)	6.1 (2.0)	<.001	1.0 (0.8)	3.2 (0.9)	<.001
Factor 1 (motor)	1.0 (1.0)	2.8 (1.0)	<.001	0.1 (0.8)	1.1 (1.1)	<.001
Factor 2 (nonmotor)	1.5 (1.0)	3.4 (1.5)	<.001	1.0 (0.8)	2.1 (1.2)	.001

Abbreviations: MCI, mild cognitive impairment; AD, Alzheimer's disease; DLB, dementia with Lewy bodies; CDR-SB, clinical dementia rating and its sum of boxes; CDR, clinical dementia rating; BP, blood pressure; UPDRS III, unified Parkinson's disease rating score–part III, motor; FAQ, functional assessment questionnaire; MMSE, mini mental state examination; HTLV, Hopkins verbal learning task; HADS, hospital anxiety and depression scale; NPI, neuropsychiatric inventory; RBD, rapid eye movement sleep behavior disorder.

internal consistency was very good to excellent for the total ($\alpha = 0.71$) and motor ($\alpha = 0.73$) scores. The internal consistency for the nonmotor was lower ($\alpha = 0.57$), likely reflecting the varied constructs contained within this factor. The LBCRS covered the entire range of possible scores, and the mean, median, and standard deviation demonstrated a sufficient dispersion of scores for the assessing and monitoring the presence and severity of dementia with low percentage of missing data. There were very low ceiling effects (1.3–2.4), and floor effects (9.4–29.9) showed good separation between groups, especially for motor domain questions. The two factors (motor and nonmotor) were moderately correlated suggesting they are related but substantially distinct. The total LBCRS was internally consistent with scale score features that demonstrated ample dispersion of scores for both the LBCRS total score and

Table 3
Mean performance on rating scales and neuropsychological tests and concurrent validity with the LBCRS

Measure	Mean (SD)	*R*	*P* value
Age, y	77.7 (8.3)	0.07	.26
Education, y	15.3 (3.6)	−0.14	.03
CDR-SB	5.2 (4.4)	0.62	<.001
CDR	0.9 (0.7)	0.60	<.001
Charlson comorbidity index	2.2 (1.4)	0.08	.23
Systolic BP, sitting, mm Hg	133.2 (21.1)	−0.23	.001
Mean arterial pressure, sitting	94.5 (12.9)	−0.24	.001
Systolic BP, standing, mm Hg	131.9 (20.8)	−0.21	.005
Mean arterial pressure, standing	94.3 (11.1)	−0.21	.003
Body mass index	25.8 (4.5)	−0.04	.56
Mini-PPT	10.3 (2.9)	−0.39	<.001
UPDRS III	12.5 (18.0)	0.78	<.001
Hoehn and Yahr Stage	0.9 (1.6)	0.79	<.001
FAQ	9.8 (9.5)	0.61	<.001
MMSE	21.8 (6.3)	−0.41	<.001
Animal naming	11.2 (6.1)	−0.41	<.001
Boston naming test	9.3 (4.2)	−0.12	.08
HTLV—total	12.4 (5.5)	−0.34	<.001
HTLV—delayed	1.6 (2.4)	−0.23	.001
HTLV—cued	6.8 (3.5)	−0.22	.002
Trail making A, s	68.8 (46.5)	0.40	<.001
Trail making B, s	140.8 (44.6)	0.24	.001
HADS—anxiety	5.9 (3.5)	0.05	.51
HADS—depression	6.1 (3.8)	0.15	.03
NPI-Q	7.9 (5.9)	0.49	<.001
Mayo fluctuation questionnaire	1.8 (1.3)	0.71	<.001
Epworth sleepiness scale	7.4 (4.8)	0.35	<.001
Alertness rating	7.0 (2.0)	−0.53	<.001
Caregiver burden	16.8 (10.1)	0.27	<.001
Caregiver depression	2.1 (2.7)	0.15	.08

Abbreviations: LBCRS, Lewy body composite risk score; SD, standard deviation; CDR-SB, clinical dementia rating and its sum of boxes; CDR, clinical dementia rating; BP, blood pressure; PPT, physical performance test; UPDRS, unified Parkinson disease rating scale; FAQ, functional activities questionnaire; MMSE, mini mental state examination; HVLT, Hopkins verbal learning test; HADS, hospital anxiety and depression scale; NPI, neuropsychiatric inventory.

subscales. The LBCRS total score ($R = 0.28$, $P < .001$) and nonmotor factor ($R = 0.29$, $P < .001$) were correlated with increasing caregiver burden. The LBCRS was not associated with increased caregiver depression.

3.3. Known-groups validity of the LBCRS

The extent to which the LBCRS total and subscales separate the known groups of cognitive impairment, defined by an independent evaluation, is evidence of known-group validity (Table 2) [46]. ANOVA p-tests demonstrated that mean LBCRS total scores were significantly different between DLB and AD ($F = 170.1$; $P < .001$) as was the motor factor ($F = 73.8$; $P < .001$) and nonmotor factor ($F = 55.5$; $P < .001$). The LBCRS scores were also significantly different between MCI due to AD versus MCI due to DLB for the total score ($F = 78.1$; $P < .001$), motor factor ($F = 26.4$; $P < .001$) and nonmotor factor ($F = 12.5$; $P = .001$). The effect size of the LBCRS, based on partial η^2 values, demonstrated that group membership was well-defined by total LBCRS ($\eta^2 = 0.73$), motor factor ($\eta^2 = 0.58$), and nonmotor factor ($\eta^2 = 0.43$). The characteristics of the LBCRS total score and individual questions by different dementia etiologies are demonstrated in Table 6. The LBCRS discriminated DLB from nearly all other dementia causes. Two VaD patients had significant vascular parkinsonism (UPDRS scores of 26 and 70) but had negative dopamine transporter scans and no response to levodopa replacement. Two other dementia patients had notable parkinsonism due to (1) severe developmental disorder and (2) normal pressure hydrocephalus.

3.4. Discriminative ability of the LBCRS

ROC curves were generated to measure the effectiveness of the LBCRS to discriminate between cognitive impairment likely due to DLB from other causes of cognitive impairment (Table 7). Using the cutoff of ≥3 (identical to the developmental research sample), the LBCRS was able to discriminate DLB from AD (AUC, 0.94; 95% CI, 0.90–0.97; $P < .001$) with a sensitivity of 94.2%, specificity of 78.2%, PPV of 68.3%, and NPV of 95.8%. The likelihood ratio of a positive test was 4.1, and the likelihood ratio of a negative test was 0.08. These data support the LBCRS should greatly facilitate

Table 4
LBCRS inter-item correlations, item-total correlations, and factor loadings

LBCRS inter-item correlation matrix											Item-total correlation	Factor loading	
	B	R	PI	T	DS	IL	SS	H	RBD	OH		Motor	Nonmotor
Bradykinesia (B)	1										0.56	0.70	
Rigidity (R)	0.36	1									0.69	0.75	
Postural instability (PI)	0.45	0.57	1								0.64	0.78	
Tremor (T)	0.25	0.47	0.35	1							0.53	0.66	
Daytime sleepiness (DS)	0.12	0.26	0.22	0.12	1						0.53		0.46
Illogical thoughts (IT)	0.02	0.13	0.09	0.04	0.14	1					0.45		0.56
Staring spells (SS)	0.11	0.18	0.15	0.05	0.18	0.25	1				0.47		0.60
Hallucinations (H)	0.24	0.39	0.38	0.27	0.17	0.22	0.20	1			0.64		0.51
RBD	0.02	0.24	0.14	0.21	0.21	0.09	0.15	0.30	1		0.49		0.62
Autonomic (OH)	0.17	0.41	0.21	0.11	0.18	0.08	0.19	0.35	0.39	1	0.48		0.58

Abbreviation: LBCRS, Lewy body composite risk score.

Table 5
LBCRS features: Internal consistency reliability, score distributions, and interscore correlations

Domain	Items	Reliability Cronbach α (95% CI)	Score features and distribution						Interscale correlation Spearman *r*		
			Range	Mean	Median	SD	% floor	% ceiling	Motor	Nonmotor	Total
Motor	4	0.73 (0.66–0.79)	0–4	1.2	1.0	1.3	29.9	6.0	1		
Nonmotor	6	0.57 (0.47–0.67)	0–6	1.8	2.0	1.4	11.5	1.7	0.39	1	
Total	10	0.72 (0.65–0.77)	0–10	2.9	2.0	2.3	9.4	1.3	0.81	0.85	1

Abbreviations: LBCRS, Lewy body composite risk score; CI, confidence interval; SD, standard deviation.
NOTE. % floor is the percentage of patients with the lowest (best) possible score. % ceiling is the percentage of patients with the highest (worst) possible score.

differentiating between the two most common dementia etiologies. Using the same cutoff of 3, the LBCRS was also able to discriminate DLB from any dementia (AUC, 0.94; 95% CI, 0.91–0.98; $P < .001$) with a sensitivity of 97.9%, specificity of 86.1%, PPV of 65.3%, NPV of 99.4%, likelihood ratio of a positive test of 7.0, and likelihood ratio of a negative test of 0.02. Although individually there were only a few cases of other non-AD dementia, we explored the ability of the LBCRS to differentiate DLB from VaD, FTD, and other dementias. The AUC for FTD was 0.96 (95% CI, 0.92–1.00; $P < .001$) and for other dementias was 0.89 (95% CI, 0.75–1.00; $P < .001$). In this cohort, the LBCRS did not differentiate between DLB and VaD (AUC 0.73; 95% CI, 0.45–1.00; $P = .09$); however, 2 of the 5 VaD cases had significant vascular parkinsonism which increased the motor factor of the LBCRS without affecting the nonmotor factor. Finally, the LBCRS was able to discriminate between two probable etiologies of MCI (DLB vs. AD) with an AUC 0.96 (95% CI, 0.91–1.00; $P < .001$) with a sensitivity of 100%, specificity of 72.9%, PPV of 46.2%, NPV of 100%, likelihood ratio of a positive test of 3.2, and likelihood ratio of a negative test of 0.

4. Discussion

We previously used an autopsy-based sample to define a clinical phenotype for Lewy body dementia [15] and created a composite risk score that allowed us to operationalize consensus criteria core, suggestive and supportive features of Lewy body dementias to increase the sensitivity and specificity of the diagnosis [14]. The LBCRS is a brief rating scale that can be completed by the clinician and provides structured questions to assess clinical signs and symptoms highly associated with underlying pathology. This may be particularly helpful concerning clinical symptoms for which there are no broadly accepted methods to assess their presence (i.e.,

Table 6
Performance of LBCRS total scores and individual questions across different dementia etiologies

LBCRS total scores	AD n = 100	LBD n = 53	VaD n = 5	FTD n = 10	Other n = 9	*P* value
Age, y	79.8 (7.5)	78.4 (7.7)	77.2 (6.2)	72.7 (8.2)	70.2 (7.5)	.001
Education, y	15.2 (2.9)	14.5 (3.6)	14.8 (3.4)	16.8 (3.3)	16.9 (3.4)	.28
Gender, % female	58.7	38.9	100.0	30.0	55.6	.02
CDR	1.0 (0.6)	1.5 (0.9)	1.7 (0.9)	0.8 (0.8)	1.0 (0.8)	<.001
CDR-SB	5.7 (3.3)	8.8 (5.2)	9.3 (6.3)	5.2 (4.7)	5.0 (4.4)	<.001
Charlson comorbidity	2.3 (1.3)	2.4 (1.5)	2.6 (1.1)	2.0 (1.3)	2.3 (2.6)	.93
MMSE	19.6 (5.5)	18.2 (7.7)	19.7 (6.0)	23.6 (1.4)	26.1 (2.2)	.005
FAQ	10.5 (8.5)	17.1 (10.1)	16.6 (13.9)	8.1 (9.9)	12.1 (9.9)	.001
NPI	7.7 (5.7)	11.6 (5.7)	11.4 (5.6)	10.5 (9.1)	6.9 (4.5)	.002
UPDRS III	6.8 (8.6)	32.7 (22.1)	30.5 (27.8)	6.7 (6.4)	4.5 (7.7)	<.001
LBCRS total score	2.4 (1.3)	6.1 (2.0)	4.0 (2.9)*	2.4 (0.9)	3.0 (1.9)	<.001
Bradykinesia, %	54.0	97.6	66.7	75.0	66.7	<.001
Rigidity, %	5.7	70.7	0.0	0.0	50.0	<.001
Postural instability, %	21.8	70.7	0.0	12.5	33.3	<.001
Rest tremor, %	9.2	36.6	0.0	0.0	16.7	.002
Daytime sleepiness, %	60.9	92.7	33.3	50.0	83.3	.002
Illogical thoughts, %	48.3	72.5	66.7	37.5	50.0	.101
Staring spells, %	23.0	55.5	33.3	50.0	33.3	.009
Hallucinations, %	9.2	53.7	0.0	0.0	16.7	<.001
RBD, %	4.6	41.5	0.0	0.0	0.0	<.001
Autonomic insufficiency, %	1.2	25.0	0.0	0.0	0.0	<.001

Abbreviations: LBCRS, Lewy body composite risk score; AD, Alzheimer's disease; VaD, vascular dementia; FTD, frontotemporal degeneration; CDR, clinical dementia rating; CDR-SB, clinical dementia rating and its sum of boxes; MMSE, mini mental state examination; FAQ, functional activities questionnaire; UPDRS, unified Parkinson disease rating scale; RBD, rapid eye movement sleep behavior disorder.
*Two patients had vascular parkinsonism with negative dopamine transporter SPECT (DAT) scans.

Table 7
Discrimination ability of the LBCRS by receiver operator characteristic curves

	Area (95% CI)	*P* value	Cutoff score	Sensitivity, %	Specificity, %	PPV	NPV	LR_{pos}	LR_{neg}
DLB versus AD	0.94 (0.90–0.97)	<.001	3	94.2	78.2	68.3	95.8	4.1	0.08
DLB versus any dementia	0.94 (0.91–0.98)	<.001	3	97.9	86.1	65.3	99.4	7.0	0.02
MCI 2° DLB versus 2° AD	0.96 (0.91–1.0)	<.001	2	100.0	72.9	46.2	100.0	3.2	0

Abbreviations: CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; LR_{pos}, likelihood ratio of a positive test; LR_{neg}, likelihood ratio of a negative test; DLB, dementia with Lewy bodies; AD, Alzheimer's disease; MCI, mild cognitive impairment.

cognitive fluctuations [29]). The LBCRS does this while maintaining the brevity (~3 minutes) and simple format of yes/no questions for use in clinical practice, clinical research, and epidemiologic projects potentially alleviating the need to perform the large number of validated scales used to derive the LBCRS. For example, outside of movement disorder clinics, physicians do not commonly perform the UPDRS due to the training required and the length of time to administer—the LBCRS simply requires the clinician to assess whether the patient has bradykinesia, rigidity, postural instability, or rest tremor without having to grade each extremity. Similarly, the LBCRS provides structured yes/no questions for six nonmotor features that are present in the large majority of Lewy body dementia patients but are much less commonly found in other forms of dementia (Table 2). These findings hold true even in the MCI cases where the cognitive tests fail to provide adequate differentiation. Most patients never receive an evaluation by a neurologist skilled in the diagnosis of Lewy body dementia [7,11] and a significant delay and frequent initial misdiagnosis occur in most patients with Lewy body dementia [7,8]. The LBCRS has the potential to provide a clearer, more accurate picture for those patients who are unable to be seen by specialists, hastening the correct diagnosis and reducing the strain and burden placed on patients and caregivers [8–10,48]. Improving sensitivity of diagnoses also (1) reduces the risk of exposure in DLB patients to medications that can have potentially serious adverse consequences (i.e., neuroleptics); (2) increases the potential opportunity to receive appropriate symptomatic therapies in a timely fashion; and (3) lessens the inappropriate exclusion from and inclusion into clinical trials [12].

The LBCRS exhibits excellent data quality including item and scale score variability with ample dispersion of scores. The LBCRS demonstrated excellent internal consistency, known-group validity, and discrimination to distinguish between DLB, AD, and other dementias. Furthermore, the LBCRS was able to discriminate between MCI due to different underlying etiologies (DLB vs. AD). Based on post hoc tests, the motor and nonmotor subdomains equally discriminated group membership. Use of the LBCRS can significantly improve ability to diagnose and classify dementia syndromes thought to be attributable to Lewy body pathology, improve clinical detection, and facilitate enrollment for clinical trials.

A number of "gold standard" evaluations for determining dementia etiology exist including detailed neuropsychological evaluations as the profile of cognitive deficits appears to be different between dementia etiologies [5]. In particular, DLB differs from AD by earlier and greater involvement in visuospatial, executive, and attention domains [5,49]. Although commonly used by neuropsychologists for diagnosis and as outcomes for clinical research projects, comprehensive neuropsychological testing requires a well-trained clinician and ample time to conduct the testing and may not be readily available for all patients. It is interesting to note that in the present study a battery of neuropsychological tests established a cognitive impairment but did not individually provide differentiation between DLB and AD [50] or between MCI due to DLB versus MCI due to AD, whereas clinical signs and symptoms provided discrimination [15,51,52].

The LBCRS was developed and validated in the context of a memory disorders center where the prevalence of MCI and dementia is high. Validation of the LBCRS in other settings where dementia prevalence is lower (e.g., community samples, primary care practices) is a reasonable next step. The internal consistency of the LBCRS was in the good to very good range suggesting that it may be most suitable for group-based discrimination. The internal consistency is marred somewhat by the diverse nature of the questions of the LBCRS (particularly nonmotor) reflecting the varied presentation of the disorder (the 10 symptoms present in 7%–91% of patients). As this is a cross-sectional study, another next step is to demonstrate the longitudinal properties of the LBCRS and determine whether those individuals with MCI due to DLB in fact develop DLB. Strengths of this study included the comprehensive cognitive-behavioral-motor evaluation and that the LBCRS was not used in the diagnosis. Another advantage of the LBCRS is that it is brief enough to be printed on one piece of paper or viewed in on single computer screenshot which should maximize its clinical utility. In establishing the validity and reliability of the LBCRS, we wanted to test its performance in a "real-world" clinic setting with patients who are referred from the community rather than in a research sample. Our clinic sample had an admixture of gender, education, comorbidities, cognitive, behavioral, affective,

motor symptoms, and diagnoses. A limitation was that the diagnoses were largely clinical based on published criteria, no biomarkers or pathology was considered in this project. As this was a clinical research project, biomarkers such as dopamine transporter scans are not FDA-approved for diagnosing DLB in the United States. However, the LBCRS was developed from autopsy-verified cases of health controls, AD, Parkinson's disease, PDD, and DLB [15] and validated in a research sample with AD biomarkers [14]. There were no PDD cases included in this study for two reasons: (1) PDD would by definition have a positive LBCRS because the four cardinal motor signs of Parkinson's disease (bradykinesia, rigidity, postural instability, and rest tremor) and (2) many of these patients are predominantly seen by the movement disorders specialist at academic centers rather than by cognitive specialists. The published LBCRS studies to date have been completed at a single site; future studies at other sites by other investigators are needed to further demonstrate utility; however, a recent presentation reported the validity of the LBCRS discriminating AD from DLB in a sample of Korean older adults with dementia [53].

The LBCRS may serve as an effective clinical research tool to improve the detection of DLB (and PDD) in the office setting, assist in the inclusion/exclusion criteria for clinical trials, and as an intermittent assessment tool to determine whether the DLB phenotype is developing. Early detection of Lewy body dementias will be important to enable future interventions at the earliest stages when they are likely to be most effective. This study provides evidence-based methodology to use the LBCRS to identify individuals likely to have Lewy bodies at autopsy in clinical practice and for participation in clinical trials, prevention studies, community surveys, and biomarker research.

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J.E.G. takes full responsibility for the data, the analyses and interpretation, and the conduct of the research; has full access to all the data; and has the right to publish any and all data, separate and apart from the guidance of any sponsor. J.E.G. conducted all statistical analyses.

RESEARCH IN CONTEXT

1. Systematic review: The author reviewed the literature using traditional (e.g., PubMed) sources. Although consensus criteria for dementia with Lewy bodies exist and have excellent specificity (79%–100%), in clinical practice, the criteria have poor sensitivity (12%–88%). This is in part due the lack of a standardized way to operationalize the core, suggestive and supportive features in a way that lends itself to clinical practice outside of specialty centers. To address this, we created and validated the Lewy body composite risk score (LBCRS).
2. Interpretation: Our findings support the LBCRS may provide a rapid method to determine the probability that Lewy body pathology is a significant contributor to the dementia syndrome and should facilitate eligibility for clinical trials and research projects, stage patients in clinical practice, and improve case ascertainment and staging in population studies.
3. Future directions: The LBCRS is robust in detecting dementia and cognitive impairment due to Lewy body pathology in a clinical sample. Future studies are needed to assess the utility of the LBCRS in other settings where dementia prevalence is lower (community cohort and primary care), examine the longitudinal properties of the LBCRS, and test its response to interventions.

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