Predictors of Clinical Progression of Subjective Memory Impairment in Elderly Subjects: Data from the Clinical Research Centers for Dementia of South Korea (CREDOS)

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Key Words
Subjective memory impairment · Mild cognitive impairment · Alzheimer’s disease · Progression · Predictors

Abstract
Background/Aims: The aims of this study were to determine baseline factors related to the progression of subjective memory impairment (SMI) in elderly subjects and to develop a new modeling scale to predict progression. Methods: Elderly subjects with SMI were recruited from the nationwide Clinical Research Centers for Dementia of South Korea (CREDOS) multicenter cohort and divided into two groups: (1) progressed to mild cognitive impairment or Alzheimer’s disease or (2) stable without progression. Baseline clinical characteristics were compared between the groups, and the most relevant predictors of progression were assessed. A new modeling scale combining the predictors was developed. Results: In total, 129 subjects with SMI were analyzed. The follow-up duration was 0.5–4.7 years, and the median time to event was 3.64 years. The progressing group (n = 29) differed from the stable group (n = 100) in terms of baseline age, apolipoprotein E4 (APOE4) status, and some cognitive domains. Older age, a lower Mini-Mental State Examination recall score, APOE4 carrier, and a lower verbal delayed recall score were the most relevant predictors of progression, and a new...
modeling scale with these 4 predictors provided a better explanation of progression. **Conclusion:** SMI subjects with a higher risk of progression can be identified using a new modeling scale and might need further evaluations and more frequent follow-up.

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**Introduction**

The neuropathological changes associated with Alzheimer's disease (AD) precede the clinical symptoms by many years [1]; hence, the early identification of AD is important because interventions that could potentially modify the progression of AD are most effective if administered during early-stage AD [2]. Subjects with subjective memory impairment (SMI) report subjective feelings of memory decline but perform within the normal range of standard neuropsychological tests [3]. SMI develops in a large proportion of elderly individuals, increases with advancing age [4], and now is regarded as a status with increased risk of AD based on previous longitudinal studies [5]. Some individuals with SMI may already have AD-related pathology [2]. However, a considerable proportion of SMI subjects exhibit 'worried well' conditions, such as anxiety, depression, and non-AD-related pathology, and do not progress to neurodegenerative disease [6]. Therefore, predicting whether an SMI subject will progress to mild cognitive impairment (MCI) or AD is important, but the predictors related to SMI progression are not well clarified.

Here, we investigated which baseline factors are related to progression from SMI to MCI or AD in subjects with SMI and developed a new modeling scale for predicting progression.

**Methods**

**Participants**

Data were collected at 31 South Korean dementia clinics associated with university-affiliated hospitals between November 2005 and January 2013. This research was performed as part of a nationwide multicenter dementia study called the Clinical Research Centers for Dementia of South Korea (CREDOS; clinicalgov.com, No. NCT01198093). The CREDOS study recruited consecutive participants who were categorized as normal, SMI, MCI, vascular MCI, AD, or subcortical ischemic vascular dementia. All participants received comprehensive neuropsychological assessments using the Seoul Neuropsychological Screening Battery (SNSB) [7] and Activities of Daily Living (ADL) scales, brain magnetic resonance imaging (MRI), and blood tests at baseline. Apolipoprotein ε (APOE) genotyping was performed if the participants and caregivers consented. Neurologists at each center clinically diagnosed all patients based on the findings. All study participants were advised to routinely receive follow-up examinations annually.

Using CREDOS data, we retrospectively identified 129 participants who were diagnosed as SMI at baseline and underwent at least 1 follow-up evaluation. SMI subjects who did not undergo any follow-up evaluation were not different from the enrolled subjects in basic characteristics (online suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000430807). The inclusion criteria for SMI were: self-reported memory decline and, therefore, visited the dementia clinic to receive work-ups but performed within the normal range on all domains of the SNSB (≥ –1.0 standard deviation [SD]). The CREDOS study asked the following question about subjective memory function: ‘Do you feel your memory is impaired?’ If the subject answered ‘yes’, they were diagnosed as SMI. We excluded patients with a history of other neurological disorders or major psychiatric illnesses (a history of depression was allowed) or significant alcohol or substance abuse. Patients with abnormal laboratory findings (e.g. abnormal thyroid function, low vitamin B12/folate, or positive syphilis serology) were also excluded, as were patients diagnosed with MCI or AD at baseline.

**Diagnosis of Progression**

If subjects with SMI at baseline were diagnosed as MCI or AD at the follow-up evaluation, they were included in the progressing group. If patients who progressed to MCI returned to SMI status at the subse-
quent follow-up, they were included in the stable group. Routine follow-up evaluations were performed annually, but if subjects reported rapid worsening of cognition or limitation of ADL, they underwent follow-up evaluation after 6 months. Subjects with SMI who did not progress to MCI or AD until the last follow-up evaluation were included in the stable group. MCI was diagnosed when the patient fulfilled the diagnostic criteria described by Petersen et al. [8], and AD was diagnosed when the patient fulfilled the criteria for probable AD according to the criteria of the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRA) [9].

This study was approved by the Institutional Review Board of St. Mary’s Hospital, and written informed consent was obtained at enrollment after providing a complete description of the study to the patients and caregivers.

**Brain MRI Parameters**

Neurologists at each center assessed the severity of white matter hyperintensities (WMH) using a visual rating of axial fluid-attenuated inversion recovery images [10]. Periventricular WMH and deep WMH were separately evaluated and were combined to rank the severity of WMH as minimal, moderate, or severe. Detailed WMH rating scales have been presented in a previous study [11]. Hippocampal atrophy and the number of lacunes were measured on MRI by a single rater blind to clinical information. Hippocampal atrophy was rated on coronal T1-weighted images using Scheltens’ visual rating scale [12]. The mean of the left and right hippocampal atrophy scores was used in the analysis. Lacunes were counted regardless of the location using the following criteria: cavitated lesion with gliotic rim, 3–15 mm in diameter, hyperintense on T2-weighted and hypointense on T1-weighted images. The interrater reliability for measuring WMH was good (intraclass correlation coefficient: 0.726–0.905), and the intrarater reliability for hippocampal atrophy and lacunes was excellent (Pearson’s correlation coefficient: 0.903–0.943).

**Neuropsychological Testing**

All participants underwent formal neuropsychological testing, including the Korean version of the Mini-Mental State Examination (K-MMSE) [13], Clinical Dementia Rating, measurements of ADL, and the SNSB, which tests for attention (Digit Span Test), language, visuospatial function [Rey Complex Figure Test (RCFT)], verbal and visual memory function [Seoul Verbal Learning Test (SVLT) and RCFT], and frontal executive function (contrasting program, go/no-go, Controlled Oral Word Association Test, and Stroop Test). These tests were administered by trained neuropsychologists. Age-, sex-, and education-specific norms based on 447 normal controls were used to interpret the SNSB results. Scores <16th percentile, which is comparable to –1 SD of the norm, were defined as abnormal.

**Statistical Analysis**

Demographics, number of lacunes, laboratory findings, and SNSB results were compared between the groups using an independent t test. Sex distribution, degree of WMH, and comorbidities were compared using a χ² test. Hippocampal atrophy was compared using cumulative logistic regression corrected for age. The hazard ratio (HR) of various predictors was evaluated using a Cox proportional-hazards regression model. We also assessed proportionality assumptions when fitting the Cox model.

To develop a new modeling scale for predicting SMI progression, multivariable analysis was performed using Cox modeling. Cox modeling with backward elimination was repeated for all 1,000 bootstrap resamplings. A 50% relative frequency of selection in the bootstrap resamplings (more than 500 times out of 1,000) was the criterion for inclusion in the final Cox model, and the maximum number of selected factors was set to 4, considering the sample size and easy applicability. Finally, the 4 top-ranked variables were chosen. To assign cutoff points to continuous values, we developed receiver operating characteristic (ROC) curves and measured the cutoff values with the highest sensitivities. The points associated with each category of each risk factor were computed using bootstrap bias-corrected regression coefficients. Finally, we estimated the 1- and 3-year risk of progression for each point total and formulated the Cox model. To evaluate this point system, Harrell’s C-index and the area under the time-dependent ROC curve (AUC) were used to measure discrimination, and the calibration curve was used to assess calibration. All two-sided statistical analyses were performed using SPSS (version 21; SPSS Inc., Chicago, Ill, USA) and R (version 3.0.2, www.r-project.org). In this study, p values <0.05 were considered statistically significant.
**Results**

The follow-up duration ranged from 0.5 to 4.7 years. Twenty-nine subjects with SMI progressed to MCI or AD, and the remaining (n = 100) did not progress during this study. Eight patients with SMI reverted to normal cognition without cognitive complaint and were included in the stable group. Twenty-three patients in the progressing group were diagnosed with MCI, and the other 6 patients were diagnosed with AD. The median time to event was 3.64 years. Baseline demographics and clinical information are shown in table 1. The progressing group was older and demonstrated a higher percentage of APOE4 carriers than the stable group. The baseline neuropsychological test results are listed in online supplementary table 2.

Table 2 shows the results of the Cox proportional-hazards regression analysis. Using univariate analysis, we identified 7 predictors that were related to progression at the level of significance of 0.1: hippocampal atrophy, old age, APOE4 carrier, lower K-MMSE recall score, lower SVLT delayed recall score, lower RCFT copy score, and lower RCFT delayed recall score. We used bootstrap resampling to select the most relevant predictors [14]. According to the bootstrap resampling, age, APOE4 carrier, K-MMSE recall score, and verbal memory delayed recall score were the most relevant predictors (table 3).

We combined these predictors to develop a new modeling scale for predicting progression. The scoring system is shown in table 3, where a higher score indicates a higher risk of progression.
As a result, the combination of all 4 of these predictors seemed to provide a better explanation of progression. The estimated progression rate was only 1.24% after 1 year for subjects with a score of 0 and increased up to 27.6% after 1 year for subjects with a score of 6 (table 4). Subjects with a score $\geq 3$ on the modeling scale demonstrated a significantly higher progression rate (HR 5.351, 95% CI 1.539–18.598, $p = 0.008$; fig. 1). The discrimination C-index according to the AUC values was 0.757 after 1 year and 0.773 after 3 years; the 1- and 3-year predictions for progression according to our new modeling scale showed good correlations with the actual progression.

### Discussion

In this study, we investigated the most relevant predictors of progression in SMI and combined them to develop a new modeling scale for better prediction and to aid early decision on further evaluation.
Old age over 60 years, APOE4 carrier, lower K-MMSE recall score, and lower verbal delayed memory score were the most relevant predictors of clinical progression of SMI. Considering that AD pathology develops for decades before the diagnosis of dementia [1], SMI might be a meaningful state within the AD continuum when combined with additional risk factors suggestive of preclinical AD [15]. A recent study compared baseline characteristics of progressing and non-progressing SMI subjects and reported that progressing subjects were older and had more AD biomarkers in the cerebrospinal fluid [6]. Another study reported that SMI subjects with APOE4 had a higher amyloid deposition, suggesting preclinical AD [16]. A cohort study composed of normal elderly and patients with subjective cognitive impairment and MCI reported that low scores in memory, naming, and semantic fluency predicted rapid progression across all groups [17]. Based on the previous reports, positive AD biomarkers, old age, low memory performance, and APOE4 carrier are risk factors for progression also in SMI subjects; the present study demonstrates consistency with the former studies and, additionally, we assessed the most relevant baseline risk factors to make a predictive modeling scale.

<table>
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<th>Total score</th>
<th>Estimate of 1-year risk</th>
<th>Estimate of 3-year risk</th>
<th>n (total)a</th>
<th>n (progression)b</th>
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</table>

a Total number of patients. b Total number of patients who progressed.

**Fig. 1.** Kaplan-Meier curves according to the new modeling scale scores. SMI subjects with high scores (≥3) show more progression to MCI or AD than those with low scores (≤2; p = 0.008, HR 5.351, 95% CI 1.539–18.598).
Combinations of predictors performed better at predicting future progression. The estimated progression rates showed trends toward increasing as the modeling scale scores increased. Cox multivariable analysis identified old age and APOE4 carrier as significant predictors, but a lower K-MMSE recall score was only marginally significant, and a lower SVLT recall score was not significant in our data. The lack of statistical significance of the verbal memory score might be due to the relatively low progression rate from the SMI stage, the small sample size, or the short follow-up duration. However, the 4 factors were selected according to the 50% frequency of selection in bootstrap resampling, and our aim was to make the best predictive model for SMI, hence all of them were included in the Cox modeling.

Hippocampal atrophy was marginally significant only in univariate analysis. Although hippocampal atrophy is reported as a risk factor for progression in normal elderly individuals [18], the correlation between hippocampal atrophy and future progression in SMI subjects has not been fully determined yet. In our study, methodological limitations of visual rating, a relatively small sample size, the age difference between the groups, and a lack of significance of hippocampal atrophy in the SMI stage might all have affected the results.

This study has some limitations. The relatively short follow-up period and various study durations might be a limitation because the CREDOS study is a registry, not a cohort study. Prospective follow-up examinations over a longer duration are needed to assess whether patients with multiple predictors eventually progress to AD. Another possible limitation is that we used clinical diagnosis without pathologic confirmation. Cerebrospinal fluid biomarkers or amyloid PET studies are better able to confirm preclinical AD and future progression [4]; however, these cannot be performed in all subjects, especially those with SMI. Moreover, clinically diagnosed probable AD patients are likely to have AD pathology based on the good sensitivity of NINCDS-ADRDA criteria [19]. Hence, a modeling scale that uses clinical data is needed for easier and wider prediction. Subjects with higher scores on the modeling scale should be examined more extensively in order to develop improved biomarker evaluation and possibly prevent AD. Lastly, subjects with SMI in this study were recruited from the ‘worried’ group who visited the memory clinic, and a selection bias could thus exist. It should be noted that we cannot determine generalized rates of progression from SMI to MCI or AD.

Our current study is strong concerning the following aspects: (1) we determined the most relevant baseline predictors and their cutoff values from multiple demographic variables, neuropsychological results, and neuroimaging parameters, and (2) we developed a new modeling scale, which could provide a new high-accuracy tool for predicting progression in SMI subjects based on a large longitudinal dataset.

In summary, advanced age, poor baseline memory scores, and APOE4 carrier status are related to progression of SMI. Predicting progression from SMI to MCI or AD could be improved by combining the 4 predictors identified in this study. A new modeling scale might help clinicians to discriminate SMI subjects with a higher risk of progression from those with a low risk and, hence, to determine whether further evaluations and more frequent follow-up evaluations are needed.

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**Disclosure Statement**

The authors declare no financial or other conflicts of interest.
References


