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Original Article

Stages of objective memory impairment (SOMI) as a predictor of clinical progression in the A4 study

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ABSTRACT

Background: About one third of amyloid positive, cognitively normal individuals develop mild cognitive impairment or clinical Alzheimer dementia (AD) over 5 years of follow-up. Sensitive cognitive measures, in addition to biomarkers of amyloid pathology, add to the efficiency of secondary prevention trials by identifying cognitively normal individuals at greatest risk of clinical progression. The Stages of Objective Memory Impairment (SOMI) system, based on the picture version of the Free and Cued Selective Reminding Test with immediate recall (pFCSRT+IR), predicted clinical progression in two observational studies.

Objective: Our objective was to extend SOMI's findings to clinical trials using participants from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's(A4) study.

Methods: Eligible participants were cognitively normal, had a Clinical Dementia Rating (CDR) =0, an elevated amyloid level, the pFCSRT+IR, pTau217, and longitudinal data on the CDR. Cox proportional hazards model was used to assess the association of baseline SOMI stage for clinical progression defined by time to the first of 2 consecutive CDRs > 0 or CDR>0 at last assessment. The sample was censored at 4.5 years of follow-up.

Results: Of the 911 eligible participants, mean age was 72 years, 59% were female, 62% were APOE ε4 carriers, and 37% progressed over 4.5 years. Hazard ratios (HR) for progression were estimated with follow-up time as the timescale and the SOMI 0 group as the reference. The HRs for progression across SOMI stage increased from 1.48 (1.15–1.92 p=.003) for SOMI-1, to 1.83 (1.32–2.54, $p \leq 0.001$) for SOMI-2, and to 3.04 (1.97–4.68, $p \leq 0.001$) for SOMI 3/4. SOMI remained an independent and significant predictor when pTau217 was added to the model.

Conclusion: SOMI's risk profile in A4 was similar to prior findings in observational cohorts. SOMI provides a low-cost, non-invasive enrichment tool for identifying individuals at risk for early cognitive decline in secondary prevention trials.

1. Introduction

The availability of biomarkers greatly facilitates the identification of cognitively normal individuals with elevated amyloid levels, now used to define preclinical Alzheimer's Disease (AD) that begins decades before cognitive impairment is detected [1]. However, amyloid burden alone is not sufficient to predict rates of progression; only 20 to 30% of amyloid positive cognitively normal individuals develop mild cognitive impairment or clinical AD over 5 years [2]. Identifying amyloid positive participants at high risk of decline would reduce sample size estimates and make for more cost-efficient screening for clinical trial enrollment in secondary prevention trials in preclinical AD which frequently target risk factors that promote a high rate of clinical progression (e.g., APOE ε4 carriership, family history of AD). While biomarkers help stratify risk, the heterogeneity of decline in cognitively normal individuals still require large sample sizes [3] (Subtle objective cognitive impairment has been identified in cognitively normal individuals and shown to predict progression in observational cohorts [4–7]. Identifying those

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participants at risk of progressing and excluding those unlikely to decline should improve the efficiency of secondary prevention trials .

A promising system to predict progression in preclinical AD is based on the Free and Cued Selective Reminding Test (FCSRT) [8]. The test was designed to distinguish between genuine memory deficits due to impairment of specific memory processes such as encoding and retrieval and apparent memory deficits due to impairment of other cognitive processes such as attention that can limit memory. The success of FCSRT's desiign is reflected in its use to define "the amnestic syndrome of the hippocampal type, a common core clinical phenotype of AD due to medial temporal damage, especially the CA1 field [9,10].

FCSRT differs from other memory tests because it controls the conditions of learning by having participants identify pictured items (e.g., grapes) in response to category cues (e.g., fruit) and then recall the items when prompted by their cues. Immediate cued recall (IR) during this study phase ensures proper encoding and provides retrieval practice before the test phase. Effective cue recall is needed for accurate measurement of memory because cued recall reveals learning not shown by free recall. The failure to retrieve an item when prompted by its cue in the test phase suggests that the item was not properly encoded and stored.

Building on the utility of the FCSRT to predict incident MCI and AD [11–15], we develope the Stages of Objective Memory Impairment (SOMI) system (Table 1) using scores from the picture version of the FCSRT with immediate recall (pFCSRT+IR) [16]. SOMI divides episodic memory functioning in the preclinical (biomarker-positive, cognitively unimpaired) and prodromal (mildly symptomatic) AD phases into 5 stages. The decline of memory storage and retrieval operations emerge at different points in the AD continuum facilitating classification. Participants classified as SOMI-0 can recall more than half of the items on their own (intact retrieval) and the remainder by cued recall (intact storage). Retrieval difficulties emerge in SOMI-1 and worsen in SOMI-2 as shown by declining free recall (FR). Importantly participants are still able to remember the items they failed to recall on their own when prompted by cues. The sum of FR and cued recall is total recall (TR). Storage impairment emerges in SOMI-3 and worsens in SOMI-4 as participants fail to retrieve a greater number of items by cued.

The SOMI system was applied to baseline pFCSRT+IR scores of cognitively normal participants (Clinical Dementia Rating [CDR] = 0) from two observational studies [17,18]. Approximately 30% of the participants in each cohort had elevated amyloid level. Individuals classified into higher SOMI stages were at higher risk of clinical progression. Compared with the SOMI-0 group, rate of progression doubled for the SOMI-2 and tripled for SOMI-3/4 participants. SOMI's risk profile was unchanged when biomarkers of amyloid, tau, and neurodegeneration were included in the models. In addition to clinical progression, SOMI is also associated with AD neuropathology [19]. SOMI-3/4 cases were 4 times as likely to have moderate or high levels of AD neuropathologic change than cases with no memory impairment (SOMI-0) and were nearly six times as likely to have more advanced Braak neurofibrillary tau pathology.

Table 1
SOMI classification defined by FR and TR score ranges and years to diagnosis on the pFCSRT + IR.

Stages of Objective Memory Impairment (SOMI) system		Free Recall Scores	Total Recall Scores	Class of Memory Impairment
0	No Memory Impairment	>30	>46	None detected by pFCSRT+IR
1	Subtle Retrieval Impairment	25–30	>46	Free recall declines. Storage is preserved as indexed by TR.
2	Moderate Retrieval Impairment	20–24	>46	Further decline in free recall. Executive dysfunction may decline. Storage is preserved.
3	Subtle Storage Impairment	any	45–46	Total recall declines as cuing fails to normalize it.
4	Significant Storage Impairment	any	33–44	Further decline in Total recall indexes additional failure of memory storage.

Abbreviations:.
ADL = activities of daily living; FR = free recall; pFCSRT+IR = picture version of the Free and Cued Selective Reminding Test With Immediate Recall; SOMI = Stages of Objective Memory Impairment; TR = total recall.

While the predictive power of SOMI has been demonstrated in observational cohorts that present with a mix of pathology and cognitive functioning, it is less clear if SOMI will be useful in highly screened populations that are suitable for secondary trials, where participants are selected to have elevated amyloid yet cognitively unimpaired by conventional criteria.

The Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) study [20], a large secondary prevention trial, provides an opportunity to test the predictive validity of SOMI for cognitive decline in ostensibly cognitively normal participants. At least 1/3 of A4 participants displayed substantial cognitive decline on the preclinical cognitive composite [21]. We sought to identify them using SOMI stage determined at screening. Our goal was to extend SOMI's findings from longitudinal observational studies to clinical trials.

To mirror the design of future clinical trials, only A4 participants who had plasma biomarkers collected at screening were included in the analyses. We used pTau-217 (phosphorylated tau at threonine-217) because it is a sensitive and reliable indicator both Aβ and tau pathology that reduces reliance on costly and burdensome PET imaging [22,23]. Higher ptau217 values reflect greater amyloid and tau burden and are associated with increased risk of clinical progression [24]

We hypothesized that higher SOMI stages would be associated with an increased risk of clinical progression in the A4 cohort, consistent with prior findings and that SOMI's risk proile would be unchanged when pTau 217 was included in the models.

2. Methods

2.1. Participants

The A4 study is an international, multicentred clinical trial to test the effectiveness of Solanezumab, a monoclonal antibody that targets soluble β-amyloid. The screening methodology and intervention protocol are described elsewhere [20]. In brief, individuals were cognitively normal adults at baseline (CDR=0), between 65 and 85 years of age, living independently, had a reliable study partner to provide information on daily functioning and cognition, scored 25–30 on the Mini-Mental State Examination (MMSE), 6 to 18 on Logical Memory Delayed Recall IIa, and PET amyloid levels ≥1.20 SUVR. The additional inclusion criteria for the current study were available pFCSRT+IR data, pTau217 data, and available CDR assessment to determine SOMI stage at baseline and at least 2 follow-up visits. Although pFCSRT+IR was collected at screening in participants undergoing amyloid PET, analyses were restricted to randomized A4 participants to focus on a biomarker-confirmed cohort with consistent longitudinal follow-up. The present report focuses on the predictive validity of the SOMI system in a sample selected for amyloid positivity, a design important in secondary prevention trials.

Solanezumab did not slow cognitive decline compared to placebo over 240 weeks [21]. A previous analysis demonstrated that SOMI's risk profile did not differ between the placebo and treatment groups (Supp Table 1). Participants were combined in the present study and classified into SOMI stages using baseline pFCSRT+IR scores. Progression was defined by two consecutive CDR scores of >0 because reversion from a CDR > 0 or from MCI back to normal are common events and we wanted to increase the specificity of our outcome measure [25,26]. A CDR >0 at last follow-up was considered an indicator of progression. We hypothesized that as SOMI stage increased, risk of progression would increase relative to SOMI-0.

2.2. FCSRT + IR

Participants were stratified into different SOMI subgroups based on score ranges of FR and TR as shown in Table 1. Participants classified into SOMI-0 have intact retrieval shown by FR>30 (max=48) and intact storage (max=48) shown by TR >46. SOMI-1 participants display a modest decline in FR (29–25) but TR is intact. In SOMI-2, FR declines further (24–20) but importantly TR is still intact. SOMI −3 emerges when more than one item is missed in cued recall; FR no longer matters. When participants' TR is ≤44, the cutoff that identified all cases of clinical dementia [27] they are classified into SOMI −4. A total of 911 participants met criteria for the current analyses. Thirty Nine (4%) participants whose FR was at or below the level of participants with a clinical dementia <20 but who retrieved all of the missed items when cues were provided (TR>46). This performance is not unlike patients with vascular dementia where storage is preserved but retrieval is impaired [28]. The retrieval impaired storage unimpaired (RISU) participants were excluded from the analysis. The prevalence of RISU participants was similar to that in observational cohorts (<5%).

2.3. Preclinical Alzheimer cognitive composite (PACC)

The PACC is comprised of scores from 4 tests [29]: FR and TR from the pFCSRT+IR [8], logical memory [30], MMSE [31], and the Digit Symbol Substitution Test [32] a test of executive functioning. The Z score created for each test is added together to create the composite score. Decline on the PACC was used as the primary outcome measure in A4. The decline shown by the treated group was not significantly different from that of the placebo group [20].

2.4. Plasma pTau217

P-tau 217 is being used here rather than amylod PET imaging to simulate the screening process in secondary treatment trials. Plasma pTau217 concentrations were quantified using Eli Lilly's analytically validated electrochemiluminescence immunoassay. The methods used in assay development, validation, and data processing for A4 have been described elsewhere [33]. The p-Tau217 value obtained at the screening visit was used in the analyses.

2.5. Statistical analysis

Statistical analyses were performed in R (v4.5.1). An α level of 0.05 was used for two- tailed tests. For comparisons between two groups (Stable vs Progressors), effect sizes were reported as the Standard mean dofference (SMD) using pooled standard deviation for continuous variables, and Cramér's V for categorical variables.

Time-to-event outcomes were analysed using Cox proportional hazards regression, with time since randomization as the time scale and up to 4.5 years of follow-up. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated for SOMI categories and adjusted for covariates (age, sex, education and APOE). Treatment arm assignment was not included as a covariate since an earlier analysis demonstrated that SOMI's risk profile was independent of trial intervention effects (Supplementary file, Table 1).

2.6 Association of SOMI stage and incident cognitive impairment

Incident cognitive impairment was defined by the transition of CDR from 0 at baseline to two consecutive CDRs >0 or CDR > 0 at last assessment. Participants meeting this definition were classified as progressors. All others were classified as stable including individuals who remained CDR = 0 throughout follow-up and those with isolated or non-consecutive CDR > 0 assessments that did not meet the progression criterion. Participants who did not progress were right-censored at the date of their last available clinical assessment. SOMI stage at baseline was treated as a categorical variable with SOMI-0 as the reference stage. Age, sex, education and APOE ε4+ status were included in all models. This base model was developed to assess the association between SOMI stage and incident cognitive impairment (Model 1). Model 2 included the pTau217 score at baseline to evaluate whether SOMI stage remained independently associated with progression after adjustment for pTau-217. A sensitivity analysis explored the interaction of SOMI stage with pTau to assess potential effect modification of SOMI-associated risk by amyloid and tau (Model 3). To increase statistical power, given the small number of participants in SOMI-3 and-4 stages, they were merged into a single group (SOMI-3/4) for the primary analyses.

Data availability

The data were accessed from the A4 clinical trial consortium (a4studydata.org). The pFCSRT+IR and the CDR were administered at the screening visit prior to randomization in the clinical trial.

3. Results

3.1. Sample characteristics

Table 2 presents baseline demographic, APOE ε4 carrier status, SOMI stage, biomarker, and cognitive characteristics for 911 A4 participants after excluding RISU participants, stratified by progression status. Overall, 578 participants remained stable and 333 progressed during follow-up. The mean age of the cohort was 72 years, 59% were female, and the mean education was 17 years. Most participants were White (95%), and 62% were APOE ε4 carriers.

Compared with stable participants, progressors were older at baseline (73 vs. 71years, $p < 0.001$) and were more often female (54%, $p = 0.025$). Education did not differ significantly between groups. APOE ε4 carrier status, race, and ethnicity also did not differ significantly between stable participants and progressors. SOMI stage distribution differed significantly by progression status ($p < 0.001$). Stable participants were more frequently classified as SOMI 0 at baseline compared with progressors (52% vs. 33%), whereas progressors had higher proportions in SOMI 2, SOMI 3, and SOMI 4. Baseline biomarker and cognitive profiles also differed between groups. Progressors had higher pTau217 levels than stable participants (0.34 vs. 0.26, $p < 0.001$). Progressors also performed worse across cognitive measures, including PACC (−0.90 vs. 0.75, $p < 0.001$), LDELTOTAL (12 vs. 13, $p < 0.001$), DIGITTOTAL (46.34 vs. 50.05, $p < 0.001$), MMSE (28.59 vs. 28.95, $p < 0.001$), Free Recall (28 vs. 31, $p < 0.001$). Effect sizes were largest for PACC, Free Recall, pTau217, and LDELTOTAL, indicating meaningful baseline differences in cognitive and biomarker measures, while demographic differences were comparatively small.

Table 3 presents baseline characteristics stratified by SOMI stage. The proportion of participants who progressed increased steadily with advancing SOMI stage: 27% in SOMI 0, 40% in SOMI 1, 52% in SOMI 2, 60% in SOMI 3, and 73% in SOMI 4. Advancing SOMI stage was associated with older age ($p < 0.001$), a higher proportion of female participants ($p < 0.001$), progressively worse cognitive performance, and higher baseline biomarker burden. APOE ε4 carrier status, race, ethnicity, and years of education did not differ significantly across SOMI stages.

Cognitive performance declined across SOMI stages. Mean PACC decreased from 1.66 in SOMI 0 to −4.89 in SOMI 4 ($p < 0.001$), Logical Memory Delayed Recall declined from 13.63 to 8.47 ($p < 0.001$), and MMSE declined from 29.08 to 27.80 ($p < 0.001$). Biomarker measures also differed by SOMI stage, with pTau217 increasing from 0.28 in SOMI 0 to 0.39 in SOMI 4 ($p = 0.014$). Effect sizes indicated the largest differences across SOMI stages for cognitive measures, especially Total Recall, Free Recall, PACC, Logical Memory Delayed Recall, and MMSE. Biomarker effect sizes was notable for pTau217.

Table 2
Baseline characteristics of the stable and progressor group in the A4 trial.

Variables	Total (911)	Stable (578)	Progressors (333)	p-value	Effect Size
Age (years)	72.01 (4.81)	71.43 (4.52)	73.01 (5.13)	<0.001	0.32
Sex				0.025	0.08
Female	535 (58.7%)	356 (61.6%)	179 (53.8%)		
Male	376 (41.3%)	222 (38.4%)	154 (46.2%)		
Education (years)	16.58 (2.79)	16.65 (2.74)	16.47 (2.89)	0.365	0.06
APOE e4				0.513	0.02
e4-	345 (37.9%)	224 (38.8%)	121 (36.3%)		
e4+	566 (62.1%)	354 (61.2%)	212 (63.7%)		
Race				0.750	0.04
White	861 (94.5%)	550 (95.2%)	311 (93.4%)		
Non-White	50 (5.5%)	28 (4.8%)	22 (6.6%)		
Ethnicity				0.115	0.07
Non-Hispanic	878 (96.4%)	562 (97.2%)	316 (94.9%)		
Hispanic	25 (2.7%)	11 (1.9%)	14 (4.2%)		
SOMI Stage				<0.001	0.23
SOMI 0	411 (45.1%)	302 (52.2%)	109 (32.7%)		
SOMI 1	336 (36.9%)	202 (34.9%)	134 (40.2%)		
SOMI 2	124 (13.6%)	60 (10.4%)	64 (19.2%)		
SOMI 3	25 (2.7%)	10 (1.7%)	15 (4.5%)		
SOMI 4	15 (1.6%)	4 (0.7%)	11 (3.3%)		
PACC	0.15 (2.57)	0.75 (2.36)	−0.90 (2.60)	<0.001	0.67
LDELTOTAL	12.73 (3.69)	13.40 (3.40)	11.56 (3.87)	<0.001	0.51
DIGITTOTAL	48.69 (9.97)	50.05 (9.89)	46.34 (9.67)	<0.001	0.38
MMSE	28.82 (1.26)	28.95 (1.15)	28.59 (1.40)	<0.001	0.29
FR	30.11 (5.47)	31.14 (5.27)	28.33 (5.36)	<0.001	0.53
TR	47.74 (0.99)	47.86 (0.55)	47.53 (1.46)	<0.001	0.30
pTau217	0.29 (0.16)	0.26 (0.12)	0.34 (0.19)	<0.001	0.51

Abbreviations: MMSE = Mini-Mental State Examination; PACC = Preclinical Alzheimer Cognitive Composite; SOMI = Stages of Objective Memory Impairment; SUVR = Standard Uptake Volume Ratio.

3.2. SOMI prediction of incident cognitive impairment (CDR>0)

Table 4 shows the results of the Cox models. In Model 1, age (HR 1.06, 95% CI 1.03–1.08, $p < 0.001$) predicted progression, but sex, education, and APOE ε4+ did not. SOMI-1 (HR 1.48, 95% CI 1.15–1.92, $p = 0.003$), SOMI-2 (HR 1.83, 95% CI 1.32–2.543, $p < 0.001$), and SOMI-3/4 (HR 3.04, 95% CI 1.97- 4.68, $p < 0.001$) were all significantly associated with incident cognitive impairment. In Model 2, the hazard ratios for SOMI stages remained significant: SOMI-1 (HR 1.46, 95% CI 1.12 −1.89, $p = 0.004$), SOMI-2 (HR 1.88, 95% CI 1.35 - 2.61, $p < 0.001$), and SOMI-3/4 (HR 2.58, 95% CI 1.67 - 3.98, $p < 0.001$). Age was also a significant predictor (HR 1.04, 95% CI 1.02- 1.07, $p < 0.001$), and plasma pTau217 was significantly associated with progression, with each 1 SD increase associated with higher hazard (HR 1.47, 95% CI 1.35–1.6, $p < 0.001$). Female was associated with lower hazard compared with male (HR 0.77, 95% CI 0.61- 0.97, $p = 0.028$), while education and APOE ε4+ status were not significant.

Including interaction terms between SOMI stage and pTau217 in Model 3 did not reveal any significant interactions: SOMI-1 x pTau217 (HR 0.95, 95% CI 0.78–1.16, $p = 0.617$), SOMI-2 x pTau217 (HR 1.10, 95% CI 0.86–1.40, $p = 0.456$), and SOMI-3/4 x pTau217 (HR 0.91, 95% CI 0.61–1.35, $p = 0.635$).

To assess whether the association between SOMI stage and progression varied by age, we included interaction terms between age and SOMI stage in Cox proportional hazards models (Supplementary file, Table 2). There was no evidence of interaction between age and SOMI stage (all $p > 0.10$), indicating that the relationship between SOMI and risk of progression was consistent across the observed age range.

Kaplan–Meier curves (Fig.1) demonstrate that cognitive impairment–free survival decreased in a stepwise fashion with increasing SOMI stage (log-rank $p < 0.0001$). The two-year progression rates for SOMI-0 and SOMI-1 are similar and slow. Participants classified into SOMI-2 or higher begin declining by 48 months.

4. Discussion

This is the first demonstration that SOMI predicts clinical progression in a secondary prevention trial, the A4 study. Overall, SOMI stage showed a robust, ordered association with progression risk that remained stable after inclusion of plasma pTau217, with no evidence that it modified SOMI's risk profile.

In contrast to standard observational studies, all participants had elevated amyloid and were considered to be cognitively normal based on CDR measurement. Participants with retrieval deficits (SOMI 1, 2), or memory storage deficits (SOMI 3 /4) were at increased risk of progression. Compared to SOMI-0, SOMI-1 displayed a ~1.4-fold hazard, SOMI-2 nearly a 1.8-fold hazard, and SOMI-3/4 nearly a 2.9-fold hazard of progression. Since SOMI's risk profile was unchanged when pTau 217 was added to the model, we infer that SOMI confers additional risk independent of AD pathology. Age continued to be a risk factor for progression but the relationship between SOMI and risk was consistent across the observed age range. Female sex reduced the risk. APOE ε4 carriership was no longer a significant predictor consistent with its shared variance with amyloid pathology. Importantly, despite enrichment for genetic and biomarker risk, SOMI remained a strong predictor of progression, indicating that it provides prognostic information beyond APOE ε4 genotype and plasma biomarkers alone. SOMI-0 and SOMI-1 show minimal separation during the first 2 years of follow-up and similar short-term risk. The number of participants at risk declines steadily over follow-up, with more rapid depletion in higher SOMI stages (SOMI 2, 3/4) beginning at 48 months, indicating earlier and more frequent progression events in these groups.

SOMI's risk profile in the current cohort of participants with elevated amyloid was broadly consistent with that observed in two observational studies, the Harvard Aging Brain Study (HABS) and the Knight ADRC, in which approximately 70% of participants were amyloid-negative [17,18]. In those studies, progression was defined by the first CDR>0; in the present study, progression was defined by two consecutive CDRs > 0 to reduce misclassification due to transient cognitive fluctuations, thereby limiting Type I error and yielding a more robust and conservative estimate of progression risk [25,26].

Fewer participants progressed in the HABS and Knight studies than in the current study (23% and 24% versus 36%). The hazard ratios associated with SOMI stages in the current study were modestly lower than those reported previously, where estimates ranged from 2.0 to 2.8 for SOMI-2 and 3.0–3.7 for SOMI-3/4. Because all participants in A4 have elevated brain amyloid, progression risk may be elevated across all SOMI stages. This may have diminished the relative hazard ratio contrasts by elevating progression rate in the denominator, among those who are SOMI-0.

In addition to its prognostic value, at cross-section, the structural and molecular neuroimaging correlates of SOMI are promising. Including the 4484 cognitively normal participants screened for A4 eligibility, participants in higher SOMI stages had higher global amyloid SUVR. Participants with both storage and retrieval deficits (SOMI-3/4) had

Table 3
Baseline characteristics of the SOMI stages in the A4 Trial.

Variables	SOMI 0	SOMI 1	SOMI 2	SOMI 3	SOMI 4	p-value
Event						<0.001
Stable	302 (73.5%)	202 (60.1%)	60 (48.4%)	10 (40.0%)	4 (26.7%)	
Progressors	109 (26.5%)	134 (39.9%)	64 (51.6%)	15 (60.0%)	11 (73.3%)	
Number of Stable	302	202	60	10	4	
Number of Progressors	109	134	64	15	11	
Age (years)	71.05 (4.18)	72.55 (4.94)	73.51 (5.52)	72.53 (5.60)	72.78 (5.57)	<0.001
Sex						<0.001
Female	292 (71.0%)	170 (50.6%)	53 (42.7%)	12 (48.0%)	8 (53.3%)	
Male	119 (29.0%)	166 (49.4%)	71 (57.3%)	13 (52.0%)	7 (46.7%)	
Education (years)	16.75 (2.87)	16.59 (2.80)	16.09 (2.57)	16.28 (2.69)	16.27 (2.28)	0.206
APOE e4						0.712
e4-	157 (38.2%)	129 (38.4%)	47 (37.9%)	9 (36.0%)	3 (20.0%)	
e4+	254 (61.8%)	207 (61.6%)	77 (62.1%)	16 (64.0%)	12 (80.0%)	
Race						0.514
White	387 (94.2%)	321 (95.5%)	117 (94.4%)	22 (88.0%)	14 (93.3%)	
Non-White	24 (5.8%)	15 (4.5%)	7 (5.6%)	3 (12.0%)	1 (6.7%)	
Ethnicity						0.760
Non-Hispanic	398 (96.8%)	321 (95.5%)	120 (96.8%)	24 (96.0%)	15 (100.0%)	
Hispanic	8 (1.9%)	12 (3.6%)	4 (3.2%)	1 (4.0%)	0 (0.0%)	
PACC	1.66 (1.96)	−0.45 (1.99)	−2.23 (2.05)	−1.99 (2.41)	−4.89 (3.97)	<0.001
LDELTOTAL	13.63 (3.41)	12.60 (3.54)	11.24 (3.55)	9.60 (4.04)	8.47 (4.98)	<0.001
DIGITTOTAL	51.51 (10.11)	47.09 (8.92)	44.67 (9.97)	45.88 (7.17)	45.27 (11.49)	<0.001
MMSE	29.08 (1.00)	28.73 (1.33)	28.34 (1.49)	28.76 (1.27)	27.80 (1.93)	<0.001
FR	34.90 (3.06)	27.87 (1.68)	22.54 (1.32)	26.20 (5.28)	18.33 (7.89)	<0.001
TR	47.93 (0.25)	47.89 (0.31)	47.81 (0.39)	45.64 (0.49)	41.80 (3.30)	<0.001
pTau217	0.28 (0.15)	0.29 (0.15)	0.30 (0.17)	0.34 (0.16)	0.39 (0.15)	0.014

Abbreviations: FR= Free Recall, TR= Total Recall, LDETOTAL= Logical Memory Delayed Recall-Total Score, MMSE = Mini-Mental State Examination; PACC = Preclinical Alzheimer Cognitive Composite; HR = Hazard Ratio, CI=Confidence Interval, SOMI =Stages of Memory Impairment, SUVR= Standard Uptake Volume Ratio.
Standardized mean differences (SMD) are calculated as (Progressors − Stable) / pooled SD; negative values indicate lower mean in Progressors.

Table 4
Cox proportional hazard models assessing SOMI Stage, pTau217, and their interaction as predictors of clinical progression defined by CDR Model 1: Base model; Model 2 Base model with pTau217; Model 3: Base model with pTau217 interactions.

Variable	Model 1			Model 2			Model 3		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.06	1.03–1.08	<0.001	1.04	1.02–1.07	<0.001	1.04	1.02–1.07	<0.001
Sex (F)	0.86	0.68–1.08	0.185	0.77	0.61–0.97	0.028	0.777	0.62–0.98	0.033
Education	0.97	0.94–1.01	0.193	0.978	0.94–1.02	0.285	0.978	0.941.02	0.286
APOE ε4+	1.21	0.96–1.52	0.110	1.156	0.92–1.46	0.215	1.14	0.90–1.44	0.278
SOMI 1	1.48	1.15–1.92	0.003	1.458	1.12–1.89	0.005	1.48	1.13–1.93	0.004
SOMI 2	1.83	1.32–2.54	<0.001	1.880	1.35–2.61	<0.001	1.84	1.32–2.58	<0.001
SOMI 3/4	3.04	1.97–4.68	<0.001	2.579	1.67–3.98	<0.001	2.75	1.68–4.51	<0.001
pTau217 (z)				1.474	1.35–1.61	<0.001	1.49	1.31–1.69	<0.001
SOMI-1 × pTau217							0.95	0.78–1.16	0.617
SOMI-2 × pTau217							1.10	0.86–1.40	0.456
SOMI-3/4 × pTau217							0.908	0.611–1.350	0.635

Abbreviations: HR: Hazard Ratio, CI: Confidence Interval, SOMI – Stages of Memory Impairment, SUVR: Standard Uptake Volume Ratio.

smaller hippocampal volume, entorhinal cortex, and inferior temporal lobe than participants with no memory impairment (SOMI 0) [34]. In the HABS cohort, participants in higher SOMI stages (SOMI3/4) had higher entorhinal and inferior temporal tau burden on PET imaging [35]. Knight ADRC participants in higher SOMI stages displayed higher CSF levels of p-Tau181 and t-Tau, but only if they were APOE ε4 carriers [36]. Hippocampal atrophy increased as SOMI stage worsened in all three cohorts.

While these findings strengthen the predictive validity of SOMI, the current study has several limitations. The generalizability of our findings is limited by the generalizability of the sample enrolled in the A4 study that had a preponderance of white, highly educated participants. Our results are most applicable to a predominately white sample in their early to mid-70 s who have biomarker evidence for amyloid positivity. The lack of diversity in AD drug trials has been a persistent problem [37]. We are optomistic that race, education and economic status will not materially affect SOMI's risk profile since the pFCSRT+IR scores on which SOMI is based were unaffected by the race and education of patients in an urban primary care practice [38].

The relatively small numbers of participants in the SOMI-3/4 group may impact estimate precision. Sensitivity analyses were attempted to address this concern but limited sample sizes remained a constraint. The merging of SOMI stages 3 and 4 may limit interpretability by making it difficult to distinguish stage-specific risk and may introduce some heterogeneity within the combined group, particularly given the wide confidence interval.

An important limitation of SOMI is that it fails to classify 4% of participants who have retrieval mpairment but storage unimpaired (RISU). RISU participants were older, more likely to be male than female, and less likely to be APOE4 positive. Their FR was at the level of patients with a clinical dementia (<20) but they recalled everything with cues (TR>46). Patients with vascular dementias display this pattern on the pFCSRT+IR which may be secondary to impairment of executive functions [28]. The exclusion of these individuals with RISU may have enriched the sample, perhaps leading to slight over-representation of Alzheimer's-type pathology while

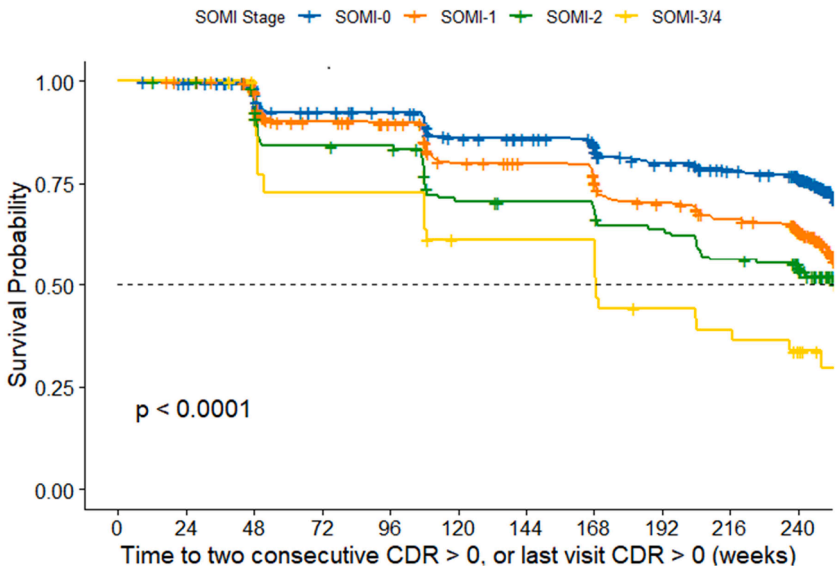

Fig. 1. Kaplan–Meier curves for cognitive impairment-free survival as a function of SOMI stages.

underrepresenting the pathology that underlies other cognitive disorders of late life.

Finally, each SOMI stage reflects increasing impairment of episodic memory functioning that is agnostic with regard to the underlying pathology. Among participants in secondary prevention trials who are AD biomarker positive, SOMI identifies those most likely to progress clinically over 3–5 years. In observational cohorts with mixed amyloid status classification into higher SOMI stages should not be interpreted as an indicator of AD pathology.

The current findings indicate that the SOMI system can be an effective second step in identifying those cognitively normal participants in secondary prevention trials who are at the greatest risk of clinical progression. The first step is to measure plasma marker p-tau217 which is highly correlated with amyloid PET imaging [39], minimizing patient burden and cost. Then, persons with elevated Ptau217 undergo the second step which is testing with the pFCSRT+IR to determine SOMI stage. Since the two year progression rates for SOMI-0 and SOMI-1 were similar and may be too slow to show clinical progression during a 3–5 year trial, they may not be ideal candidates for inclusion. In contrast, participants classified into SOMI- 2 or higher begin declining by 48 months and should be referred to the next steps in eligibility determination. Another approach to enriching the sample is to restrict it to participants who have both an abnormal plasma level and impaired episodic memory (SOMI −2 and higher). This approach can reduce sample size estimates and makes for more cost-efficient screening [40].

5. Conclusion

The similarity of stage-specific progression risks associated with the SOMI system across observational and clinical trials and its association with in-vivo and post-mortem biomarkers suggests that SOMI has translational utility for cost effective screening and clinical stratification in secondary prevention trials.

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Consent statement

This was a secondary analysis of A4 study data whose participants provided informed consent.

Declaration of generative AI and AI-assisted technologies in the writing process

Generative AI was used for sentence correction.

Data statement

The data were accessed from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) clinical trial consortium (a4studydata.org). The pFCSRT+IR and the CDR were administered at the screening visit prior to randomization in the clinical trial.

CRediT authorship contribution statement

Priyanka Kumari: Writing – review & editing, Formal analysis, Data curation. **Richard B. Lipton:** Writing – review & editing, Supervision, Funding acquisition. **Andrew J. Aschenbrenner:** Writing – review & editing. **Reisa Sperling:** Writing – review & editing, Data curation. **Michael C. Donohue:** Writing – review & editing. **Ellen Grober:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100641.

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