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Original Research Article

Brief Tests such as the Clock Drawing Test or Cognistat Can Be Useful Predictors of Conversion from MCI to Dementia in the Clinical Assessment of Outpatients

Magnar Nesset[a] Hege Kersten[b] Ingun Dina Ulstein[b, c]

[a]Department of Psychogeriatry, Telemark Hospital Trust, Skien, [b]Old Age Psychiatry Research Network, Telemark Hospital Trust and Vestfold Hospital Trust, Tønsberg, and [c]Department of Psychiatry of Old Age, Oslo University Hospital, Asker, Norway

Key Words
Mild cognitive impairment · Dementia · Predictors · Neuropsychological tests

Abstract
Background: The identification of patients with mild cognitive impairment (MCI) who are at high risk of conversion to dementia is a challenging clinical task. ***Aims:*** To investigate whether simple cognitive screening tests can predict the conversion from MCI to dementia and to study the impact of different patient characteristics on the progression rate. ***Methods:*** A retrospective, longitudinal study of 90 outpatients diagnosed with MCI at a psychogeriatric clinic in Norway was conducted. Baseline scores on the Mini-Mental State Examination (MMSE), Clock Drawing Test (CDT), and Neurobehavioral Cognitive Status Examination (Cognistat) were related to ICD-10 diagnosis during 46 months. The influence of demographic, life situational, and clinical data were analyzed. ***Results:*** Sixty-four patients were diagnosed with dementia, significantly more females (82%) than males (50%) ($p < 0.01$). Low scores on the CDT [adjusted hazard ratio (HR) = 0.85; 95% CI 0.73–0.97; $p = 0.020$] and Cognistat (adjusted HR = 0.78; 95% CI 0.65–0.93; $p = 0.007$) significantly predicted the conversion from MCI to dementia, whereas the MMSE score did not. ***Conclusions:*** A high proportion of patients converted from MCI to dementia within 46 months, and females seem to be at higher risk. CDT and Cognistat significantly predicted the conversion from MCI to dementia and are therefore considered appropriate tests in clinical practice.

Magnar Nesset
Department of Psychogeriatry, Telemark Hospital Trust
Ulefossveien 55
NO–3710 Skien (Norway)
E-Mail nesm@sthf.no

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Introduction

There is an increasing focus on the detection of preclinical dementia to optimize preventive and therapeutic strategies for this group of patients. Mild cognitive impairment (MCI) is regarded as a risk factor or transitional state of dementia [1, 2]. To enable targeted interventions, it is of great importance to identify patients with MCI who are at high risk of developing dementia. Hence, there is a widespread ambition for clinicians to differentiate precisely between MCI and the early stages of dementia [3]. Consequently, there is a high demand for good-quality clinical assessments of MCI and early dementia, which is a challenge that has to be met in daily clinical practice.

Many studies have explored the prevalence of MCI and the rate of progression to dementia in different populations [4]. The expected conversion rate is higher in clinical populations than in nonclinical ones [5]. Accordingly, Farias et al. [6] found annual conversion rates of 13% in a clinical sample and 3% in a community sample. In a meta-analysis of clinical studies from 2009, the annual progression rate from MCI to dementia was estimated to be 9.6% for clinical populations [4], whereas a recent review reported that the conversion rate to Alzheimer's dementia ranged from 10.2 to 33.6% in different clinical cohorts [7].

The considerable differences in the estimates of the annual progression rate from MCI to dementia reported previously show that there still is a need to explore the factors that affect the rate of progression from MCI to dementia in different cohorts.

Simple and easy-to-administer cognitive tests have become indispensable tools for the effective and reliable assessment of dementia. Correspondingly, the development of simple tools that would allow a more accurate differentiation between MCI and early-stage dementia and the identification of subjects at high risk of developing dementia would be of great clinical value. Thus, the aims of this study were to investigate whether simple cognitive screening tests can predict the conversion from MCI to dementia and to study the impact of different patient characteristics on the progression rate from MCI to dementia in a clinical population.

Methods

Study Population

In this retrospective study, we used data from the medical records of patients who had been referred to an outpatient psychogeriatric clinic because of memory problems or suspicion of dementia. The sample consisted of patients who had been subjected to a comprehensive clinical assessment consisting of clinical interviews and cognitive tests and imaging, and were diagnosed with MCI at baseline. All patients attended follow-up assessments at the clinic one or several times over a period of 5–46 months. In most cases, a close relative or another informant who knew the patient well was interviewed as part of the assessment, focusing on themes that were relevant for the diagnoses as well as checking and supplementing the clinical information given by the patient.

Diagnosis

The diagnosis of dementia was established by a team consisting of psychiatrists, clinical psychologists and trained psychiatric nurses, and was in accordance with the classification of mental and behavioral disorders included in the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) and with the guidelines from the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [8, 9]. Primary and secondary diagnoses of mental disorders were established according to the ICD-10 criteria [8]. Diag-

nostic practice for the MCI diagnosis was in accordance with the criteria recommended by the working groups of Winblad et al. [2] and Portet et al. [10], e.g., subjective memory complaint was not a necessary condition for this diagnosis, as in the Mayo definition [11].

Cognitive Assessment Tools

Three cognitive assessment tools were used routinely to assess cognitive function. The Mini-Mental State Examination (MMSE) is a widely used 11-item cognitive screening instrument with a test score ranging from 0 to 30, with a higher score denoting better cognitive functioning [12]. The Neurobehavioral Cognitive Status Examination (Cognistat) is a short cognitive test battery that was designed to provide a profile from different cognitive domains based on 10 subtests regarding orientation, attention, understanding of simple commands, repetition of sentences, naming, visuoconstruction, verbal memory, calculation, similarities/verbal abstraction, and everyday/concrete judgment [13]. The total score reflects the number of cognitive functions that are intact: a score within the normal range is scored '1', whereas a lower score is denoted '0', giving a total sum score that ranges from 0 to 10 [14]. The cutoff point is age corrected for subjects aged 65–74 and 75–84 years [15]. The Clock Drawing Test (CDT) is a frequently used screening tool in which the subject is asked to draw a clock with correct numbers and pointers on it. There are several published versions of this test. In this study, a 7-point version was used, with a score of 7 indicating better functioning [16–18]. The CDT taps into a series of cognitive domains (i.e., verbal understanding, memory, spatial knowledge, abstract thinking, concentration, and visuoconstructive skills), including executive functions [19].

Covariates

Demographic data such as gender, age, number of years of education, marital/cohabitant status, life situation (e.g., housing and other household members), formal help (e.g., nurse and help with cleaning and hot meals), and other services (e.g., attending seniors' centers) were collected at baseline.

Most of the patients had undergone one or more types of brain imaging: magnetic resonance imaging, computed axial tomography, or single-photon emission computer tomography. The conclusions drawn from the brain imaging were categorized as 'normal', 'uncertain', or 'pathological' (the latter when significant substance loss, infarct, clearly expanded ventricles, or chronic ischemia were observed).

No formal assessment tools had been used routinely to assess activities of daily living (ADL). Thus, the patient files were searched for relevant information regarding instrumental and personal ADL functioning, and the explicit evaluations of ADL by the clinicians were categorized as 'reduced', 'normal', or 'not assessed'.

Anticholinergic medication was recorded in accordance with the Anticholinergic Cognitive Burden List (ACB-list), which was developed by the Aging Brain Program at the Indiana University Center for Aging Research [20]. Drugs with scores of 2 or 3 on the ACB-list were labeled anticholinergic.

Ethics

The study has been presented to the Regional Committee for Medical Research Ethics in South-Eastern Norway and approved by the Norwegian Social Science Data Service.

Statistical Analyses

The patients were divided into two groups according to their diagnosis. One group retained their MCI diagnosis and was denoted the nonconverter (NonC) group, whereas the other group received a dementia diagnosis and was denoted the converter (C) group.

Distributions of the predictive variables across the two diagnostic outcome categories were compared using the Mann-Whitney U test for continuous variables and Pearson's χ^2 test for categorical variables. Spearman's rank correlation matrix was inspected to identify collinearity between the variables.

The three cognitive tests and the significantly unbalanced covariates that showed associations with outcome variables at a significance level of $p < 0.1$ in a univariate analysis were entered as independent variables into the multivariate Cox proportional hazards model, using diagnostic outcomes as the dependent variable. Time to conversion was defined as the time in months from baseline to the assessment that led to the diagnosis of dementia. The software used was SPSS for Windows, release 19.0.0.2 [21].

Results

Ninety-three patients satisfied the inclusion criteria. Among the 93 patients with a primary diagnosis of MCI, 3 were diagnosed with mood disorder and did not have MCI at the first follow-up; therefore, they were excluded from the study. The remaining 90 patients comprised 60 females with a mean age of 75.5 years (SD 7.0) and 30 males with a mean age of 69.4 years (SD 7.9) who had been reassessed from one to seven times, with a median interval between the assessments of 8.0 months (range 43.5). Sixty-four of these individuals (49 females and 15 males) developed dementia (C group). Thirty-six (56.3%) individuals in the C group were diagnosed with dementia of Alzheimer's type, 11 with vascular dementia, 7 with frontotemporal dementia, 3 with dementia associated with other diseases, and 7 with unspecified dementia. Twenty-six patients retained their MCI diagnosis (NonC group) (table 1).

The median time from baseline to the dementia diagnosis was 12.0 months (range 41.0), and more than 50% of the total sample were diagnosed with dementia within 18 months. The median time from the first assessment to the last follow-up in the NonC group was 17.5 months (range 32.0). The time between the follow-ups varied between the subjects, and the NonC group was on average followed for a longer total period than the C group.

None of the dementia diagnoses was removed at later follow-ups. However, the type of dementia was changed in 2 patients: one from frontotemporal to unspecified dementia and the other one vice versa. The characteristics of the two diagnostic subgroups in the study cohort are shown in table 1.

The bivariate analysis showed that four variables were significantly associated with the diagnostic outcome: gender (Pearson's χ^2 test, $p = 0.002$), marital status ($p = 0.027$), living situation (living alone, $p = 0.037$), and CDT (Mann-Whitney U test, $p = 0.045$, one-tailed). The mean score was 6.0 (SD 1.3) for the NonC and 5.1 (SD 1.9) for the C group (table 1).

The correlation matrix revealed a very high correlation between marital status and living situation (living alone). As these variables were nearly identical, living situation was excluded from further analyses. The three cognitive screening tests were significantly correlated ($p < 0.05$), with the strongest correlation observed between the CDT and Cognistat (Spearman's rho = 59.2, $p = 0.001$). Univariate Cox regressions were performed to determine unadjusted hazard ratios (HRs) for conversion to dementia. Low scores on the CDT (HR 0.85; 95% CI 0.74–0.98) and the Cognistat (HR 0.78; 95% CI 0.65–0.93) were significantly associated with the relative risk of conversion to dementia, whereas the MMSE score was not significantly associated with the diagnostic outcome variable. In addition, age, gender and marital status were significantly associated with diagnostic outcome ($p < 0.1$) in bivariate analyses; therefore, they were included in the multivariate regression model to determine the adjusted HRs. The results of this analysis are presented in table 2. CDT and Cognistat were strongly correlated,

Table 1. Demographic and clinical variables and conversion to dementia (n = 90)

	Diagnostic outcome	
	NonC (n = 26)	dementia (n = 64)
Age, years	72.1±7.62	74.0±7.94
Education, years	10.4±3.05	9.3±2.36
Females	11 (42.3)	49 (76.6)[a]
Married	20 (76.9)	33 (51.6)[b]
Living alone	6 (23.1)	30 (46.9)[b]
No home services	20 (76.9)	39 (60.9)
Pathological brain imaging (n = 73)	5 (26.3)	15 (27.8)
Reduced ADL (n = 62)	4 (15.4)	14 (21.9)
KEH (n = 87)	7 (26.9)	21 (32.8)
Antichol. (n = 87)	2 (7.7)	6 (9.4)
MMSE (n = 87)	26.1±1.62	26.2±2.33
CDT (n = 87)	6.0±1.27	5.1±1.88[c]
Cognistat (n = 76)	7.4±1.47	6.9±1.63

Values are represented as mean ± SD or n (%). Brain imaging: CT = 59, MRI = 13, SPECT = 1. Antichol. = Receiving known anticholinergic medication. KEH = Using cholinesterase-inhibiting medication.

[a] Pearson χ^2 test: $p < 0.01$ (females: χ^2 9.763, d.f. = 1). [b] Pearson χ^2 test: $p < 0.01$ [(married: χ^2 4.912, d.f. = 1); (living alone: χ^2 4.363, d.f. = 1)]. [c] Mann-Whitney U test: $p < 0.05$ (one-tailed).

Table 2. Results of the univariate and multivariate Cox proportional hazards model for correlates of the conversion to dementia (n = 90)

Variable		Univariate		Multivariate			
				CDT not in model 1		Cognistat not in model 2	
		HR	95% CI	HR	95% CI	HR	95% CI
Age		1.0	0.96–1.03	0.98	0.95–1.02	0.98	0.94–1.02
Gender	Female	1.51	0.84–2.70	1.71	0.83–3.55	1.67	0.85–3.27
Married	Not married	0.91	0.55–1.50	0.94	0.51–1.73	1.19	0.67–2.10
CDT		0.85[a]	0.74–0.98			0.85[a]	0.73–0.97
Cognistat		0.78[b]	0.65–0.93	0.78[b]	0.65–0.93		
MMSE		0.10	0.90–1.11				

Due to collinearity between Cognistat and CDT, two separate multivariate models were made: in model 1 CDT was excluded, and in model 2 Cognistat was excluded. [a] $p < 0.05$ (CDT, $p = 0.02$; CDT $p = 0.020$). [b] $p < 0.01$ (Cognistat, $p = 0.007$; Cognistat, $p = 0.007$).

and there was a probable multicollinearity. Consequently, separate multivariate models were established for CDT and Cognistat that included the variables age, gender, and marital status. When controlling for age, gender, and marital status, the association between a reduction in the total score on Cognistat or the CDT and an increase in the risk of conversion to dementia remained significant (CDT: HR = 0.85; 95% CI 0.73–0.97; Cognistat: HR = 0.78; 95% CI 0.65–0.93) (table 2).

Discussion

This study showed that a reduction in the sum scores on the simple cognitive tests CDT and Cognistat was associated with an increased relative risk of conversion from MCI to dementia. Thus, the CDT and the short cognitive test battery Cognistat are significant predictors of diagnostic outcome and could be used to identify persons with MCI that are at higher risk of developing dementia, whereas the general screening tool MMSE showed no predictive value. Although the MMSE is a common dementia screening tool, it seems to lack the sensitivity required to assess MCI and differentiate between patients at higher risk and those at moderate risk of conversion to dementia. The present results are in accordance with the conclusions of the meta-analysis by Mitchell [22] who suggested that the MMSE had a limited value in differentiating MCI from healthy controls and modest rule-out accuracy.

Cognistat is a selection of 10 tests that cover different aspects of cognitive functioning and impairment, whereas CDT is a very simple and less time-consuming tool. Hence, Cognistat could be expected to have the highest sensitivity to differentiate between MCI and early dementia and the strongest predictive value regarding the diagnostic outcome in this study. However, according to our findings, CDT exhibited a similar predictive strength as Cognistat, and the results from the different statistical analyses were more consistent. A likely explanation for this observation is that a successful result on the CDT depends on a series of different cognitive functions [19]; thus, the test results differentiate between degrees of impairment, even at an early stage. A review article published in 2008 by Peters and Pinto [23] concluded that the CDT was possibly a useful tool for identifying cognitive decline earlier than is possible using other traditional screening tests. However, there are conflicting propositions in the literature. Ehreke et al. [24] claimed that the CDT does not exhibit sufficient quality to screen for MCI. Nevertheless, in a later publication, these authors recommended it as a possible predictive test for dementia [25]. A validation study of Cognistat concluded that this tool has moderate validity in the detection of MCI and mild dementia but that, on its own, it is not sufficient for diagnosing MCI or mild dementia [26]. Although the present study showed that CDT and Cognistat have predictive value in a clinical setting, the results should be interpreted in accordance with the previous literature, which suggests that the predictive strength is insufficient to justify using either of these two tests as a single predictive test; rather, they should be applied in combination with other assessment tools.

The females included in the study population had a higher mean age than the males. Moreover, the progression rate from MCI to dementia was significantly higher in the females than in the males. This is in accordance with the hypothesis of Petersen et al. [27] who suggested that in females we see transition from normal cognition directly to dementia at a later age, but more abruptly than among males. This hypothesis is further strengthened by the facts that our study cohort consisted mostly of females, that the total proportion of subjects who converted from MCI to dementia was relatively high, and that the conversion took place rapidly. Seventy-one percent of the sample converted to dementia within 46 months. Moreover, as the time between assessments varied, it is possible that some patients would have received a dementia diagnosis even more rapidly if reassessed earlier, which eventually would render the risk ratio curve steeper. Despite this possible underestimation, our results suggested an annual rate that was similar to the higher rates published previously [4, 7].

Strengths

To our knowledge, this is the first study on the progression rate from MCI to dementia among Norwegian outpatients. The patients had undergone a comprehensive diagnostic assessment by a team of clinical specialists, and the study provided a new and clinically

relevant contribution to knowledge regarding the assessment of MCI patients and the prediction of conversion to dementia.

Limitations

The high proportion of patients who converted from MCI to dementia in our study might be explained by the characteristics of the study cohort, indicating that the selected clinical population might be at an extremely high risk of developing dementia. Another possible explanation is that the diagnostic decisions made at the first assessment might have been too conservative, resulting in a rapid dementia diagnosis later on. However, the inclusion criteria were wide, and the cohort comprised all patients with MCI who visited our clinic over a defined period. Hence, the population used and results obtained reflect a naturalistic clinical setting.

There are obvious limitations to the retrospective design of this study. From the clinical records, it was not possible to assess whether there were any systematic differences between the final sample, which consisted of patients who were assessed twice or more times, and the possibly equally sized group of persons who were not subjected to a second assessment. Furthermore, the follow-ups were at variable intervals, and the predictors in the survival analyses might be related to follow-up rather than conversion to dementia. However, this seems less likely, as the more stable MCI group (NonC) was on average followed for a longer total period than the C group, and the descriptive analysis also showed that the predictors separated the two diagnostic outcome groups. Unfortunately, ADL and brain scan results were difficult to score from the reports, as no standardized scales were used. Therefore, possible predictive associations with diagnostic outcome could not be detected.

Conclusions

CDT and Cognistat both showed predictive value. Neither of these two tests is recommended as a single test; rather, they should be used in combination with other tools for the prediction of individuals who are at higher risk of conversion from MCI to dementia. Although both tests are easy to administer, the CDT, which is less time-consuming, should be preferred to Cognistat for this purpose. CDT is also easy to combine with other tools in a routine clinical assessment.

We found a relatively high rate of conversion from MCI to dementia in our sample. In the descriptive analyses, female gender was associated with a higher conversion rate compared with male gender; however, this was not confirmed in further analyses.

Further research is required to establish which combinations of CDT or Cognistat with other assessment tools should be recommended for the clinical assessment of MCI and the identification of patients at higher risk of developing dementia.

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Disclosure Statement

There are no conflicts of interest to declare.

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