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Biomarker-integrated Prognostic Stagings for Alzheimer's Disease

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Abstract

Accurately predicting disease progression remains a major challenge in Alzheimer's disease (AD). Here we show that a biomarker-integrated prognostic staging system can stratify progression risk across the disease course by jointly incorporating cognitive status, established risk factors, plasma biomarkers, and neuroimaging measures. In the K-ROAD cohort ($N = 1,263$), the dominant prognostic contributors varied by clinical context—GFAP in cognitively unimpaired individuals, hippocampal volume in mild cognitive impairment, and age in dementia—while plasma phosphorylated tau-217 provided consistent secondary prognostic information across stages. Outcome-specific staging captured clinically meaningful gradients of progression risk and informed construction of a unified six-stage framework (Stage 0–IVB) with distinct inflection points of accelerated decline. External validation in the ADNI cohort ($N = 290$) demonstrated consistent patterns of worsening prognosis, particularly in early and intermediate stages. This system provides a clinically interpretable approach to risk stratification and may serve as an exploratory framework for biomarker-integrated prognostic stratification in AD.

Introduction

Alzheimer's disease (AD) has a multifactorial etiology, with advanced age as the strongest risk factor, while genetic predisposition (apolipoprotein [APOE] ε4 carrier status) and female sex also significantly increase susceptibility^{1,2}. These risk factors may influence not only the likelihood of developing AD but also the rate of clinical progression^{3,4}. Clinically, AD is characterized along a continuum of cognitive stages ranging from cognitively unimpaired (CU) to mild cognitive impairment (MCI) and ultimately dementia⁵. Importantly, the rate of progression along this continuum can vary according to the specific cognitive status⁶ and underlying risk profile⁷⁻¹².

Neuropathologically, AD features amyloid-β (Aβ) plaques, tau tangles, and neurodegeneration such as hippocampal atrophy¹³. These define the A/T/N (amyloid/tau/neurodegeneration) biomarker framework, but the cost and invasiveness of these methods drive the need for scalable plasma biomarkers¹⁴. To overcome these limitations, substantial efforts have been devoted to developing blood-based biomarkers that can capture A/T/N categories¹⁵⁻¹⁷. Core plasma biomarkers include Aβ42/40 ratio and phosphorylated tau species such as pTau181, pTau217 and pTau231, while non-specific markers—such as glial fibrillary acidic protein (GFAP) and neurofilament light chain (NfL)—reflect astrocytic activation/inflammation and axonal injury/neurodegeneration, respectively¹⁴. These plasma biomarkers have shown high concordance with their PET or MRI counterparts and have demonstrated utility not only for diagnosing AD but also for predicting prognosis, including rates of cognitive decline and progression across the disease continuum¹⁸⁻²⁰. Among them, pTau217 stands out for its exceptional performance in detecting both amyloid and tau pathology^{18,21,22}. In this study, preclinical AD was operationally defined as Aβ+ CU individuals, consistent with

current secondary prevention trials²³. Plasma pTau217 was used as an indirect correlate of tau pathology rather than a direct measurement¹⁸; therefore, the proposed framework does not constitute a biological staging system based on combined amyloid and tau positivity.

To date, most studies have focused on identifying prognostic factors within individual cognitive stages of AD. However, as clinical trials and therapeutic options continue to advance, there is a growing need for a unified prognostic framework to provide stage-consistent and biologically informed risk stratification across the disease continuum^{24,25}. Such a system would enable more consistent communication about prognosis, harmonized interpretation of biomarker profiles, and standardized comparison of disease trajectories across studies²⁶.

In this work, we develop and externally validate a prognostic staging system for AD, integrating traditional cognitive status with risk factors and multiple plasma and imaging markers to stratify dementia progression risk. To achieve this, we first identify prognostic subgroups using survival prediction modeling within each cognitive status, then develop outcome-specific stages by merging similar-risk subgroups for each of dementia progression outcomes, and finally integrate them into a comprehensive staging framework across the Alzheimer's spectrum.

Results

Demographics of study participants

The study included 1,263 participants from the Korea-Registries to Overcome dementia and Accelerate Dementia research (K-ROAD) cohort, comprising 224 CU individuals, 779 with MCI, and 260 with dementia. As detailed in **Table 1**, mean \pm standard deviation (SD) of age was 71.8 ± 8.1 years, with female participants constituting 62.5%. A β PET positivity demonstrated incremental elevation across initial cognitive status (36.2%, 59.8%, and 84.2%,

respectively). Longitudinal CDR-SB scores were obtained with a median of 2 assessments per participant (interquartile range [IQR] 2–3) over a median follow-up duration of 2.1 years (95% confidence interval [CI] 2.0 to 2.2). Clinically meaningful decline was defined using clinical dementia rating sum of boxes (CDR-SB) thresholds: ≥ 3 for very mild dementia, ≥ 4.5 for mild dementia, and ≥ 9.5 for moderate dementia.

Phase 1. Identifying prognostic risk subgroups through survival prediction modeling

Participants were classified into prognostic subgroups within each baseline cognitive status (CU, MCI, and dementia), with adjacent categories merged based on clinical and statistical validation (**Fig. 1a**). This resulted in 2 subgroups for CU, 3 for MCI, and 2 for dementia, totaling 7 refined subgroups (**Fig. 2**). In CU, participants were grouped by GFAP and pTau217: C1 (GFAP ≤ 195 pg/ml and pTau217 ≤ 0.62 pg/ml) and C2 (GFAP ≤ 195 pg/ml and pTau217 > 0.62 pg/ml or GFAP > 195 pg/ml) (**Fig. 2a**). In MCI, hippocampal volume (HV) and pTau217 were the main discriminators: M1 (HV > 2815 mm³ and pTau217 ≤ 0.68 pg/ml), M2 (HV > 2815 mm³ with pTau217 > 0.68 pg/ml or HV ≤ 2815 mm³ with GFAP ≤ 122 pg/ml), and M3 (HV ≤ 2815 mm³ with GFAP > 122 pg/ml) (**Fig. 2b**). In dementia, subgroups were defined by age and pTau217: D1 (> 60 years with pTau217 ≤ 1.1 pg/ml) and D2 (> 60 years with pTau217 > 1.1 pg/ml or ≤ 60 years regardless of pTau217) (**Fig. 2c**). Adjusted survival curves showed significant differences in progression risk across subgroups for CU ($P = 0.011$), MCI ($P < 0.001$), and dementia ($P < 0.001$), with incidence rates and 3-year cumulative incidences supporting discriminative validity (**Supplementary Table 1**).

Phase 2 – Developing unified prognostic staging across the Alzheimer's disease continuum

Prognostic subgroups from Phase 1 were used to generate outcome-specific stages for each of three progression outcomes (**Fig. 1a**): very mild dementia (N = 923), mild dementia (N = 1,120), and moderate dementia (N = 1,263). These outcome-specific stages were integrated into a six-stage unified prognostic system (Stage 0–IVB) reflecting increasing dementia severity (**Fig. 3**). Detailed procedures to develop a unified prognostic staging system is presented in **Supplementary Method 3**.

Adjusted survival curves confirmed effective separation between stages (**Fig. 4a**), and pairwise comparisons demonstrated significant differences in progression risk between all adjacent stages (all $P < 0.05$) (**Fig. 4b**). Notably, early to intermediate stages (Stage 0–III) were primarily distinguished by very mild and mild dementia outcomes, whereas advanced stages (Stage IVA–IVB) were driven by moderate dementia outcomes. Higher stages were consistently associated with increasing CDR-SB and decreasing MMSE scores (both $P < 0.001$) (**Fig. 4c**). Marked inflection points in incidence rates and 3-year cumulative incidence were observed at Stage 0→I, Stage I→II, Stage II→III, and Stage III→IVA (**Table 2**), highlighting clinically meaningful thresholds for prognosis and intervention. For clarity, we emphasize these key transitions, particularly between mid-level stages, as they represent sharp increases in progression risk and may serve as optimal points for clinical decision-making.

External validation of the unified staging system using the ADNI cohort

For external validation, we utilized an independent cohort from the Alzheimer's Disease Neuroimaging Initiative (ADNI), comprising 290 participants (160 CU, 118 MCI, and 12 dementia) with a median follow-up of 5.5 years (95% CI 5.1 to 6.0 years) (**Table 1**). Adjusted survival curves showed consistent patterns of worsening prognosis across stages for very mild

and mild dementia outcomes, although moderate dementia differentiation was less distinct due to limited event occurrences in lower stages (**Fig. 5a, 5b**). Also, stages III, IVA, and IVB were excluded from analysis due to small sample sizes ($N \leq 10$ each). Cognitive trajectories indicated progressive worsening, with increasing CDR-SB and decreasing MMSE scores at higher stages, aligning with severity escalation (**Fig. 5c**). Similar patterns were confirmed by 3-year cumulative incidence and incidence rates (**Supplementary Table 2**).

Discussion

In this study, we developed a proof-of-concept prognostic staging framework for AD that integrates cognitive status, traditional risk factors, plasma biomarkers, and neuroimaging markers to stratify progression risk across the disease continuum. Unlike prior studies that identified prognostic factors within each cognitive stage independently, our approach unifies CU, MCI, and dementia into a single continuous framework, enabling stage-consistent interpretation of prognosis and transitions over time.

Our first major finding was that primary prognostic discriminators varied across cognitive stages (CU, MCI, and dementia), reflecting the evolving pathophysiology of AD. Specifically, the primary discriminators were non-specific markers rather than core AD biomarkers: CU – GFAP, representing neuroinflammation; MCI – hippocampal atrophy, representing neurodegeneration. In CU, the prominence of GFAP aligns with prior studies showing that it predicts future tau accumulation and cognitive decline^{27,28}, likely reflecting early astrocytic responses to amyloid pathology¹³. In MCI, hippocampal atrophy has consistently been shown to predict progression to dementia, particularly in the prodromal phase, reinforcing its central prognostic role during this transitional stage^{29,30}. In dementia, younger age emerged as the

strongest predictor of faster progression³, a pattern consistent with extensive evidence that early-onset AD follows a more aggressive clinical course. Individuals with early-onset AD typically show markedly higher amyloid positivity rates³¹, greater tau burden on PET³², and more severe and widespread cortical atrophy³³ compared with late-onset AD. These biological differences—rather than chronological age itself—likely account for the accelerated progression observed in younger patients^{34,35}.

Across all stages, plasma pTau217 consistently served as a secondary discriminator, reinforcing its relevance as a dynamic biomarker that tracks both amyloid- and tau-related processes.^{18,36,37} Indeed, plasma pTau217 has demonstrated independent associations with both amyloid and tau pathology.^{18,38} Notably, our recent work³⁹ demonstrated that pTau217 predicts both A β (AUC 0.96) and tau (AUC 0.90) PET positivity and distinguishes longitudinal cognitive decline across plasma-defined AT profiles, underscoring its utility for prognostic stratification even without tau PET. However, GFAP and NfL are not disease-specific, and even pTau217 partly reflects non-AD processes—including ageing⁴⁰, cerebrovascular burden⁴¹, and other neurodegenerative conditions—so these markers should be interpreted as indicators of broader neural vulnerability rather than AD-specific pathology.

Our second major finding was that outcome-specific prognostic staging revealed complementary patterns of progression. Early-to-intermediate stages (0–III) were primarily separated by very mild and mild dementia outcomes, while later stages (IVA–IVB) were distinguished by moderate dementia outcomes. This hierarchical organization enabled us to preserve unique prognostic information from each outcome domain before integrating them into a unified system. Unlike biological staging frameworks such as A/T/N²⁴, our model does not incorporate regional tau PET or quantitative pathological burden and therefore should not be

viewed as a biological classification system. Instead, it is an outcome-driven, prognostic framework built from T1 biomarkers, non-specific plasma markers, and known clinical risk factors—intended to complement, not replace, biological staging approaches. Because T2 biomarkers such as tau PET are not yet widely available in routine research or clinical settings, the present framework necessarily emphasizes prognostic rather than biological classification. Within each cognitive stage, individuals exhibited substantial heterogeneity in progression risk^{7,8,12,42}, and this variability was captured by the combined contribution of plasma biomarkers, neurodegeneration measures, and clinical risk factors.

Our final major finding was that the unified six-stage system (0–IVB) produced clear, stepwise gradients in functional and cognitive decline and identified reproducible inflection points at which clinical worsening accelerated. These thresholds may facilitate standardized prognostic communication and research-level stratification across the AD continuum. However, this framework is not designed for therapeutic decision-making. In particular, eligibility for monoclonal antibody therapy requires confirmed amyloid positivity and treatment-response biomarkers⁴³—elements that the present system does not assess. Therefore, this model should be used strictly for prognostic stratification rather than for guiding treatment selection.

External validation using the ADNI cohort supported stage-dependent prognostic patterns, particularly for early and intermediate stages. However, only 290 of the 378 eligible participants could be analyzed because complete plasma pTau217, GFAP, hippocampal volume, A β PET, and longitudinal CDR data were required for consistent modeling. This resulted in a biomarker-enriched subset that underrepresented advanced dementia and limited evaluation of later-stage performance. Broader validation using population-based and clinically heterogeneous cohorts will therefore be necessary to establish generalizability.

The strengths of our study include a relatively large sample size with well-balanced representation across the Alzheimer's continuum. However, several limitations should be considered. First, although the K-ROAD cohort used a hybrid recruitment strategy from both memory clinics and community dementia prevention centers, it nonetheless represents a selectively ascertained research sample rather than a fully population-based or memory-clinic cohort. Although individuals with extensive cerebrovascular disease were excluded, only limited vascular and genetic variables (age, hypertension, diabetes mellitus, APOE ε4 carrier status, and education) were included, and detailed vascular imaging markers or social determinants of health were not available—factors that may contribute to mixed pathology. Second, the dataset did not include systematic measurements of modifiable lifestyle risk factors (e.g., diet, physical activity, sleep, cardiovascular behaviors)⁴⁴, precluding evaluation of lifestyle-related predictors commonly observed in population-based cohorts. Because such assessments are required to model prevention in cognitively unimpaired individuals, the present framework should not be interpreted as a prevention model. Third, the cohort did not include individuals with atypical AD presentations, who may follow distinct clinical trajectories; future studies should examine whether this framework generalizes across phenotypic heterogeneity⁴⁵. Finally, longitudinal follow-up will be required to determine whether the staging system reliably predicts long-term clinical trajectories. Despite these limitations, this study proposes a unified, biomarker-informed prognostic framework that captures heterogeneous progression patterns across the AD continuum and provides a structured foundation for future prognostic research, particularly as multimodal biomarkers, tau PET, and population-based datasets become increasingly available.

In conclusion, this study introduces a stage-spanning prognostic structure that leverages cognitive status, established risk factors, and scalable biomarker modalities to delineate

progression risk across the Alzheimer's continuum. Rather than functioning as a biological staging tool, the framework provides a pragmatic foundation for future work aimed at refining individualized prognosis—particularly as broader tau biomarkers, multimodal datasets, and population-based cohorts become more widely available.

Methods

For the K-ROAD cohort, the study was approved by the institutional review board of Samsung Medical Center (No. 2021-02-135). All participants provided informed consent, and the study was conducted in accordance with the Declaration of Helsinki. The ADNI study was also approved by the institutional review boards of all participating sites, and written informed consent was obtained from all participants. All data were handled in accordance with relevant data protection and privacy regulations.

Participants selection

We included 1,416 participants with CU, MCI and dementia from K-ROAD project, all of whom had available data on baseline demographics including comorbidities, plasma and imaging markers, and longitudinal CDR-SB assessments. The K-ROAD project is a nationwide initiative involving 25 university-affiliated hospitals across South Korea⁴⁶. Recruitment was conducted both through memory disorder clinics and government-commissioned community dementia prevention centers, resulting in a hybrid cohort. However, we emphasize that this hybrid structure does not make the cohort representative of either the general population or a typical memory clinic population, as participants were selectively enrolled based on research-appropriate clinical evaluations and biomarker availability. Inclusion and exclusion criteria for

this study have been described in detail elsewhere¹⁸. In summary, CU participants met the following conditions: (1) no major medical or psychiatric illness that could affect cognitive function, and (2) no objective cognitive impairment in any cognitive domain^{47,48}. MCI participants met: (1) subjective cognitive complaints reported by the participants or caregiver; (2) objective cognitive impairment in one or more cognitive domains (defined as performance below -1.0 SD in memory and/or -1.5 SD in other domains, based on age- and education-adjusted norms); and (3) preserved instrumental activities of daily living⁴⁹. Dementia participants fulfilled the National Institute on Aging - Alzheimer's Association (NIA-AA) core clinical criteria for probable AD dementia⁵⁰. Notably, baseline cognitive classifications (CU, MCI, and dementia) were determined independently of both CDR-SB and biomarker data (e.g., A β PET or plasma biomarkers), based solely on standard diagnostic procedures including neuropsychological testing, structured interviews, and functional assessments. As a result, each group may include individuals with or without biomarker positivity. The comprehensive participant selection flow is detailed in **Supplementary Fig. 1**.

Plasma biomarkers measurement

Plasma A β 40, A β 42, GFAP, and NfL concentrations were measured using the commercial Neurology 4-Plex E kit (Quanterix, Billerica, MA, USA). Plasma pTau181 and pTau231 concentrations were measured using in-house Simoa assays developed at the University of Gothenburg, and pTau217 concentration was measured using the commercial ALZpath pTau217 assay kit. All samples were analyzed in a single run with one batch of reagents, and the intra-assay coefficient of variation was below 10%. All measurements were performed by analysts blinded to clinical data.

Brain MRI and hippocampal volume measurement

Three-dimensional T1-weighted turbo field echo imaging was performed for all participants, with a sagittal slice thickness of 1.0 mm and 50% overlap. As previously described, hippocampal volume was quantified using an automated segmentation method that combines a graph cut algorithm with atlas-based segmentation and morphological opening⁵¹.

A β PET acquisition and quantification

A β PET scans were performed using either ¹⁸F-Florbetaben (FBB) or ¹⁸F-Flutemetamol (FMM), following each manufacturer's standardized imaging protocols. A β PET binding was quantified using the regional direct comparison centiloid (rdcCL) method, with the whole cerebellum as a reference region⁵². This method allows harmonization of FBB and FMM tracers without requiring ¹¹C-labelled Pittsburgh compound B images. A β PET positivity was defined using a global MRI-based rdcCL threshold of 25.5, derived via Gaussian mixture modeling³⁹. All imaging data were processed at the Samsung Medical Center laboratory, which served as the core center. The median time interval between plasma sampling and A β PET imaging was 4 days (IQR 0 to 69 days).

Physical comorbidities

Information on vascular risk factors, including hypertension and diabetes mellitus, was obtained from self-reported medical history or from records of current use of antihypertensive or antidiabetic medications.

Longitudinal cognitive assessments

The CDR-SB score is a measure of cognition and function, obtained by interviewing both patient and care partner. Its longitudinal assessments (i.e., CDR-SB profile) are used to track dementia progression over time. In this study, baseline CDR-SB was defined as the first assessment conducted within ± 1 years of either blood sampling or A β PET imaging. All participants had at least two CDR-SB assessments with a minimum interval of 3 months between visits.

Three survival outcomes of dementia progression were defined using CDR-SB cutoffs of ≥ 3.0 (very mild dementia), ≥ 4.5 (mild dementia), and ≥ 9.5 (moderate dementia), supported by both prior literature⁵³⁻⁵⁵ and validation within our cohort. Staging based on CDR-SB cutoffs of 0.5, 4.5, and 9.5 showed high concordance with global CDR scores (Cohen's $\kappa = 0.923$ [95% CI, 0.910–0.936]; **Supplementary Fig. 2**). To refine early-stage classification, we compared individuals with CDR-SB scores of 0.5–2.5 versus 3.0–4.0. The two groups showed differences in baseline MMSE, plasma biomarker levels, and A β PET positivity (**Supplementary Fig. 3a**). They also exhibited distinct longitudinal MMSE trajectories with least squares mean plot using generalized estimating equation model (**Supplementary Fig. 3b**), supporting the use of 3.0 as the cutoff for very mild dementia.

For each dementia progression outcome, the time-to-progression was defined as the interval from the baseline date to the first visit when CDR-SB exceeded the corresponding cutoff. Participants with CDR-SB above the cutoff at the baseline were excluded from the analysis of that outcome.

Development process of a unified prognostic staging system

Phase 1. Identifying prognostic risk subgroups through survival prediction modeling

In Phase 1, the entire cohort was divided into three sub-cohorts by initial cognitive status (CU, MCI, and dementia) (**Fig. 1a**). Stratification within each sub-cohort was conducted independently by developing a survival prediction model for the corresponding dementia progression outcome: very mild dementia for CU, mild dementia for MCI, and moderate dementia for dementia. Candidate prognostic features included risk factors such as age, sex, education year, *APOE ε4* carrier status, the presence of hypertension and diabetes mellitus, plasma biomarkers such as Aβ42/40 ratio, pTau181, pTau217, pTau231, GFAP, and NfL, and imaging markers including Aβ PET positivity and MRI hippocampal volume.

Random survival forest (RSF) was utilized to identify prognostically similar subgroups within each cognitive status based on survival outcomes of dementia progression ⁵⁶ (**Fig. 1b**). Modifications on RSF were made to select optimal prognostic features with their robust cutoff points. Firstly, the tree structure was restricted to a maximum depth of one (i.e., performing only a single split of each parent node). An optimal cutoff point was determined to enable bifurcation based on a numeric feature. For each node, we generated 1,000 bootstrap samples to create 1,000 single-split trees, each of which was represented by a best-splitting feature with its optimal cutoff point. The optimal prognostic feature was selected as the most frequently chosen feature across all single-split trees. When the selected feature was numeric, we employed weighted averaging of all identified cutoff points to determine the robust cutoff point. Among all unique values of the identified cutoff points, we chose the 5 or 10 most frequently identified values and averaged them. Following binary partitioning of a parent node, this algorithmic process was applied recursively to each resultant child node. The stopping rule for tree expansion was established by limiting the numbers of events and participants within a candidate parent node, so that a node

cannot be split if it has less than the specified numbers. The cumulative hazard function served as the risk score of RSF⁵⁶, and log-rank splitting^{57,58} or global non-quantile Brier score splitting⁵⁹ were employed for splitting rule. Detailed process was described in **Supplementary method 2**, and modified RSF was applied only in Phase I.

Phase 2. Developing a unified prognostic staging system

The second phase employed a three-step process to develop a unified prognostic staging system (**Fig. 1a**). Initially, outcome-specific staging was developed by merging prognostic risk subgroups with similar risk of each dementia progression based on clinical evaluation: visually overlapped adjusted survival curves with non-significant differences in pairwise comparison, and similar incidence metrics. Prognostic risk subgroups remained separate if their curves were visually distinct and incidence metrics were notably differed, even without statistical significance. In the second step, we integrated these outcome-specific categorizations into a unified prognostic staging system encompassing dementia progression and cognitive status information. Specifically, early stages were derived by focusing on the very mild dementia-specific categorization; intermediate stages were formed by considering the mild dementia-specific categorization; and advanced stages were created based on the moderate dementia-specific categorization. In the final step, the recombined stages were labelled from stage 0 to stage IV, with each progressive stage representing increasing disease severity. Adjacent stages with overlapping 95% CI for three-year cumulative incidence or incidence rates were assigned to the same primary stage, with further refinement into subcategories (A or B) within primary stages. **Supplementary method 3** illustrates the detailed process for developing the unified prognostic staging system.

The unified prognostic stages were clinically validated by comparing survival curves for dementia progression outcomes, and longitudinal cognitive trajectories for CDR-SB and MMSE with adjustment for age, sex, education, and apolipoprotein E (APOE) ε4 status.

External validation with ADNI dataset

The unified staging system underwent external validation using ADNI dataset, with detailed procedures described in the **Supplementary method 1**. A total of 290 ADNI participants with available plasma pTau217, GFAP, hippocampal volume on MRI, and longitudinal CDR-SB data were included to match the derivation criteria and minimize selection bias. After applying the proposed staging criteria to classify ADNI participants, we assessed whether three-year cumulative incidence and incidence rates demonstrated clear differentiation between adjacent stages in this independent cohort. Similarly, adjusted survival curves were generated and pairwise comparisons using multivariable Cox proportional hazard regression models were conducted to evaluate stage differentiation. Finally, the cognitive trajectory according to follow-up duration was also assessed whether the magnitude and progression rate of cognitive impairment differed between stages in this validation cohort, thereby confirming the generalizability of the staging system.

Statistical methods

Descriptive statistics were calculated for each cohort and proposed staging category, with continuous variables presented as mean (SD) and categorical variables as frequencies (proportion). Median follow-up duration with corresponding 95% CIs was determined using the reverse Kaplan-Meier method⁶⁰.

All proposed subgroups, categories and the unified staging system were evaluated through multiple measures. Incidence rates of dementia per 100 person-years with exact Poisson 95% CIs were calculated⁶¹, along with three-year cumulative incidence of dementia with 95% CIs (derived as one minus the Kaplan-Meier estimated survival probability at three years)⁶². We assessed whether incidence rates and three-year cumulative incidence demonstrated sufficient discrimination between adjacent stages. Adjusted survival curves were drawn using inverse probability weights to evaluate potential overlap in dementia progression between stages⁶³. These adjusted survival curves for all groups were compared using a log-rank test corrected for weighting to check whether all proposed categories have the same curves about probability of non-dementia across follow-up time⁶⁴. Additionally, all pairwise comparisons were conducted using multivariable Cox proportional hazards regression models. The P values for all pairwise comparisons were adjusted using the Benjamini-Hochberg procedure to account for multiplicity, thereby controlling the false discovery rate⁶⁵. Firth's bias correction was adopted when some groups or categories contain very small number of events⁶⁶. The longitudinal trajectories were estimated using least squares mean plot derived from generalized estimating equations^{67,68}. Age, sex, the period of education, and *APOE ε4* carrier status were considered as the covariates for adjustment.

Statistical significance was defined as two-sided P values less than 0.05. All statistical analyses and RSF modeling were conducted with SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 4.4.1 (The R Foundation, www.R-project.org).

Statistics & Reproducibility

Sample sizes were determined by the availability of eligible participants in the K-ROAD and ADNI cohorts, with predefined exclusion criteria applied to ensure adequate longitudinal follow-up and suitability for survival analyses. This study was observational study and did not involve randomization. Plasma biomarker analyses were conducted by investigators blinded to clinical and imaging data.

Data availability

The data supporting the findings of this study include plasma biomarker data, brain MRI, and PET imaging data from the K-ROAD cohort, as well as imaging and clinical data from the ADNI cohort. These datasets contain sensitive human participant information, which carry a potential risk of participant re-identification. Due to ethical restrictions imposed by the institutional review boards and the informed consent provided by study participants, the K-ROAD data cannot be made publicly available without restriction. De-identified K-ROAD data are available from the corresponding authors upon reasonable request and subject to approval by the relevant institutional review boards and data use agreements. Requests for data access will be reviewed and responded to within 2–4 weeks of receipt. Inquiries regarding K-ROAD data access should be directed to the corresponding authors (S.W. Seo; sangwonseo@empas.com). ADNI data are publicly available through the ADNI data sharing platform (<https://adni.loni.usc.edu>) upon registration and approval, in accordance with ADNI data use policies. Source data underlying the figures and tables presented in this study are provided with this paper.

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Authors Contributions Statements

D.E. Shin, S.J. Lee, S.W. Seo, and K.A. Kim conceived and designed the study. S.J. Lee and K.A. Kim performed the statistical analyses. D.E. Shin, S.J. Lee, S.W. Seo, and K.A. Kim wrote the manuscript. D.E. Shin, S.J. Lee, J.P. Kim, H.M. Jang, J.H. Yun, M.Y. Chun, J.H. Ahn, S.M. Kim, K.M. Kim, S.Y. Yoon, H.J. Kim, H.K. Kang, S.H. Yim, H.K. Park, S.H. Kim, D.L. Na, H. Zetterberg, K. Blennow, F. Gonzalez-Ortiz, and N.J. Ashton, M.W. Weiner, S.W. Seo, and K.A. Kim conducted data preprocessing, interpretation and critically revised the manuscript for intellectual content. S.W. Seo and K.A. Kim supervised the study. All authors approved the final version of the manuscript.

Competing Interests Statements

Henrik Zetterberg has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZPath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has delivered lectures in symposia sponsored by Alzecure, Biogen, Cellecrticon, Fujirebio, Lilly, Novo Nordisk, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). Kaj Blennow has served as a consultant and on advisory boards for Abbvie, AC Immune, ALZPath, AriBio, BioArctic, Biogen, Eisai, Lilly, Moleac Pte. Ltd, Novartis, Ono Pharma, Prothena, Roche Diagnostics, and Siemens Healthineers; has served on data monitoring committees for Julius Clinical and Novartis; has delivered lectures, produced educational materials, and participated in educational programs for AC Immune, Biogen, Celdara Medical, Eisai and Roche Diagnostics; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, outside the work presented in this paper. The remaining authors declare no competing interests

Table 1. Baseline characteristics of K-ROAD and ADNI cohorts

Variables	K-ROAD				ADNI Total (N = 290)
	CU (N = 224)	MCI (N = 779)	Dementia (N = 260)	Total (N = 1,263)	
Age, years	71.0 ± 8.0	72.4 ± 7.8	70.7 ± 8.8	71.8 ± 8.1	73.7 ± 7.1
Female, n (%)	144 (64.3)	480 (61.6)	166 (63.8)	790 (62.5)	142 (49.0)
<i>APOE ε4</i> carriers, n (%)	70 (31.2)	350 (44.9)	150 (57.7)	570 (45.1)	97 (33.4)
Education years	10.5 ± 4.7	10.8 ± 4.7	10.2 ± 4.9	10.6 (4.7)	16.4 ± 2.6
Clinical diagnosis	-	-	-	224 (17.7) / 779 (61.7) / 260 (20.6)	160 (55.2) / 118 (40.7) / 12 (4.1)
CU / MCI / dementia, n (%)	-	-	-	-	-
Abeta PET positivity, n (%)	81 (36.2)	466 (59.8)	219 (84.2)	766 (60.6)	50 (44.6)
MRI Hippocampal volume, mm ³	2945.9 ± 597.9	2614.8 ± 546.0	2300.8 ± 536.8	2608.9 ± 588.1	3858.3 ± 506.4
Plasma Abeta42/40	0.06 ± 0.01	0.06 ± 0.02	0.06 ± 0.01	0.06 ± 0.02	-
Plasma pTau181, pg/ml	6.7 ± 5.8	8.2 ± 7.4	10.3 ± 9.8	8.4 ± 7.8	-
Plasma pTau217, pg/ml	0.5 ± 0.4	0.8 ± 0.6	1.1 ± 0.8	0.8 ± 0.6	0.4 ± 0.3 ^a
Plasma pTau231, pg/ml	8.9 ± 4.1	10.6 ± 5.5	12.5 ± 5.4	10.7 ± 5.4	-
Plasma GFAP, pg/ml	112.0 ± 54.3	156.0 ± 135.9	182.7 ± 79.0	153.7 ± 117.0	157.3 ± 90.1 ^a
Plasma NfL, pg/ml	25.2 ±	32.6 ±	36.1 ± 30.8	32.0 ± 25.7	-

11.9 26.4

Data are shown as mean (standard deviation) unless otherwise stated

^a Plasma pTau217 and GFAP values were harmonized to the K-ROAD cohort using the conversion equations (Supplementary Method 1)

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Table 2. Incidence rates and cumulative incidences at three years of the unified staging system according to the progression of dementia

Progression outcome	N ^a	The number of events	Incidence rates per 100 person-year (95% CI)	Three-year Cumulative incidence ^b (95% CI)
<i>Very mild dementia</i>				
Stage 0	162	3	0.8 (0.2 to 2.4)	0.00 (0.00 to 0.00)
Stage I	240	32	5.2 (3.7 to 7.4)	0.18 (0.11 to 0.24)
Stage II	220	92	19.1 (15.6 to 23.4)	0.47 (0.38 to 0.55)
Stage III	267	172	35.6 (30.7 to 41.3)	0.79 (0.72 to 0.85)
Stage IVA	21	17	70.3 (43.7 to 113.1)	-
Stage IVB	13	13	75.9 (44.1 to 130.7)	0.92 (0.49 to 0.99)
<i>Mild dementia</i>				
Stage 0	164	1	0.3 (0.0 to 1.8)	0.00 (0.00 to 0.00)
Stage I	253	27	4.1 (2.8 to 6.0)	0.14 (0.08 to 0.20)
Stage II	251	76	13.2 (10.5 to 16.5)	0.34 (0.26 to 0.42)
Stage III	329	163	24.5 (21.0 to 28.6)	0.59 (0.51 to 0.66)
Stage IVA	73	54	46.2 (35.4 to 60.3)	0.75 (0.59 to 0.85)
Stage IVB	50	44	58.1 (43.2 to 78.0)	0.91 (0.74 to 0.97)
<i>Moderate dementia</i>				
Stage 0	164	0	0.0 (0.0 to 0.0)	0.00 (0.00 to 0.00)
Stage I	253	5	0.7 (0.3 to 1.8)	0.02 (0.00 to 0.05)
Stage II	254	16	2.5 (1.5 to 4.1)	0.05 (0.01 to 0.09)
Stage III	332	45	5.8 (4.4 to 7.8)	0.14 (0.08 to 0.20)
Stage IVA	132	30	9.5 (6.7 to 13.6)	0.23 (0.12 to 0.33)
Stage IVB	128	63	22.0 (17.1 to 28.1)	0.54 (0.41 to 0.65)

^a The number of participants

^b Cumulative incidence of dementia to three years

Abbreviation: CI, confidence interval

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FIGURE LEGENDS

Fig. 1 | Development process of a unified prognostic staging system. **a**, Overall scheme to develop a unified prognostic staging system. **b**, Detailed process for feature selection and cutoff determination to identify prognostic risk subgroups in Phase 1.

Abbreviations: CU, cognitively unimpaired; MCI, mild cognitive impairment; Dem, dementia; CDR-SB, clinical dementia rating—sum of boxes

Fig. 2 | Prognostic risk subgroups identified within initial cognitive status sub-cohorts in Phase 1. **a**, Risk subgroups in cognitively unimpaired (CU) group. **b**, Risk subgroups in mild cognitive impairment (MCI) group. **c**, Risk subgroups in Alzheimer's type (dementia) group. Left panel illustrates survival prediction models developed with selected features and their cutoff points within cognitive status sub-cohorts. The resulting prognostic risk subgroups are displayed with identical colors designating the same category: C1 and C2 in CU, M1 to M3 in MCI, and D1 and D2 in dementia. In the right panel, adjusted survival curves along with p-values indicate statistically significant progressive deterioration across prognostic subgroups ($P = 0.0106$ in CU, $P = 2.68 \times 10^{-13}$ in MCI, and $P = 0.0005$ in dementia). Adjusted survival curves were estimated with inverse probability weights and were compared using a log-rank test corrected for weighting. All statistical tests were two-sided, and source data are provided as a Source Data file.

Fig. 3 | Outcome-specific progression stages and a unified prognostic staging system across the Alzheimer's disease continuum. Unified prognostic staging system defined through the integration of outcome-specific stages. C1 and C2 are prognostic risk subgroups in the cognitively unimpaired (CU) group. M1 to M3 are prognostic risk subgroups in the mild

cognitive impairment (MCI) group, while D1 and D2 are prognostic risk subgroups in the dementia group. Prognostic risk subgroups positioned at the same horizontal level represent equivalent stage. Stage labels (e.g., IVA, IVB) reflect clinical progression severity. Detailed methods are provided in Supplementary Method 3.

Fig. 4 | Clinical validation of the unified prognostic staging system. Unified prognostic stages were clinically validated by comparing dementia progression curves and longitudinal cognitive trajectories with adjustment for age, sex, education, and apolipoprotein E (APOE) ε4 status. Stage labels reflect clinical progression severity. **a**, Adjusted survival curves for each dementia progression outcome show effective stage differentiation across the cognitive spectrum: very mild dementia outcome differentiated lower stages, mild dementia outcome distinctly identified intermediate stages, and moderate dementia outcome distinguished advanced stages. Overall differences among stages were assessed using a log-rank test corrected for weighting ($P = 2.68 \times 10^{-13}$ in very mild dementia, $P = 4.74 \times 10^{-41}$ in mild dementia, and $P = 2.05 \times 10^{-18}$ in DAT). **b**, Adjusted pairwise comparisons were conducted using multivariable Cox proportional hazards models, and demonstrated statistically significant differences between adjacent stages, confirming discriminative validity. P values within each survival outcome were corrected for multiple hypothesis testing using a Benjamini-Hochberg procedure. **c**, Longitudinal cognitive trajectories for each stage, measured by clinical dementia rating—sum of boxes (CDR-SB) and mini-mental state examination (MMSE), show progressively greater decline in higher stages over time. Data are presented as least squares means (LSmeans) with 95% confidence intervals estimated using generalized estimating equations. All statistical tests were two-sided, and source data are provided as a Source Data file.

Fig. 5 | External validation of the unified prognostic staging system using the ADNI cohort.

a, Adjusted survival curves for very mild and mild dementia outcomes shows consistent separation of worsening prognosis across stages, while less differentiation is found for moderate dementia outcome due to limited event occurrence. A log-rank test corrected for weighting was used to assess overall differences among stages, yielding $P = 2.03 \times 10^{-6}$ for very mild dementia and $P = 3.52 \times 10^{-5}$ for mild dementia, and $P = 0.0419$ for moderate dementia. Stages with fewer than 10 participants (i.e. III, IVA, IVB) were excluded from this analysis. **b**, Pairwise comparisons between stages using multivariable Cox proportional hazards models demonstrated significant differences in progression risk for adjacent stage pairs, supporting external discriminative validity. P values within each survival outcome were corrected for multiple hypothesis testing using a Benjamini-Hochberg procedure. **c**, Longitudinal changes in clinical dementia rating—sum of boxes (CDR-SB) and mini-mental state examination (MMSE) also showed progressively steeper decline in higher stages over time. Data are presented as least squares means (LSmeans) and their 95% confidence intervals estimated with generalized estimating equations. All statistical tests were two-sided, and source data are provided as a Source Data file.

Editorial Summary

This study develops and validates a prognostic staging framework for Alzheimer's disease by integrating cognitive status with blood-based biomarkers, and neuroimaging data, to improve risk stratification across the disease continuum.

Peer review information: *Nature Communications* thanks the anonymous reviewers for their contribution to the peer review of this work. A peer review file is available.

a

Phase 1: Identifying prognostic risk subgroups through survival prediction modeling

CU sub-cohort

MCI sub-cohort

Dementia sub-cohort

Optimal feature selection and robust cutoff determination to identify subgroups having similar prognostic risk

- Candidate prognostic features**
Age, sex, education, APOE4 carrier comorbidities, plasma biomarkers, amyloid β positivity, MRI hippocampal volume
- Dementia progression outcomes**
Very mild dementia outcome (CDR-SB ≥ 3.0) for CU
Mild dementia outcome (CDR-SB ≥ 4.5) for MCI
Moderate dementia outcome (CDR-SB ≥ 9.5) for Dementia

Prognostic risk subgroups in CU

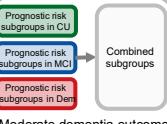
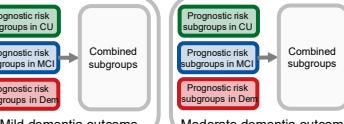
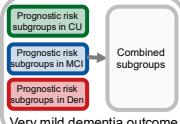
Prognostic risk subgroups in MCI

Prognostic risk subgroups in Dementia

Phase 2: Developing unified prognostic staging across the Alzheimer's disease continuum

Step 1: Development of outcomespecific progression stages

Combining prognostic risk subgroups with similar risk based on clinical evaluation



Step 2: Integration based on outcomespecific progression stages

Early stages
Focused on the results of very mild dementia outcome

Intermediate stages
Focused on the results of mild dementia outcome

Advanced stages
Focused on the results of moderate dementia outcome

Step 3: Labeling from Stage 0 to Stage IV

b

Each initial cognitive status subcohort with a corresponding dementia progression outcome

Survival random forest with 1000 trees
(Each tree with maximum depth of 1)

Bootstrap sample 1
Child 1-1 feature \leq cutoff 1
Selected feature 1 with cutoff 1

Bootstrap sample 2
Child 1-2 feature $>$ cutoff 1
Selected feature 2 with cutoff 2

Bootstrap Sample 1000
Child 1000-1 feature \leq cutoff 1000
Child 1000-2 feature $>$ cutoff 1000
Selected feature 1000 with cutoff 1000

Feature selection and cutoff determination

- Feature selection based on selection stability:
Select the most frequently chosen feature across 1,000 trees
- Cutoff determination via weighted averaging:
Among all identified cutoff values for the selected feature, choose the 5 or 10 most frequently identified values and average them

Split parent node using the optimal feature and cutoff

Child node 1
Selected feature \leq Determined cutoff
Not satisfying stopping rule

Child node 2
Selected feature $>$ Determined cutoff
Not satisfying stopping rule

Clinical evaluation of derived risk subgroups

- Comparison of incidence rates and 3-year cumulative incidence
- Assessments of any overlap of adjusted survival curves
- Pairwise comparison using Cox proportional hazard models

If indistinguishable

a

Prognostic risk subgroups in CU sub-cohort

Level 0

CU
(n=221)

Level 1

GFAP \leq 195
(n=201)

GFAP $>$ 195
(n=20)

Level 2

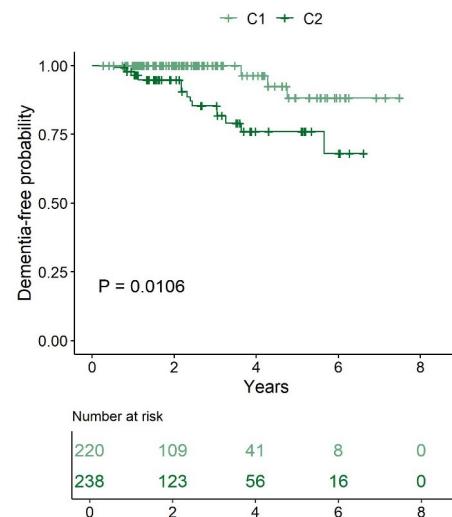
pTau217 \leq 0.62
(n=162)

pTau217 $>$ 0.62
(n=39)

C1

C2

C2

**b**

Prognostic risk subgroups in MCI sub-cohort

Level 0

MCI
(n=773)

Level 1

MRI HV
 $>$ 2815
(n=274)

MRI HV
 \leq 2815
(n=499)

Level 2

pTau217
 \leq 0.68
(n=193)

pTau217 $>$ 0.68
(n=81)

GFAP \leq 122
(n=170)

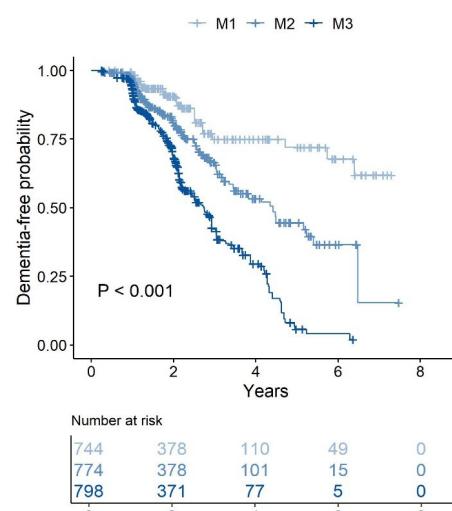
GFAP $>$ 122
(n=329)

M1

M2

M2

M3

**c**

Prognostic risk subgroups in Dementia sub-cohort

Level 0

Dementia
(n=260)

Level 1

Age $>$ 60
(n=222)

Age \leq 60
(n=38)

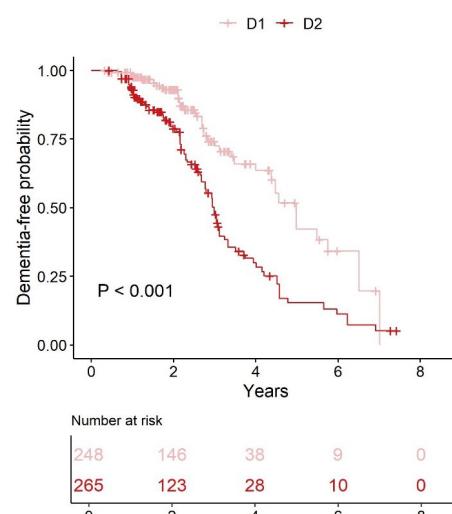
Level 2

pTau217 \leq
1.1
(n=132)

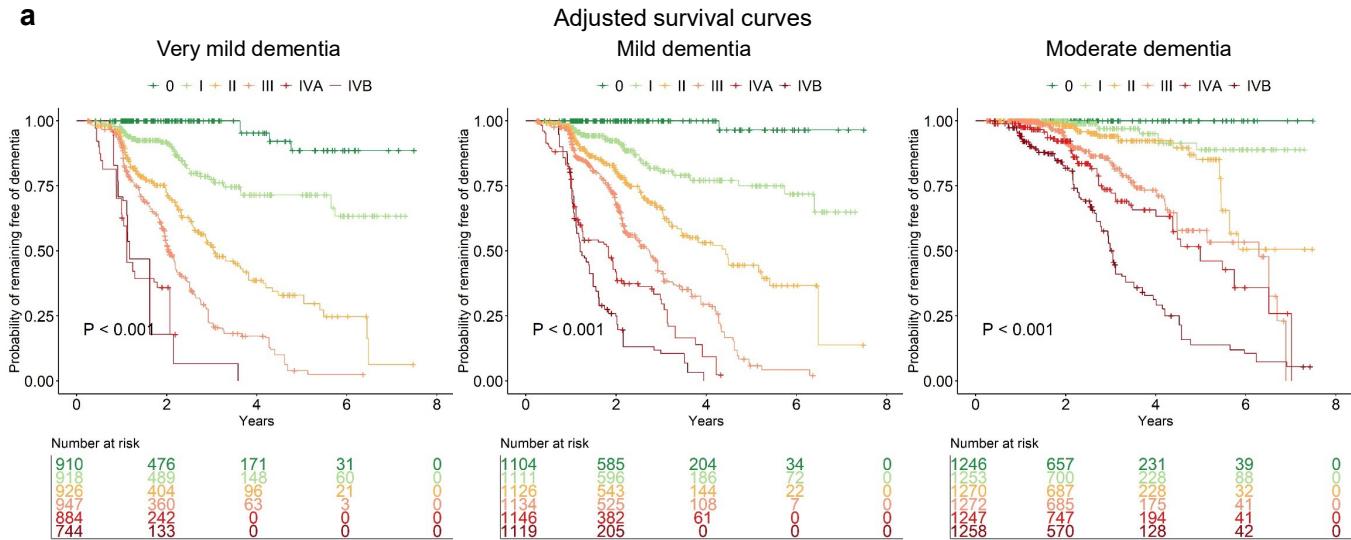
pTau217 $>$
1.1
(n=90)

D1

D2



Stage	CU	MCI	DAT
0	C1	-	-
I	C2	M1	-
II	-	M2	-
III	-	M3	-
IVA	-	-	D1
IVB	-	-	D2

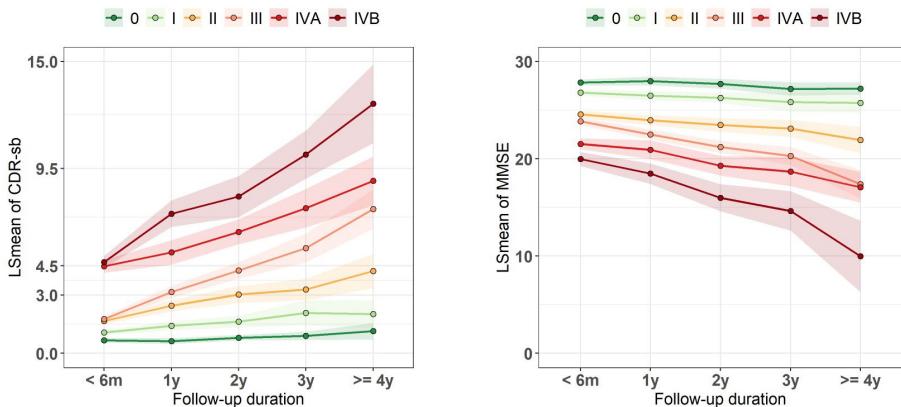
a**b**

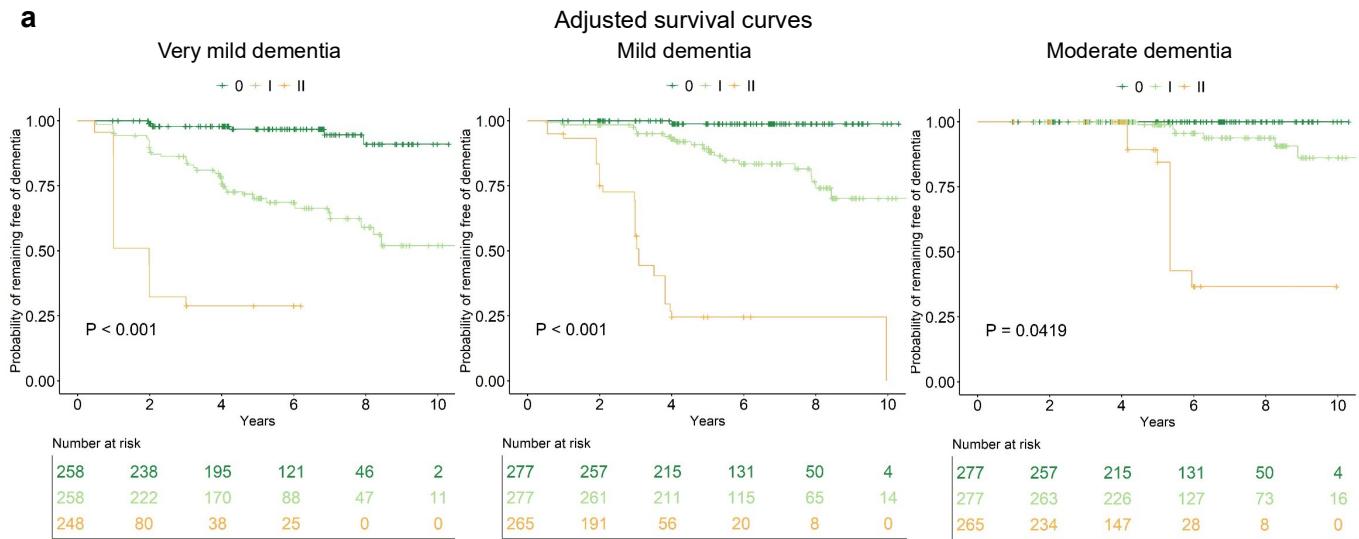
P-values obtained from pairwise comparisons

Very mild dementia						Mild dementia						Moderate dementia						
	0	I	II	III	IVB		0	I	II	III	IVB		0	I	II	III	IVB	IVB
0	0.0016	<0.0001	<0.0001	<0.0001	<0.0001		0.0067	0.0001	<0.0001	<0.0001	<0.0001		0.1138	0.0004	<0.0001	<0.0001	<0.0001	
I		<0.0001	<0.0001	<0.0001	<0.0001			<0.0001	<0.0001	<0.0001	<0.0001			0.0065	<0.0001	<0.0001	<0.0001	
II			<0.0001	<0.0001	<0.0001				<0.0001	<0.0001	<0.0001			0.0005	<0.0001	<0.0001	<0.0001	
III				<0.0001	0.0001					<0.0001	<0.0001				0.0830	<0.0001		
IVB					0.8624						0.0164						0.0003	

c

Longitudinal cognitive trajectories for CDR-SB and MMSE



a**b****P-values obtained from pairwise comparisons**

Very mild dementia			Mild dementia			Moderate dementia					
	0	I	II		0	I	II		0	I	II
0				0.0001	<0.0001				0.0219	0.0001	
I						0.0103					0.0049
II							<0.0001	<0.0001			

c**Longitudinal cognitive trajectories for CDR-SB and MMSE**