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

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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 (A−T−N+; 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 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− and A+T+N+), and non-Alzheimer’s pathological change (A−T+N−, A−T+N+ and A−T+N+). If the
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 (18F-flortaucipir (FTP)) positron emission tomography (PET) scans between May 2015 and December 2021. All participants underwent neuropsychological tests, brain MRI and Aβ (18F-florbetaben (FBB) or 18F-flumetamol (FMMI)) 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 criteria10 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: (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.11-13

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) infections other than vascular pathology, including radiation injury, multiple sclerosis, vasculitis, leukodystrophy or metabolic disorders; (5) a history of 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 STc 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 STc 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 V6.0 (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, insimus, 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 (V2.1.0).21 Native MRIs were registered to the MNI-152 template by linear transformation22 and corrected for intensity non-uniformity using the N3 algorithm.23 The detailed methods for adjusted HV (HVs) 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 studies24 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 cm³, HVs 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.18 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

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Normal AD biomarker</th>
<th>Non-Alzheimer's pathological change</th>
<th>Alzheimer's pathological change</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>V−</td>
<td>V+</td>
<td>V−</td>
<td>V+</td>
</tr>
<tr>
<td>No</td>
<td>205</td>
<td>21</td>
<td>12</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>74.1±8.6</td>
<td>73.4±5.2</td>
<td>70.2±6.5</td>
<td>78.1±7.8</td>
<td>80.0±5.5</td>
</tr>
<tr>
<td>Sex, female, n (%)</td>
<td>129 (62.9)</td>
<td>15 (71.4)</td>
<td>5 (41.7)</td>
<td>9 (60.0)</td>
<td>14 (82.4)</td>
</tr>
<tr>
<td>Education, years, mean (SD)</td>
<td>10.2±5.3</td>
<td>10.7±5.8</td>
<td>6.1±5.5</td>
<td>9.1±6.2</td>
<td>9.7±5.0</td>
</tr>
<tr>
<td>ε4 carrier, n (%)</td>
<td>89 (43.4)</td>
<td>4 (19.0)</td>
<td>4 (33.3)</td>
<td>7 (46.7)</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>Aβ PET dcCL, mean (SD)</td>
<td>64.6±51.0</td>
<td>1.5±11.0</td>
<td>3.6±5.1</td>
<td>1.7±0.4</td>
<td>1.8±0.3</td>
</tr>
<tr>
<td>HV volume (mm³), mean (SD)</td>
<td>21 923.3±23 648.2</td>
<td>2978.7±330.6</td>
<td>3180.8±428.7</td>
<td>2714.3±522.2</td>
<td>2240.2±433.3</td>
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</tr>
</tbody>
</table>

**Note:** APOE, apolipoprotein E; Aβ, 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.
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:

\[
CDR-SOB = \text{age + sex + education + } \beta \text{-amyloid + } dcCL + FTP SUVR \text{ at Braak III/IV ROI + HV CSVD marker + (t) + CSVD marker \times (t)}.
\]

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 (41.4%) (\( p = 0.174 \)).

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).
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 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.

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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 23% of A+ subcortical vascular cognitive impairment were categorised as A+T+, while 70% of A+T-related cognitive impairment were categorised as A+T+0. 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. 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. These findings might be related to several hypotheses, including alterations in microvascular integrity, the neuroinflammatory cascade and blood–brain barrier disruption. 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. In order to develop the ATV(N) system, efforts to prove the influence of V biomarker on AT(N) at the multomics 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. 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.

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Contributors

MYC, HJ and SWS devised the project and the main conceptual framework. MYC, HJ, SN, YC, DB, HB, HB, HJK, ML, YC, SHM and KRN led the data collection. MYC and JYC and investigated the findings of the work. MYC and HJK drafted the manuscript and SWS revised the first draft. MYC, HJ, SN, YC, DB, HB, HB, HJK, ML, YC, SHM, JYC, KRN, BHC and SWS contributed to the project and consented to publication. MYC, HJ, SN, YC, DB, HB, HB, HJK, ML, YC, SHM, JYC, KRN, BHC and SWS reviewed the manuscript.

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Competing interests

None declared.

Patient consent for publication

Not applicable.

Ethics approval

This study involves human participants and this study was approved by the Institutional Review Board of Samsung Medical Center (IRB No: 2018-10-120). Written informed consent for participating in the study and publication was obtained from participants and their caregivers. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Data are available on reasonable request. Data will be made available to qualified investigators on reasonable request to the corresponding authors and approval from the contributing institutions.

Supplemental material

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