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Authors

Chun, Min
Jang, Hyemin
Kim, Soo-Jong
et al.

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Emerging role of vascular burden in AT(N) classification in individuals with Alzheimer's and concomitant cerebrovascular burdens

Min Young Chun ,[1,2,3] Hyemin Jang ,[1,4,5,6] Soo-Jong Kim,[1,4,6,7] Yu Hyun Park,[1,4,6,7] Jihwan Yun,[1] Samuel N Lockhart ,[8] Michael Weiner,[9] Charles De Carli,[10] Seung Hwan Moon,[11] Jae Yong Choi,[12] Kyung Rok Nam,[12] Byung-Hyun Byun,[13] Sang-Moo Lim,[13] Jun Pyo Kim,[1,4,5,14] Yeong Sim Choe,[1] Young Ju Kim,[1,4] Duk L Na,[1,4,5,15] Hee Jin Kim,[1,4,5,6] Sang Won Seo[1,4,5,6,16]

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For numbered affiliations see end of article.

Correspondence to
Dr Sang Won Seo and Dr Hyemin Jang, Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul, South Korea; sangwonseo@empas.com, hmjang57@gmail.com

HJ and SWS contributed equally.

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ABSTRACT

Objectives Alzheimer's disease (AD) is characterised by amyloid-beta accumulation (A), tau aggregation (T) and neurodegeneration (N). Vascular (V) burden has been found concomitantly with AD pathology and has synergistic effects on cognitive decline with AD biomarkers. We determined whether cognitive trajectories of AT(N) categories differed according to vascular (V) burden.

Methods We prospectively recruited 205 participants and classified them into groups based on the AT(N) system using neuroimaging markers. Abnormal V markers were identified based on the presence of severe white matter hyperintensities.

Results In A+ category, compared with the frequency of Alzheimer's pathological change category (A+T–), the frequency of AD category (A+T+) was significantly lower in V+ group (31.8%) than in V– group (64.4%) (p=0.004). Each AT(N) biomarker was predictive of cognitive decline in the V+ group as well as in the V– group (p<0.001). Additionally, the V+ group showed more severe cognitive trajectories than the V– group in the non-Alzheimer's pathological changes (A–T+, A–N+; p=0.002) and Alzheimer's pathological changes (p<0.001) categories.

Conclusion The distribution and longitudinal outcomes of AT(N) system differed according to vascular burdens, suggesting the importance of incorporating a V biomarker into the AT(N) system.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cerebral small vessel disease vascular (V), which is one of most important cause of cognitive impairments, has an additive or synergistic effect on cognitive impairments with Alzheimer's disease (AD) markers.

WHAT THIS STUDY ADDS

⇒ Our study indicated that the distribution of AT(N) classification varied depending on the presence of V, and cognitive decline trajectories of the AT(N) system were more exacerbated in the presence of V.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings suggest the possibility that the V biomarker could be incorporated into the AT(N) system. Combination therapies targeting both V and AD burdens may more effectively preserve cognitive functions than single-target therapies in clinical practice.

INTRODUCTION

Based on Alzheimer's disease (AD) pathological features, which can be assessed using β-amyloid (Aβ) accumulation (A), tau (T) and neurodegeneration (N) biomarkers, the National Institute on Aging-Alzheimer's Association (NIA-AA) proposed the AT(N) classification system.[1] Each of the AT(N) biomarkers could be binarised into normal/abnormal (–/+), resulting in eight possible biomarker profiles, which are then grouped into four possible biomarker categories: normal AD biomarker (A–T–N–), Alzheimer's pathological change (A+T–N– and A+T-N+), AD (A+T+N– and A+T+N+) and non-Alzheimer's pathological change (A–T–N+, A–T+N– and A–T+N+). If the effects of new categories on AD pathophysiology might be demonstrated, the AT(N) system could evolve by the addition of new categories (the X component of ATX(N)) to the existing AT(N) system.[1]

AD is a heterogeneous disease with multiple contributors to its pathophysiology, including vascular dysfunction. Previous pathological studies have shown that concomitant cerebral small vessel disease (CSVD) burden is often found in participants with AD pathology.[2 3] The presence of CSVD burden is also associated with impaired cognitive performance.[3 4] Furthermore, CSVD burden correlates with Aβ (A) in the posterior region[5] and tau (A) in the inferior temporal region.[6] Eventually, our previous studies suggested that CSVD and Alzheimer's burdens synergistically affected the cognitive impairments.[7–9]

In this study, we applied the AT(N) system to individuals with Alzheimer's and concomitant CSVD burdens. First, we determined whether participants with significant CSVD burden (V+

group) could be categorised using the AT(N) system. We also investigated whether AT(N) biomarkers might be predictive of cognitive decline in the V+ group as well as in the V– group. Finally, we determined whether cognitive decline trajectories among each AT(N) category based on biomarker profiles might be more prominent in the V+ group than in the V– group.

METHODS

Study participants

We prospectively recruited 210 participants who visited the memory clinic of the Samsung Medical Center (SMC) in South Korea and underwent tau (^{18}F-flortaucipir (FTP)) positron emission tomography (PET) scans between May 2015 and December 2021. All participants underwent neuropsychological tests, brain MRI and Aβ (^{18}F-florbetaben (FBB) or ^{18}F-flutemetamol (FMM)) PET scans. They were classified using the syndromal cognitive staging proposed by the NIA-AA Research Framework as cognitively unimpaired (CU), mild cognitive impairment (MCI) and dementia.[1] CU individuals met the following criteria: (1) no medical history that is likely to affect cognitive function based on Christensen's health screening criteria[10] and (2) no objective cognitive impairment from a comprehensive neuropsychological test battery in any cognitive domains (above the −1.0 SD of age-matched and education-matched norms in memory and −1.5 SD in other cognitive domains).[11] All participants with MCI met the following criteria[12]: (1) subjective cognitive complaints by the participants or caregiver; (2) objective cognitive impairment in any cognitive domain (below −1.0 SD of age-matched and education-matched norms in memory and −1.5 SD in other cognitive domains); (3) no significant impairment in activities of daily living and (4) no dementia. The participants with dementia met the NIA-AA criteria.[13]

We excluded participants who had any of the following conditions: (1) white matter hyperintensities (WMH) due to aetiologies other than vascular pathology, including radiation injury, multiple sclerosis, vasculitis, leukodystrophy or metabolic disorders; (2) traumatic brain injury; (3) territorial infarction; (4) brain tumour and (5) rapidly progressive dementia.

Amyloid PET imaging acquisition, analysis and Centiloid values

All participants underwent either FBB or FMM PET at SMC using a Discovery STe PET/CT scanner (GE Medical Systems, Milwaukee, Wisconsin, USA) in the three-dimensional (3D) scanning mode that examined 47 slices of 3.3 mm thickness spanning the entire brain.[14] The detailed imaging acquisition protocols are described in online supplemental method 1.

PET images were coregistered on individual 3D-T1-weighted MR images that were normalised to the T1-weighted MNI-152 template using Statistical Parametric Mapping (SPM) 8. Specifically, Aβ uptakes were quantified using BeauBrain Morph of BeauBrain Healthcare, which performs fully automated image analysis of Aβ uptakes on PET images. The detailed imaging acquisition protocols and conversion equations of the standardised uptake value ratio (SUVR) into a direct comparison of Centiloid units (dcCL) are described in online supplemental method 2.

To obtain the dcCL cut-off value for Aβ positivity, we performed receiver operating characteristic (ROC) analysis using Aβ positivity based on the SUVR cut-off for each PET scan as the standard of truth. We defined Aβ positivity (A+) according to the cut-off value of the FBB or FMM PET global dcCL, which was previously computed as 25.11.[15]

Tau PET imaging acquisition and analysis

All FTP PET images were acquired using a Discovery STE PET/CT scanner (GE Healthcare) at the SMC (n=109) and a Biograph mCT PET/CT scanner (Siemens Medical Solutions) at Gangnam Severance Hospital (n=97). The detailed protocols are described in online supplemental method 3.

The FTP PET images were coregistered onto individual MR images using SPM V.12. For the regional SUVR analysis, we used FreeSurfer V.6.0 (http://surfer.nmr.mgh.harvard.edu) to delineate the region of interest (ROI) masks in the native space. The detailed methods are presented in online supplemental method 4. We excluded two patients because of segmentation errors during the FTP analysis.

To obtain the FTP SUVR positivity cut-off value, we performed ROC analysis as an analytical method. FTP SUVR using Braak III/IV ROI (Braak III: parahippocampal, fusiform, lingual gyrus, amygdala; Braak IV: inferior temporal cortex, middle temporal cortex, temporal pole, thalamus, caudal, rostral, isthmus, posterior cingulate, insula) was used to predict the classification of Aβ– CU (n=14) and Aβ+ AD dementia (n=55). We defined tau positivity (T+) when the FTP SUVR at Braak III/IV ROI was higher than the cut-off of 1.406.

Brain MRI acquisition

All participants underwent 3D-T1 turbo field echo images and 3D fluid-attenuated inversion recovery (FLAIR) at SMC using a 3.0T MRI scanner (Philips 3.0T Achieva; Philips Healthcare, Andover, Massachusetts, USA), as previously described.[16]

Measurement of hippocampal volume

We defined (N) using HV on brain MRI. Hippocampal atrophy is a well-established (N) biomarker of AD,[17] which was proposed by the NIA-AA and the National Institute of Neurological Disorders and Stroke-Alzheimer Disease and Related Disorders working groups for research criteria for the diagnosis of AD.[12 18–20]

The images were processed using the CIVET anatomical pipeline (V.2.1.0).[21] Native MRIs were registered to the MNI-152 template by linear transformation[22] and corrected for intensity non-uniformity using the N3 algorithm.[23] The detailed methods for adjusted HV (HVa) measurements are available in online supplemental method 5. We excluded one patient because of a segmentation error during HV measurement. Therefore, the final study sample consisted of 205 participants.

To develop the cut-off for HV, we applied machine learning K-means clustering methods, which have been widely used in previous studies[24 25] due to its efficiency and simplicity.[26] The detailed methods are available in online supplemental method 6. As the K-means revealed a cut-off value of −0.363 cm^3, HVa below the cut-off was defined as abnormal (N+).

Assessment of CSVD scores

The WMH visual rating scale proposed by the Clinical Research Center for Dementia of South Korea was used to investigate WMH in the deep subcortical and periventricular regions on FLAIR images.[27 28] Details of measurement of WMH volume and rating of lacunes and microbleeds are described in online supplemental method 7.

We defined V+ as severe levels of WMH visual rating scales based on our classification system for ischaemia.[28] This classification system distinguished the presence of vascular risk factors (hypertension, diabetes and history of stroke) and the severity of CSVD markers including WMH volume, number of lacunes and

Table 1 Baseline characteristics of participants according to AT(N) category and CSVD burden

	Total	Normal AD biomarker		Non-Alzheimer's pathological change		Alzheimer's pathological change		AD	
		V–	V+	V–	V+	V–	V+	V–	V+
No	205	21	12	15	17	44	15	74	7
Age, years, mean (SD)	74.1±8.6	73.4±5.2	70.2±6.5	78.1±7.8	80.0±5.5	77.3±8.2	80.9±3.3	71.5±8.6	82.0±6.1
Sex, female, n (%)	129 (62.9)	15 (71.4)	5 (41.7)	9 (60.0)	14 (82.4)	19 (43.2)	14 (93.3)	50 (67.6)	3 (42.9)
Education, years, mean (SD)	10.2±5.3	10.7±5.8	6.1±5.5	9.1±6.2	9.7±5.0	11.3±5.1	8.6±5.1	10.4±4.8	7.4±7.6
APOE ε4 carrier, n (%)	89 (43.4)	4 (19.0)	4 (33.3)	7 (46.7)	3 (17.6)	19 (43.2)	5 (33.3)	45 (60.8)	2 (28.6)
Aβ PET dcCL, mean (SD)	64.6±51.0	1.5±11.0	3.6±5.1	−0.2±13.5	5.0±8.9	87.2±32.6	69.3±34.6	103.3±29.7	93.9±17.6
Tau PET SUVR at Braak 34 ROI, mean (SD)	2.1±0.7	1.5±0.1	1.5±0.1	1.7±0.4	1.8±0.3	1.6±0.4	1.7±0.1	2.8±0.7	2.3±0.3
HV volume (mm^3), mean (SD)	2424.1±582.3	2978.7±330.6	3180.8±428.7	2174.3±522.2	2240.2±443.3	2705.0±498.9	2221.2±442.3	2163.2±551.6	2014.0±333.1
WMH volume (mm^3), mean (SD)	21 923.3±23 648.2	7712.6±8265.3	54 915.8±21 601.9	19 365.8±13 529.8	58 084.3±17 544.3	12 297.6±11 221.2	55 207.6±19 884.5	7984.8±8299.2	48 370.1±1435.6
Baseline CDR-SOB, median (IQR)	2.0 (0.5–3.5)	0.5 (0.5–1.0)	2.5 (0.5–3.5)	1.75 (1.0–3.5)	1.5 (0.5–6.0)	0.5 (0.5–2.0)	2.0 (1.0–2.5)	2.5 (1.5–4.5)	1.75 (1.5–4.0)

APOE, apolipoprotein E; Aβ, β-amyloid; CDR-SOB, clinical dementia rating sum of box scores; CSVD, cerebral small vessel disease; dcCL, direct comparison of Centiloid units; HV, hippocampal volume; n, number; PET, positron emission tomography; ROI, region of interest; SUVR, standard uptake value ratio; WMH, white matter hyperintensities.

number of microbleeds.[28] Based on our previous results,[28] we defined vascular positivity (V+) when the WMH visual rating scale was classified as severe.

Neuropsychological assessments

For the baseline cognition evaluation, all participants underwent a standardised neuropsychological test battery that is widely used in South Korea.[29] The detailed items of battery are included in online supplemental method 8.

For the follow-up observation, we used clinical dementia rating sum of box (CDR-SOB) scores, which are useful for determining staging severity and widely used in clinical trials of cognitively impaired patients. We obtained retrospective longitudinal CDR-SOB scores from 188 participants. The study participants were examined for 4.9±3.8 years retrospectively from baseline. Our participants underwent longitudinal neuropsychological tests, ranging from 2 to 16 time points.

Statistical analysis

To compare the distributions of the AT(N) framework according to the V biomarker, the χ^2 test was used for categorical variables.

To investigate the effects of the presence of A, T or N biomarkers (binarised by each cut-off) on longitudinal cognitive changes over time in the V– and V+ groups, we performed linear mixed-effects (LME) models. We included fixed effects as follows: age, sex, years of education, the presence of A, T or N biomarkers (binarised by each cut-off), time interval (t) between baseline and each follow-up time point (years), and two-way interaction terms of the presence of A, T or N biomarkers and time interval (t). In order to investigate the effects of the presence of A, T or N biomarkers on longitudinal cognitive changes over time in V– and V+ groups, two-way interaction terms of presence of A, T or N biomarkers and time interval (t) were included in the fixed effects. The patients were included as random effects. The equations of the LME models in V– and V+ groups were as follows:

CDR-SOB~age+sex+education+A group+T group+N group+(t)+A group × (t).

CDR-SOB~age+sex+education+A group+T group+N group+(t)+T group×(t).

CDR-SOB~age+sex+education+A group+T group+N group+(t)+N group×(t).

To determine whether the presence of V biomarker affects longitudinal CDR-SOB changes over time in four AT(N) biomarker categories including normal AD biomarker, non-AD pathological change, Alzheimer's pathological change and AD categories, we applied LME models. We included fixed effects as follows: age, sex, years of education, Aβ dcCL, FTP SUVR at Braak III/IV ROI, HVa (continuous variables) and the presence of V biomarker (categorical variable), time interval (t) between baseline and each follow-up time point (years), and two-way interaction terms of presence of V biomarker and time interval (t). Continuous variables of Aβ dcCL, FTP SUVR at Braak III/IV ROI and HVa were included as fixed effects in the model to minimise the loss of information of each quantitative variables in each AT(N) category. In order to determine whether the presence of V biomarker affects longitudinal CDR-SOB changes over time in each AT(N) category, we used two-way interaction terms. The patients were included as random effects. The equation of the LME model for the four AT(N) biomarker categories was as follows:

CDR-SOB~age+sex+education+Aβ dcCL+FTP SUVR at Braak III/IV ROI+HVa+V group+(t)+V group×(t).

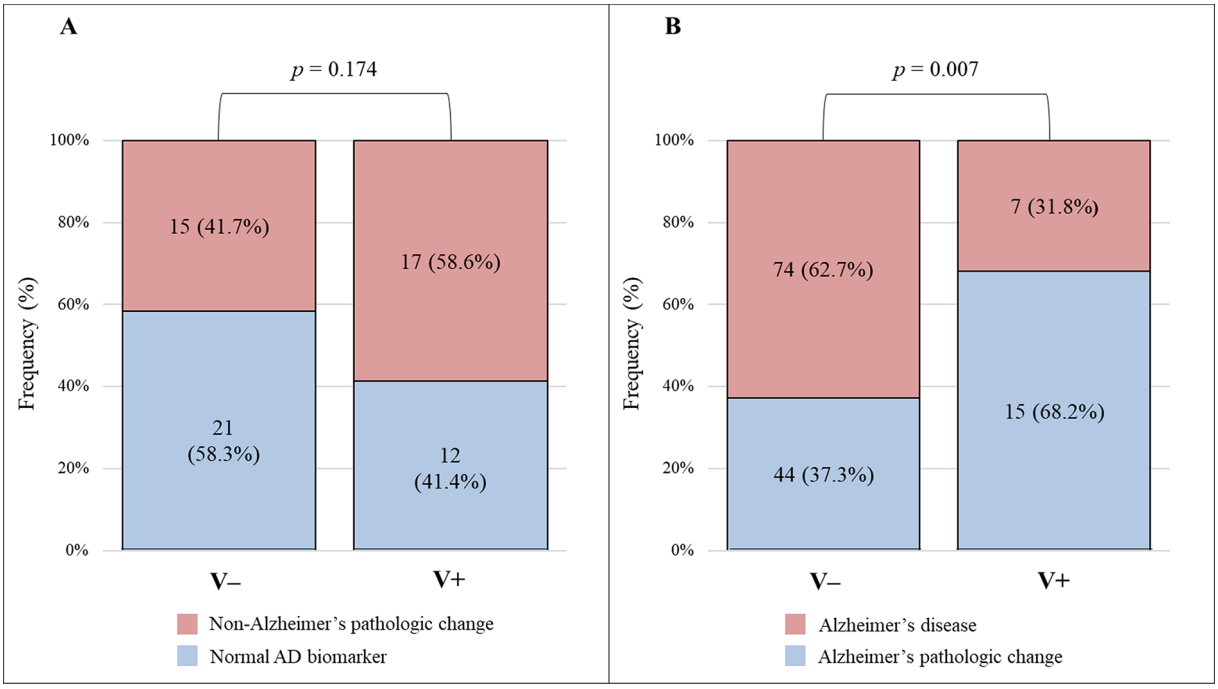

Figure 1 Distribution of participants according to AT(N) category and CSVD burden in (A) A– and (B) A+ groups. p values were generated by the χ^2 tests for the distribution of AT(N) categories and CSVD burden. A, β-amyloid; AD, Alzheimer's disease; N, neurodegeneration; V, cerebral small vessel disease.

To investigate the multiple CSVD markers including WMH volume, number of lacunes and number of microbleeds on longitudinal cognitive changes, separate LME models were performed for each of the CSVD markers. Specifically, we analysed the equation of the LME model for each CSVD marker within the four AT(N) biomarker categories as follows:

CDR-SOB~age+sex+education+Aβ dcCL+FTP SUVR at Braak III/IV ROI+HV CSVD marker+(t)+CSVD marker×(t).

Statistical analyses were conducted using STATA V.15 (StataCorp), and a p<0.05 was considered statistically significant for all analyses.

RESULTS

Study participants

Detailed characteristics of the 205 participants are described in table 1. The age of the participants was 74.1±8.6 (mean±SD) years, and the proportions of female and apolipoprotein E ε4 carriers were 62.9% and 43.4%, respectively. The frequencies of A+, T+, N+ and V+ were 68.3, 42.0, 64.4 and 24.9%, respectively.

Distribution of participants according to AT(N) system in the V– and V+ groups

Figure 1 shows the number of participants with AT(N) categories in V– and V+ groups. In the A– category, compared with the frequency of normal AD biomarker, there was a trend that the frequency of non-Alzheimer's pathological change was higher in the V+ group (58.6%) than in the V– group (41.7%) (p=0.174). In contrast, in A+ category, compared with the frequency of Alzheimer's pathological change category, the frequency of AD category was significantly lower in V+ group (31.8%) than in V– group (62.7%) (p=0.007).

Effects of each AT(N) biomarker on cognitive decline in the V– and V+ groups

In the V– group, the A+, T+ and N+ groups showed steeper increases in CDR-SOB than those in the A– (p<0.001), T– (p<0.001) and N– (p<0.001) groups (figure 2A). In the V+ group, the A+, T+ and N+ groups also showed steeper increases in CDR-SOB than those in the A– (p=0.001), T– (p<0.001) and N– (p<0.001) groups (figure 2B).

In both the V– and V+ groups, the A+ and T+ groups showed worse performances in visuospatial, language, memory and frontal/executive domains than those in the A– (p<0.05 for all comparisons) and T– (p<0.05 for all comparisons) groups (online supplemental table 1).

Effects of V biomarker on cognitive decline in AT(N) categories

Figure 3 shows the effects of the V biomarker on CDR-SOB changes in AT(N) categories. The V biomarker had effects on CDR-SOB changes in the non-Alzheimer's pathological change category (p=0.001) and Alzheimer's pathological change category (p<0.001). That is, in the non-Alzheimer's pathological change and Alzheimer's pathological change categories, cognitive decline developed over time, and their impact was higher in the V+ group than in the V– group. In the AD category, the V+ group tended to show a faster decline in CDR-SOB changes than the V− group, but the difference was insignificant (p=0.137).

The V biomarker had effects on changes of visuospatial and memory functions in the non-Alzheimer's pathological change and the Alzheimer's pathological change categories (p<0.05 for all comparisons) and changes of memory function in the AD category (p=0.008) (online supplemental table 2).

The WMH volume (continuous variable) affected on CDR-SOB changes over time in the non-Alzheimer's pathological change category (p=0.047) and Alzheimer's pathological change category (p<0.001) (online supplemental table 3).

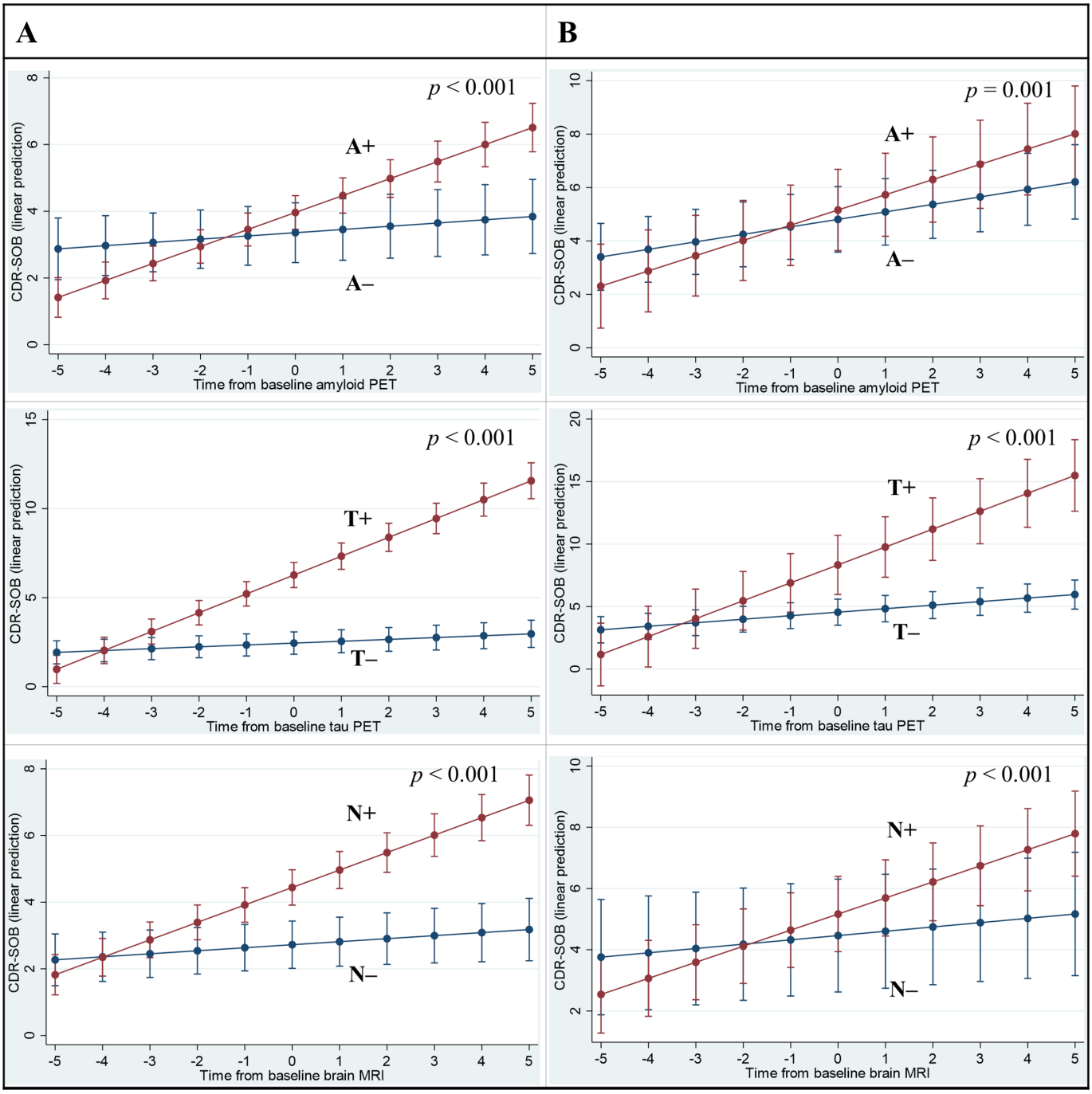

Figure 2 Distinctive cognitive trajectories according to each AT(N) biomarker in V– (A) and V+ (B) groups. Linear mixed effects models were performed in V– (A) and V+ (B) groups in order to investigate the effects of the presence of A, T or N biomarkers (binarised by each cut-off) on longitudinal cognitive changes over time in V– and V+ groups. Each p value is for two-way interaction term of each pathological burden (presence of A, T or N biomarkers) and time interval on longitudinal cognition changes in V– and V+ groups. A, β-amyloid; CDR-SOB, clinical dementia rating sum of boxes scores; N, neurodegeneration; PET, positron emission tomography; T, tau; V, cerebral small vessel disease.

DISCUSSION

In this study, we applied the AT(N) system to a prospectively designed cohort of participants with Alzheimer's and concomitant CSVD burdens. These participants underwent non-invasive Aβ and tau PET imaging and structural MRI to assess AT(N) biomarkers. Our major findings were as follows: First, within the Alzheimer's continuum (A+), compared with the frequency of the Alzheimer's pathological change (A+T–), the frequency of AD (A+T+) was lower in the V+ group than in the V– group. Second, each AT(N) biomarker independently acted as a predictor of cognitive decline in the V+ group as well as in the V– group, showing the prognostic value of the AT(N) system in the V+ group. Finally, cognitive decline trajectories of Alzheimer's pathological change (A+T–) were exacerbated in the V+ group. Taken together, our findings suggest that CSVD burden might influence the earlier stages of Alzheimer's pathophysiology, synergistically contributing to the development of cognitive decline. Furthermore, this study suggests the potential of incorporating the V biomarker into the existing AT(N) system in participants with Alzheimer's and concomitant CSVD burdens.

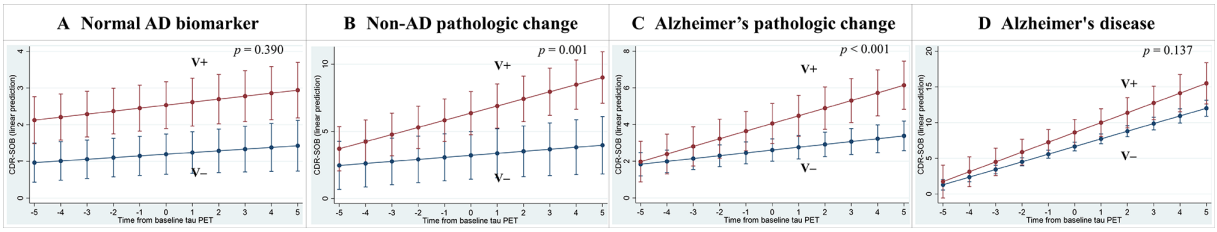

Figure 3 Effects of V biomarker on CDR-SOB changes in each AT(N) framework category (A–D). Linear mixed effects models were performed in normal AD biomarker (A), non-AD pathological change (B), Alzheimer's pathological change (C) and AD (D) categories in order to determine whether the presence of V biomarker affects longitudinal CDR-SOB changes over time. Each p value indicates a two-way interaction term of presence of V biomarker and time interval on longitudinal cognition changes in normal AD biomarker, non-AD pathological change, Alzheimer's pathological change and AD categories. AD, Alzheimer's disease; CDR-SOB, clinical dementia rating sum of boxes scores; V, cerebral small vessel disease.

Our first major finding was that, within the Alzheimer's continuum, compared with the frequency of Alzheimer's pathological change, the frequency of AD was lower in the V+ group than in the V– group. Our findings were consistent with the result of a previous study by our group showing that 25% of A+ subcortical vascular cognitive impairment were categorised as A+T+, while 70% of A+AD-related cognitive impairment were categorised as A+T+0.[7] Considering that T biomarkers were highly correlated with cognitive impairment, our findings suggest that CSVD burden may have a tau-independent effect on cognitive impairment. In addition, considering that Alzheimer's pathological change represents the earlier form of the Alzheimer's continuum than AD, our findings leave the potential that CSVD burdens might have an influence mainly on the earlier stages of Alzheimer's pathophysiology.

Our second major finding was that each AT(N) biomarker was independently predictive of cognitive decline in the V+ group as well as in the V– group. Recently, there has been emerging evidence for the prognostic value of the AT(N) system.[30–32] In this regard, the practical value of the AT(N) system extends from a research framework for diagnosis to prognostic evaluation and therapeutic decision-making. Considering our new findings on the effects of AT(N) biomarkers on cognitive decline in the V+ group, it is reasonable to expect that the AT(N) system can not only have diagnostic added value but also have important relevance for determining the prognosis of cognitive evolution in individuals with Alzheimer's disease and concomitant V burden. Our results could, therefore, encourage further investigation into the potential of the AT(N) system as a prognostic tool for Alzheimer's and concomitant non-Alzheimer's pathological changes.

Our final major finding was that the cognitive decline trajectories of Alzheimer's pathological changes were exacerbated in the V+ group. Our findings could be supported by previous findings from our group showing that Aβ deposition and V burden synergistically affect cognitive impairments.[7–9] These findings might be related to several hypotheses, including alterations in microvascular integrity, the neuroinflammatory cascade and blood–brain barrier disruption.[33 34] However, the whole-group analysis did not show the exacerbation of cognitive decline trajectories of AD in the V+ group. Considering that the effects of V burden on cognitive decline were more prominent in Alzheimer's pathological change than in AD, it is possible that V burden might have an influence on the earlier stages of Alzheimer's pathophysiology, synergistically contributing to the development of cognitive decline. Therefore, our findings suggest that combination therapies targeting both V and AD burdens, especially in the earlier process of Alzheimer's pathophysiology, may more effectively preserve cognitive functions than single-target therapies. Furthermore, we found that, in the non-Alzheimer's pathological change group, cognitive decline was more prominent in the V+ group than in the V– group.

The NIA-AA research framework suggested the possibility of adding the V biomarker to the existing AT(N) system and expanding AT(N) to the ATV(N) system.[1] In order to develop the ATV(N) system, efforts to prove the influence of V biomarker on AT(N) at the multiomics level and to develop and validate new V biomarker are needed. Nonetheless, considering our findings on the effects of V biomarker on the cognitive trajectory of the AT(N) system, we suggest the possibility that the ATV(N) system may enhance the understanding of the heterogeneous pathophysiology and improve the prediction of the prognosis of individuals with Alzheimer's and concomitant V burdens.

The strength of our study is that participants were recruited using a standardised diagnostic protocol, including Aβ and tau PET and brain MRI, to assess AT(N) biomarkers. However, this study had some limitations. First, we used A and T biomarkers on PET and N and V biomarkers on MRI instead of performing pathological confirmation. Although the system was developed for the categorisation of living individuals, there is a possibility that our participants were misclassified into A, T, V and N biomarker groups. Second, there exist numerous methods for classifying A, T, V and N abnormality, and a consensus within the field remains elusive; however, this limitation might be mitigated by the fact that the method to obtain the cut-off value for each biomarker abnormality has been widely used in other studies.[15 35] Third, in terms of the 'V' biomarker, we need a clearer definition of V+ to develop the ATV(N) framework. Additionally, there may be alternative definitions, particularly ones that incorporate multiple CSVD markers besides WMH. Nonetheless, we deemed it appropriate to define 'V+' using severe WMH since this classification system has been well validated. Fourth, the tau PET data were acquired on two different PET scanners, either at SMC or Gangnam Severance. However, such variability was minimised by analysing the tau PET data centrally at the SMC with a uniform pipeline. Finally, we recruited participants with either a high Aβ burden or a high V burden, which may limit the generalisability to the community-based population. Nevertheless, our finding related to the effects of V burden on cognitive trajectories of AT(N) categories support the importance of interventions targeting both AD and V burden to attenuate disease progression in participants with Alzheimer's and concomitant V burdens if these treatments become a clinical reality in the future. Our idea of CSVD burden influencing the earlier stages of Alzheimer's pathophysiology requires further

evidences from longitudinal studies examining the cognitive trajectories of V+ and V− individuals as they progress along the Alzheimer's continuum.

In conclusion, our study showed that the V burden affected the cognitive decline trajectories across the AT(N) system, suggesting the possibility that the V biomarker could be incorporated into the AT(N) system to gain a better understanding of AD pathophysiology and help reduce modifiable risks.

Author affiliations
[1]Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Gangnam-gu, Seoul, South Korea
[2]Department of Neurology, Yonsei University College of Medicine, Seoul, South Korea
[3]Department of Neurology, Yongin Severance Hospital, Yonsei University Health System, Yongin, South Korea
[4]Neuroscience Center, Samsung Medical Center, Seoul, South Korea
[5]Samsung Alzheimer's Convergence Research Center, Samsung Medical Center, Seoul, South Korea
[6]Department of Health Sciences and Technology, SAIHST, Sungkyunkwan University, Seoul, South Korea
[7]Department of Intelligent Precision Healthcare Convergence, Sungkyunkwan University, Suwon, South Korea
[8]Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA
[9]Department of Radiology and Biomedical Imaging, University of California, San Francisco, California, USA
[10]Department of Neurology, University of California-Davis, Davis, California, USA
[11]Departmentof Nuclear Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea
[12]Division of Applied RI, Korea Institute of Radiological and Medical Sciences, Seoul, South Korea
[13]Department of Nuclear Medicine, Korea Cancer Center Hospital, Korea Institute of Radiological and Medical Sciences, Seoul, South Korea
[14]Center for Neuroimaging, Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, Indiana, USA
[15]Cell and Gene Therapy Institute (CGTI), Research Institute for Future Medicine, Samsung Medical Center, Seoul, South Korea
[16]Department of Digital Health, SAIHST, Sungkyunkwan University, Seoul, South Korea

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ORCID iDs
Min Young Chun http://orcid.org/0000-0003-3731-6132
Hyemin Jang http://orcid.org/0000-0003-3152-1274
Samuel N Lockhart http://orcid.org/0000-0002-0893-5420

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