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Original Research Article

The Pentagon Copying Test and the Clock Drawing Test as Prognostic Markers in Dementia with Lewy Bodies

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Keywords
Dementia with Lewy bodies · Pentagon copying test · Clock drawing test · Prognostic marker

Abstract
Aims: To determine whether the pentagon copying test (PCT) and the clock drawing test (CDT) are associated with nursing home admission or survival in dementia with Lewy bodies (DLB). ***Methods:*** The PCT and/or the CDT were retrospectively collected from 103 clinically diagnosed probable DLB patients at a university medical center and general hospital. Patients with high versus low scores on these tests were compared. ***Results:*** Kaplan-Meier analysis showed that patients with a low score on the PCT had a shorter time to nursing home admission than patients with a high score (log-rank χ^2 = 6.1, p = 0.01). Patients with a low score on the PCT or the CDT had a shorter survival than patients with a high score (log-rank χ^2 = 5.4, p = 0.02, and log-rank χ^2 = 11.2, p < 0.001, respectively). Cox regression analyses showed the same associations with an HR of 2.2 (95% CI 1.2–4.1) for the PCT and an HR of 2.9 (95% CI 1.6–5.4) for the CDT. ***Conclusion:*** The PCT and the CDT may function as prognostic markers in DLB. This finding is clinically relevant as these tests can be applied easily in the clinical setting and can provide valuable prognostic information. Furthermore, it may improve disease management and patient selection for research purposes.

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Introduction

Dementia with Lewy bodies (DLB) is a common neurodegenerative disease and is characterized by progressive cognitive decline, parkinsonism, hallucinations, fluctuations, and REM sleep behavior disorders [1]. Cognitive impairment is typically observed in attention, executive functioning, and visuospatial/constructional abilities [2–4]. Both the clinical symptoms and disease course of DLB are very heterogeneous [5]. The median time from diagnosis to nursing home admission and death varies widely, ranging from 1.8 [6] to 6.1 years [7] and from 4.7 [8] to 7.3 [7] years, respectively. As a consequence, the prognosis of patients with DLB is hard to predict. Identification of prognostic factors of DLB is therefore important to improve patient care and research.

Factors that could predict nursing home admission and survival have been studied thoroughly in dementia [9–11], but have been less abundantly studied in DLB specifically. Nevertheless, there are some studies which reported an association between several factors and prognosis in DLB. Male sex and the use of antipsychotic medications have been associated with an increased risk of nursing home admission, whereas the use of cholinesterase inhibitors had a protective effect on nursing home admission and survival in DLB patients [6, 12]. Several clinical symptoms, such as visual hallucinations, fluctuating cognitive functioning [13], and orthostatic hypotension [14], were associated with a high mortality in DLB and Parkinson's disease dementia. Furthermore, Alzheimer's disease co-pathology was associated with earlier nursing home admission and shorter survival in DLB patients [7, 15–18].

Knowledge about the association between specific cognitive impairments and prognosis is lacking in DLB. As visual hallucinations have been associated with visuospatial impairment and a shorter survival in DLB [13, 19], we hypothesized that patients who perform poorly on tests measuring visuospatial/constructional abilities have a worse prognosis than patients with more preserved visuospatial/constructional abilities (independent of visual hallucinations). In this study, we investigated whether the pentagon copying test (PCT) and the clock drawing test (CDT), two tests which evaluate among others visuospatial/constructional abilities, are associated with nursing home admission or survival in DLB patients.

Materials and Methods

Study Design and Participants

In this retrospective study we included participants from a university medical center (Erasmus Medical Center, Rotterdam) and a general hospital (Elisabeth-TweeSteden Ziekenhuis, Tilburg) in the Netherlands. Participants were included if they visited these centers between 2001 and 2016 and received a clinical diagnosis of probable DLB (according to McKeith et al. [20]). Furthermore, a PCT or a CDT had to be available for each participant.

Procedure

Demographic and clinical data were obtained from patient records. General practitioners were contacted to supplement missing data about nursing home admission. Missing data about survival was obtained by consulting the "Basisregistratie personen," a registration system containing demographic data about all Dutch citizens. Date of nursing home admission and date of death were collected until September 1, 2016.

Measurements

For the PCT, patients were asked to copy a figure of two overlapping pentagons by standardized instructions. We used the qualitative scoring method of Caffarra et al. [21] (13-point scale; can be provided by the authors on request). For the CDT, patients were asked to draw the face of a clock, place hours 1 through 12, and place the hands at a specified time by standardized instructions. A free-drawn method was used at Erasmus Medical Center and a pre-drawn circle method was used at Elisabeth-TweeSteden Ziekenhuis. We used the modified scoring method of Royall et al. [22] to score the CDT (11-point scale; can be provided by

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the authors on request). Modifications to the original scoring method of Royall et al. were made with the purpose of combining the free-drawn method and the pre-drawn circle method. Therefore, points regarding the drawing of the face of the clock and the sequence of placing the numbers 3, 6, 9, and 12 were not included for the patients at Erasmus Medical Center. Several methods have been proposed to score the PCT and the CDT [21, 23, 24]. We chose the qualitative scoring method of Caffarra et al. [21] for the PCT and a modified scoring method of Royall et al. [22] for the CDT, as we assumed that these scoring methods have a moderately high discriminative value due to their relatively wide scoring range. Two researchers (L.J.M.V. and A.G.K.) scored the PCT and CDT of all patients independently. Tests with discordant scores were discussed thoroughly to reach a consensus.

Statistical Analyses

Differences in demographic and clinical characteristics between DLB patients with high versus low scores on the PCT and the CDT were analyzed with the independent Student *t* test, the Mann-Whitney U test, or the χ^2 test where appropriate.

Survival analyses were performed using Kaplan-Meier analyses and Cox regression analyses. Sex, age at PCT or CDT, level of education, presence of visual hallucinations before or at the time of PCT or CDT, and time between first symptom and PCT, CDT, or Mini-Mental State Examination (MMSE) score were included as covariates in the Cox regression analyses. Separate analyses were performed with use of antipsychotics, use of cholinesterase inhibitors, or fluctuations during the disease as covariates instead of presence of visual hallucinations before or at the time of PCT or CDT. A selection of covariates was included when the statistical model did not tolerate the use of all covariates.

Additional post hoc Kaplan-Meier analyses were performed to examine the specificity of the PCT and the CDT as prognostic markers. Therefore, we analyzed all neuropsychological tests for which data was available in 30 patients or more. Statistical analyses were performed in IBM SPSS Statistics 21.0 for Windows (SPSS Inc., Chicago, IL, USA). *p* values <0.05 were considered statistically significant.

Results

Demographic and Clinical Characteristics

A total of 103 probable DLB patients were included in this study. Table 1 shows the demographic and clinical characteristics of these patients. The mean age at first symptom was 69.9 ± 8.2 years and 79.6% of patients were male. The CDT was available in all and the PCT in 92.2% of patients. The median score on the PCT was 11 (IQR 8–12) and the median score on the CDT was 6 (IQR 3–8) (medians were used since both scores were not normally distributed). The median time from first symptom to nursing home admission and death was 5.0 (IQR 3.1–7.0) and 5.3 (IQR 2.8–8.3) years, respectively.

Table 2 shows the demographic and clinical differences between patients with a low versus high score (stratified on the median) on the PCT or the CDT. There were no significant differences in sex, age at first symptom, center, or level of education. Of clinical symptoms and medication use, only the frequency of visual hallucinations before or at the time of PCT or CDT was higher in the group of patients with a low score compared to the group of patients with a high score on the PCT or the CDT (61.0 vs. 36.0%, $p = 0.02$, and 63.6 vs. 40.0%, respectively, $p = 0.02$). The median MMSE score was higher in the group with a high score on the PCT or the CDT compared to the group of patients with a low score on these tests (22 [IQR 19–26] vs. 26 [IQR 24–27], respectively, $p = 0.003$, and 22 [IQR 19–25] vs. 26 [IQR 24–27], respectively, $p < 0.001$).

Nursing Home Admission

Figure 1 shows the Kaplan-Meier curves for time from PCT or CDT to nursing home admission. Patients with a low score on the PCT showed a shorter time to nursing home admission than patients with a high score on the PCT (log-rank $\chi^2 = 6.1$, df = 1, $p = 0.01$). There

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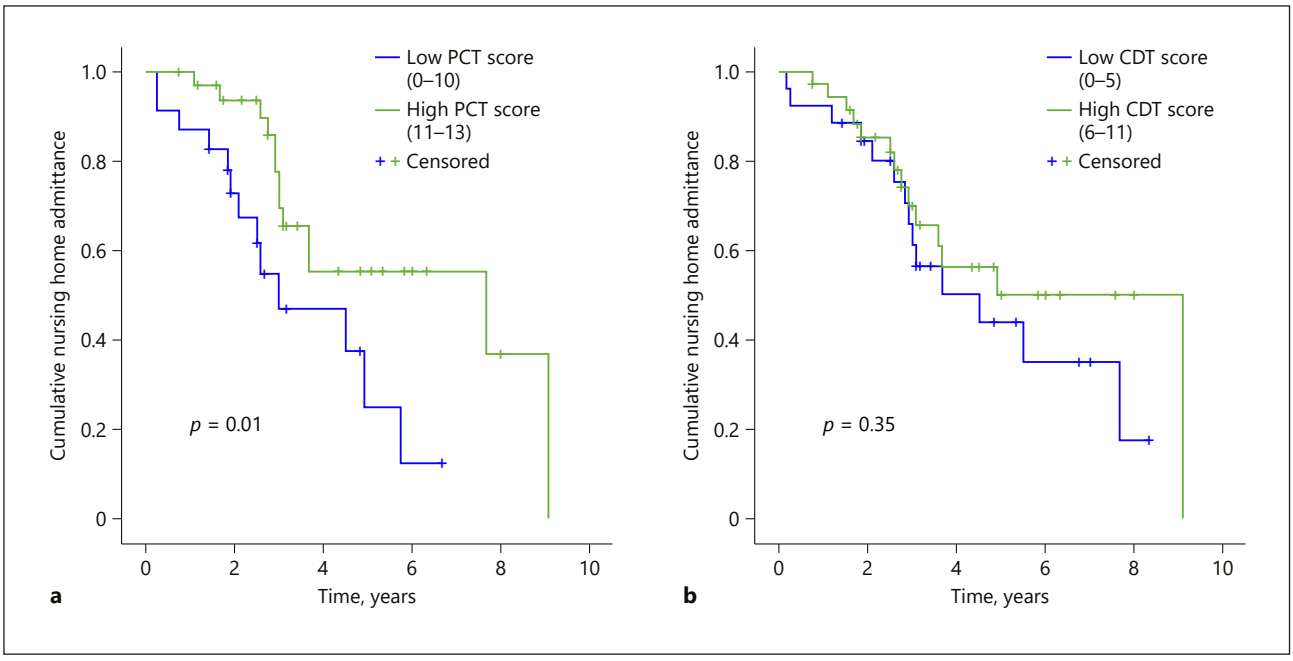

Fig. 1. Kaplan-Meier curves of low versus high score on the PCT (**a**) or the CDT (**b**) and nursing home admission. Test scores were stratified on the median. Differences between distributions were analyzed using the log-rank test. CDT, clock drawing test; PCT, pentagon copying test.

Table 1. Demographic and clinical characteristics of DLB patients (*n* = 103)

Demographics	
Sex, male	82 (79.6%)
Age at first symptom, years	69.9 (8.2)
Center, Erasmus Medical Center	40 (38.8%)
Education, Verhage's classification (*n* = 97)	4 (2–5)
Admission to nursing home (*n* = 64)	30 (46.9%)
Deceased (*n* = 102)	59 (57.8%)
Symptoms	
Parkinsonism	85 (82.5%)
Visual hallucinations	78 (75.7%)
Visual hallucinations before PCT or CDT (*n* = 99)	50 (48.5%)
Cognitive scores	
MMSE score (*n* = 102)	25 (22–26)
PCT score (*n* = 95)	11 (8–12)
CDT score	6 (3–8)
Disease course	
Time from first symptom to nursing home admission, years (*n* = 26)	5.0 (3.1–7.0)
Time from first symptom to death, years (*n* = 59)	5.3 (2.8–8.3)
Time from first symptom to censoring (nursing home), years (*n* = 34)	6.4 (4.1–8.9)
Time from first symptom to censoring (death), years (*n* = 43)	6.7 (4.1–7.7)

Values are presented as mean (SD), median (IQR), or *n* (%). CDT, clock drawing test; DLB, dementia with Lewy bodies; MMSE, Mini-Mental State Examination; PCT, pentagon copying test.

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Table 2. Differences between patients with low versus high score on the PCT and the CDT

	PCT			CDT		
	low score (n = 42)	high score (n = 53)	p value	low score (n = 47)	high score (n = 56)	p value
Demographics						
Sex, male	32 (76.2%)	45 (84.9%)	0.28	36 (76.6%)	46 (82.1%)	0.49
Age at first symptom, years	70.9 (8.4)	69.4 (8.3)	0.36	71.1 (7.5)	68.8 (8.7)	0.16
Center, Erasmus Medical Center	16 (38.1%)	17 (32.1%)	0.54	16 (34.0%)	24 (42.9%)	0.36
Education, Verhage's classification (n = 38;52|44;53)	4 (2.8–5)	4 (2.3–5)	0.68	4 (2–5.8)	4 (2.5–5)	0.85
Admission to nursing home (n = 23;34|27;37)	13 (56.5%)	14 (41.2%)	0.26	15 (55.6%)	15 (40.5%)	0.24
Deceased (n = 41;53|46;56)	28 (68.3%)	24 (45.3%)	**0.03**	32 (69.6%)	27 (48.2%)	**0.03**
Symptoms/medication						
Parkinsonism	34 (81.0%)	43 (81.1%)	0.98	39 (83.0%)	46 (82.1%)	0.91
Visual hallucinations	32 (76.2%)	38 (71.7%)	0.62	39 (83.0%)	39 (69.6%)	0.12
Visual hallucinations before or at PCT or CDT (n = 41;50|44;55)	25 (61.0%)	18 (36.0%)	**0.02**	28 (63.6%)	22 (40.0%)	**0.02**
Fluctuations	36 (85.7%)	44 (83.0%)	0.72	39 (83.0%)	47 (83.9%)	0.90
Antipsychotic medication	17 (40.5%)	19 (35.8%)	0.64	15 (31.9%)	23 (41.1%)	0.34
Cholinesterase inhibitors	39 (92.9%)	47 (88.7%)	0.49	44 (93.6%)	50 (89.3%)	0.44
Cognitive score						
MMSE (n = 46;56)	22 (19–26)	26 (24–27)	**0.003**	22 (19–25)	26 (24–27)	**<0.001**
Disease course						
Age at time of PCT	73.7 (7.8)	71.8 (7.6)	0.25	NA	NA	NA
Age at time of CDT	NA	NA	NA	74.0 (7.0)	71.2 (7.8)	0.06
Time between first symptom and PCT, years	2.0 (1.1–3.6)	1.8 (1.3–3.3)	0.97	NA	NA	NA
Time between first symptom and CDT, years	NA	NA	NA	2.1 (1.4–4.2)	1.7 (1.1–3.0)	0.12
Time between MMSE and PCT, months	0.0 (0.0–2.3)	0.0 (0.0–0.0)	0.26	NA	NA	NA
Time between MMSE and CDT, months (n = 46;56)	NA	NA	NA	0.0 (0.0–0.0)	0.0 (0.0–1.0)	0.24

Values are presented as mean (SD), median (IQR), or n (%). Group differences were analyzed by χ^2 test (sex, center, admission to nursing home, deceased, parkinsonism, visual hallucinations [before or at PCT or CDT], fluctuations, antipsychotic medication, cholinesterase inhibitors), independent Student t test (age), and Mann-Whitney U test (education, MMSE, time between first symptom/MMSE and PCT or CDT). p values <0.05 are depicted in bold. Groups were stratified on the median (low PCT, ≤10; high PCT, >10; low CDT, ≤5; high CDT, >5). CDT, clock drawing test; MMSE, Mini-Mental State Examination; NA, not applicable; PCT, pentagon copying test.

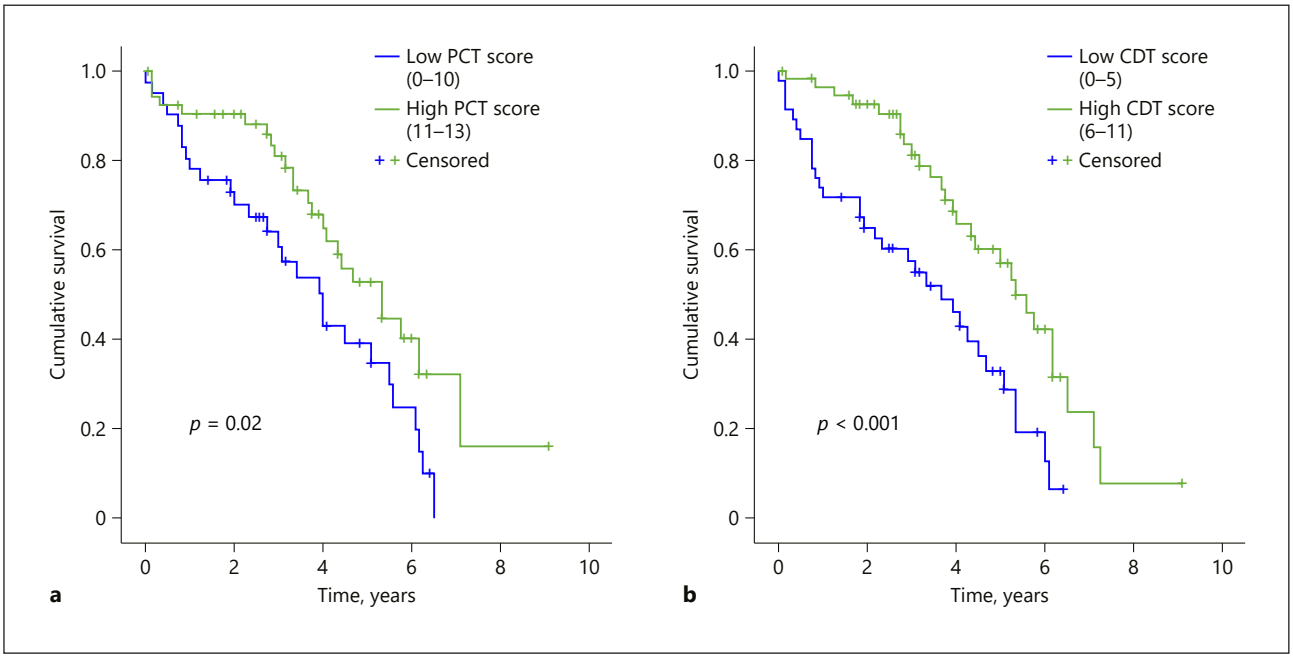

Fig. 2. Kaplan-Meier curves of low versus high score on the PCT (**a**) or the CDT (**b**) and survival. Test scores were stratified on the median. Differences between distributions were analyzed using the log-rank test. CDT, clock drawing test; PCT, pentagon copying test.

was no difference in time to nursing home admission between the groups with low versus high score on the CDT (log-rank χ^2 = 0.87, df = 1, p = 0.35). Cox regression analysis with adjustment for sex and age at PCT or CDT showed the same associations between the tests and nursing home admission (PCT: HR 2.35, 95% CI 1.01–5.47; CDT: HR 1.30, 95% CI 0.59–2.88). Furthermore, Cox regression analysis with adjustment for time between first symptom and PCT or CDT or MMSE score showed the same associations between the tests and nursing home admission (PCT: HR 2.57, 95% CI 1.14–5.78; CDT: HR 1.35, 95% CI 0.58–3.13, both adjusted for time between first symptom and PCT or CDT; PCT: HR 2.75, 95% CI 1.70–6.47; CDT: HR 1.55, 95% CI 0.69–3.51, both adjusted for MMSE score).

Survival

Figure 2 shows the Kaplan-Meier curves for time from PCT or CDT to death. Patients with a low score on the PCT showed a shorter survival than patients with a high score on the PCT (log-rank χ^2 = 5.4, df = 1, p = 0.02). The same association was found between the scores on the CDT and survival (log-rank χ^2 = 11.2, df = 1, p < 0.001). After 5 years, 39.1% of patients survived in the group with a low score on the PCT compared to 52.8% in the group with a high score on the PCT. Furthermore, the 5-year survival was 32.9% in the group with a low score on the CDT compared to 57.0% in the group with a high score on the CDT.

Cox regression analysis with adjustment for sex, age at PCT or CDT, level of education, presence of visual hallucinations before or at the time of PCT or CDT, and time between first symptom and PCT or CDT also showed that patients with a low score on the PCT or the CDT had a shorter survival than patients with a high score on these tests (PCT: HR 2.17, 95% CI 1.16–4.05; CDT: HR 2.89, 95% CI 1.56–5.37). When adjusting for MMSE score instead of time between first symptom and PCT or CDT, the same associations were found (PCT: HR 1.90, 95% CI 1.00–3.64; CDT: HR 2.49, 95% CI 1.28–4.85). However, the association between the

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Table 3. Kaplan-Meier analyses of low versus high scores on other cognitive tests and nursing home admission or survival

	Nursing home admission					Survival				
	patients, *n*	events, *n*	median	χ^2	*p* value	patients, *n*	events, *n*	median	χ^2	*p* value
Dutch RAVLT	34	14	24	0.004	0.95	39	20	24	0.03	0.87
Animal fluency	38	18	12	0.52	0.47	43	23	12	0.02	0.90
Trail-Making Test Part A	36	17	98	0.001	0.98	43	24	94.5	0.001	0.98
Stroop III/II ratio	30	12	2.0	0.85	0.36	35	17	62.0	0.009	0.92

Test scores were stratified on the median. Differences between distributions were analyzed using the log-rank test. RAVLT, Rey Auditory Verbal Learning Test.

PCT and survival just reached significance. Correction for use of antipsychotics, use of cholinesterase inhibitors, or fluctuating cognitive functioning instead of visual hallucinations before or at PCT or CDT did not change the effects found (values not shown).

Other Cognitive Tests

To test the specificity of the association between the PCT or the CDT and nursing home admission and survival, four other cognitive tests were used post hoc. These tests included the Dutch Rey Auditory Verbal Learning Test, a category fluency test (animal naming), the Trail-Making Test Part A, and the Stroop Color Word Test III/II ratio. Kaplan-Meier analyses showed no associations between these tests and time to nursing home admission or survival (Table 3).

Discussion

This study suggests that the PCT and the CDT are markers for survival in DLB. Patients with a low score on the PCT or the CDT had approximately a 2- to 3-fold lower survival rate than patients with a high score on these tests (independently of sex, age at test, level of education, presence of visual hallucinations before or at the time of testing, and time between first symptom and test or MMSE score). In addition, this study showed that the PCT may be a marker for the time to nursing home admission. These associations may be specific to these tests, as no associations were found when analyzing four other cognitive tests and nursing home admission or survival.

Similar studies have been performed concerning the association between the PCT or the CDT and cognitive function in patients with DLB and Parkinson's disease [25, 26]. One study showed that DLB patients with low scores on the CDT had faster cognitive decline than DLB patients with high scores on the CDT [25]. Another study showed that low scores on the PCT were associated with cognitive decline in Parkinson's disease [26]. These results are in line with our findings, as patients with a faster cognitive decline have, in general, an increased risk of mortality compared to patients with a slower cognitive decline [27]. This is the first study which shows that the PCT and the CDT are directly associated with survival in DLB.

In this study, we tried to adjust our results for disease severity at the moment of the PCT or the CDT using the time between first symptom and test or the MMSE score as potential confounders. Both variables are not optimal to adjust for disease severity, but can be seen as

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best available surrogates. When using time between first symptom and test, we assume that the decay of functions is constant over time and approximately the same between patients. When using the MMSE score to adjust for disease severity, the observed effect of the PCT or the CDT may decrease, as measured cognitive functions in the PCT and the CDT are also included in the MMSE. However, although overcorrection may be present when using the MMSE score as a potential confounder, the effect of the PCT and the CDT on survival was still found. Therefore, our data suggest that the PCT and the CDT, regardless of disease severity measured by time between first symptom and test or MMSE score, are associated with survival.

Both the PCT and the CDT assess visuospatial/constructional abilities. However, other cognitive skills, such as executive functioning, verbal understanding, and memory are also needed to complete these tests [21, 22, 28, 29]. This is the case for the CDT in particular, in which executive functioning is a very large part of what is measured. It is not clear why a more impaired PCT or CDT in the beginning of the disease predicts an earlier death. Brain imaging studies have shown that visuospatial/constructional abilities are associated with the parietal cortex [30] and that executive functioning is associated with the anterior cingulate/posterior medial frontal cortex and lateral prefrontal cortices [31]. It has been hypothesized that increased cholinergic deficits and/or a higher Lewy body load in these brain regions can lead to more pronounced visuospatial/constructional or executive dysfunction [32, 33]. The PCT and the CDT may be sensitive to assess these cognitive changes and may therefore be a specific marker of disease severity (independent of time between first symptom and test or MMSE score) and may predict a more malignant disease course.

Although we took potential confounders into account (sex, age, level of education, presence of visual hallucinations before or at the time of testing, time between first symptoms and test or MMSE), other factors may have influenced our findings. Especially those factors associated with survival which have been found by others, such as use of antipsychotics [34] or cholinesterase inhibitors [6], presence of hallucinations, and fluctuating cognitive functioning [13] are important potential confounders. However, as has been shown in this study, these factors had no effect on the associations found.

This study has some limitations. One is that the DLB diagnoses of our patients were based on clinical criteria [20] and were not pathologically confirmed. The clinical criteria of DLB have a relatively low specificity (81%) [35], and therefore it is possible that false-positive patients were included in our study. Another limitation is the possible introduction of information bias. For example, the exact time of symptom onset is often very hard to pinpoint for patients and their caregivers. We chose to use the time of first symptom in our analyses as this is more comparable between patients than the time of diagnosis. The latter varies widely due to the doctor's delay that is often seen in DLB [36]. Furthermore, it is possible that clinical symptoms such as hallucinations have been missed because they may not always be reported by the patient or recognized as such by the physician.

Although this study was conducted in a large set of DLB patients, reproduction of our findings is needed. Future research should ideally focus on prospective longitudinal data of DLB patients with pathological confirmation of the diagnosis.

Conclusion

This is the first study which shows that the PCT and the CDT may function as prognostic markers in DLB. This finding is clinically relevant as the PCT and the CDT can be applied easily in the clinical setting and can provide valuable prognostic information for patients and caregivers. Furthermore, it may improve disease management and the selection of patients for research purposes.

Acknowledgments

We would like to thank all patients who participated in this study.

Statement of Ethics

This study was approved by the Medical Ethics Committee of Erasmus Medical Center. All living patients provided informed consent for the use of their data for research purposes. In concordance with Dutch legislation, deceased patients who had not raised objections against the use of their data for research purposes during life were also included in the study.

Disclosure Statement

The authors declare that no competing interests exist. There were no funding sources.

Author Contributions

L.J.M. Vergouw: study concept and design, acquisition, analysis, and interpretation of data, statistical analysis, manuscript preparation. M. Salomé: study concept and design, acquisition, analysis, and interpretation of data, statistical analysis. A.G. Kerklaan: acquisition, analysis, and interpretation of data, statistical analysis, manuscript preparation. C. Kies: acquisition, analysis, and interpretation of data, statistical analysis. G. Roks: study concept and design, analysis and interpretation of data. E. van den Berg: study concept and design, analysis and interpretation of data, statistical analysis. F.J. de Jong: study concept and design, analysis and interpretation of data. All authors critically reviewed the manuscript.

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