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Exaggerated blood pressure variability is associated with memory impairment in very elderly patients

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We investigated the association between working memory (WM) impairment and blood pressure variability (BPV) in very elderly patients. Japanese outpatients ≥80 years who engaged in normal activities of daily living were the study cohort. WM function was evaluated by a simple visual WM test consisting of 3 figures. We considered the number of figures recalled by the patient his/her test score. We defined the patients with a score of 0 or 1 as those with WM impairment and those with scores of 2 or 3 as those without. To investigate the relative risk of WM impairment, we evaluated each patient's 24 hour ambulatory systolic blood pressure (SBP) and its weighted standard deviation (SD_{SBP}), office SBP, and the visit-to-visit SD_{SBP} during the 1 year period from the patient's enrollment. A total of 66 patients (mean 84 ± 3.6 years) showed WM impairment, and 431 patients (mean 83 ± 3.1 years) showed no WM impairment. There were no significant differences in 24 hour ambulatory SBP or office SBP between these two groups. However, the WM impairment patients showed significantly higher weighted SD_{SBP} and visit-to-visit SD_{SBP} values compared to the no-impairment group even after adjusting for age. Among these ≥80-year-old patients, those with the highest quartile of both weighted SD_{SBP} (≥21.4 mm Hg) and visit-to-visit SD_{SBP} (≥14.5 mm Hg) showed the highest relative risk (odds ratio 3.52, 95% confidence interval 1.42-8.72) for WM impairment. Exaggerated blood pressure variability parameters were significantly associated with working memory impairment in very elderly individuals.

1 | INTRODUCTION

Elevated blood pressure (BP) is a major negative factor in the development of cognitive dysfunction in middle age.[1-6] However, there is no consensus about the association between elevated BP and cognitive function in later life.[7] The data on the association between antihypertensive treatment and altered cognitive function in elderly populations are limited.[8] Antihypertensive treatment targeting lower BP levels in elderly patients (≥80 years) resulted in a non-significant reduction of cognitive dysfunction.[9] Therefore, other factor(s), not the BP level, might be associated with cognitive function in individuals ≥80 years.

Blood pressure variability (BPV) has been highlighted as a surrogate marker of target organ damage[10-15] and as a prognostic factor of future cardiovascular events.[16-21] Several studies have revealed that exaggerated short-term BPV (ie, ambulatory BPV)[22,23] and exaggerated long-term BPV (ie, visit-to-visit BPV)[24-28] are significant indicators of global cognitive dysfunction. However, no study has investigated the association between both short-term and long-term exaggerated BPV and cognitive dysfunction in the same patient group. In addition, there is no information regarding the direct relationships between working memory (WM) impairment (which is a core feature of cognitive dysfunction)[29,30] and BPV parameters, especially in very elderly individuals. In the present study, we considered ≥80 years as "very elderly."

In the present study, we therefore used data from the Japanese-based study known as the SEARCH (search longevity in very elderly

with ambulatory pressure in Tochigi) study, a prospective observational study of elderly patients (≥80 years), to test our hypothesis that the indices of BPV would be significantly associated with WM impairment in very elderly individuals. We also assessed whether the individuals with both exaggerated short-term BPV and exaggerated long-term BPV showed a high relative risk for WM impairment.

2 | METHODS

2.1 | Patients

The SEARCH study examined 525 elderly outpatients who were recruited between September 2008 and December 2013 and followed up through June 2015 by 26 doctors at 21 institutions (including two specialized university hospitals). Details of the study design and methods are described in the present study's Data S1.

The 3 inclusion criteria were: (1) age ≥80 years, (2) ability to attend a clinic or hospital without difficulty in walking, and (3) living without assistance. The exclusion criteria were: (1) prevalent cardiovascular disease or cerebrovascular disease, excluding transient ischemic attack, within 6 months; (2) current dialysis; (3) malignant disease at baseline; and (4) inability to provide informed consent due to severe cognitive dysfunction or dementia. All participants provided written informed consent, and the ethics committee of the Jichi Medical University School of Medicine approved the study.

2.2 | BP and other measurements

The office BP of each patient was measured at each visit to the participating institution, with the use of a validated cuff oscillometric device in accord with the Japanese Society of Hypertension 2004 guidelines.[31] BP was measured after the patient rested for at least 5 minutes in a seated position. Two consecutive BP measurements were taken at a 1-2 minute intervals and the average of the measurements was used as the office BP value. We measured office BP at baseline and at each office visits during the 1-year period from the patient's enrollment.

Non-invasive 24-hour ambulatory BP monitoring (ABPM) was carried out at the baseline with a validated automatic device (TM-2425 or TM-2431) that recorded the patient's BP using an oscillometric method at 30-minute intervals throughout the 24-hour day. Morning BP was defined as the average of BP values during the first 2 hours of being awake. Nighttime BP was defined as the average BP value from those taken at bedtime and when the patient got out of bed in the morning. Daytime BP was defined as the average BP value for the rest of the day.

For the short-term BPV parameters, we calculated the standard deviation (SD), coefficient of variation (CV), and the weighted SD of the 24-hour ambulatory systolic BP (SBP) and diastolic BP (DBP) values. For the long-term BPV parameters, we calculated the SD, CV, and maximum and minimum BP difference (MMD) of the visit-to-visit SBP and DBP values. The weighted SD was the average daytime and nighttime BP SD divided by the duration in hours of each time period. The MMD was calculated as the maximum BP minus the minimum BP in the follow-up period.

Fasting blood and spot urine samples were collected in the morning at baseline. All samples were sent to a single laboratory (SRL, Tokyo) within 24 hours of collection. Questionnaires were used to collect demographic data and clinical and behavioral characteristics of patients (details are provided in the Data S1). Pre-existing

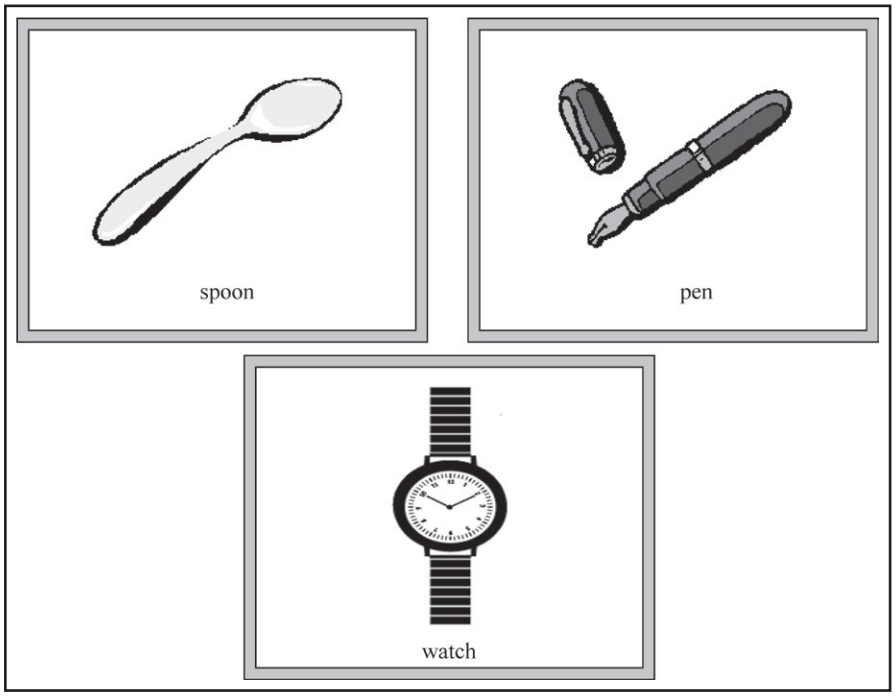

FIGURE 1 The three figures used in the simple visual working memory test

cardiovascular disease (CVD) was defined as pre-existing angina pectoris, myocardial infarction, or stroke.

2.3 | Working memory assessment

We used a simple visual WM test to evaluate the WM function of study patients. This test was a part of the mini-mental state examination (MMSE), whose validity and reproducibility have been confirmed;[32,33] it was conducted by trained medical staff upon patient entry. Each patient was shown the same 3 figures (a spoon, a pen, and a watch; Figure 1) and asked to name each figure out loud and to memorize the names. All of the patients correctly named the figures when they saw them. After patients had memorized the 3 figures, and before they were asked to recall them, the medical staff collected the demographic data and clinical and behavioral characteristics of patients (see the Data S1). Then, at 5 minutes after presentation of the figures, patients were asked to recall the names of the figures. The number of figures that the patient was able to recall was counted as the patient's test score, with a larger score indicating better WM function. We defined the patients with 0 or 1 of the test score as those with WM impairment and the patients with the score 2 or 3 as those without WM impairment.

2.4 | Statistical analysis

Statistical analyses were performed with SPSS software ver. 24.0 (SPSS). We used a two-sided unpaired *t*-test to compare the clinical parameters in patients with versus without WM impairment. Clinical parameters that are evaluated as percentages were compared using chi-squared statistics. We used Pearson's correlation coefficient for a bivariate analysis examining SD_{BP} versus other BPV parameters. To assess the differences in BPV parameters between the "with" and "without" WM impairment groups, we conducted a logistic regression analysis with adjustment for age. A *P*-value <.05 was considered significant.

3 | RESULTS

3.1 | Patient characteristics

Of the 525 participants for whom entry data were obtained, we excluded 1 participant who had no information on age, 5 participants who did not take the WM test, 5 participants who did not have ABPM, and 17 participants who visited their physician's offices only 1 time during the 1-year follow-up period after their inclusion in this study. The included participants (n = 497) had higher percentages of calcium-channel blockers and angiotensin-converting

TABLE 1 Baseline characteristics of the patients with or without working memory impairment (n = 497)

Variable	With WM impairment (n = 66)	Without WM impairment (n = 431)	*P*-value
Age, yrs	84.0 ± 3.6	83.0 ± 3.1	.015
Male, n (%)	24 (36.4)	196 (45.5)	.165
BMI, kg/m^2	22.5 ± 3.9	23.4 ± 3.4	.056
Current smoking, n (%)	4 (7.0)	25 (7.7)	.859
Daily drinker, n (%)	14 (21.5)	115 (26.7)	.378
Antihypertensive medication			
Calcium-channel blockers, n (%)	40 (60.6)	288 (66.8)	.321
ACE inhibitors, n (%)	20 (30.3)	102 (23.7)	.243
Angiotensin receptor blockers, n (%)	29 (43.9)	210 (48.7)	.469
Diuretics, n (%)	13 (19.7)	118 (27.4)	.187
Alpha-blockers, n (%)	3 (4.5)	38 (8.8)	.240
Beta-blockers, n (%)	9 (13.6)	82 (19.0)	.292
Hypertension, n (%)	55 (83.3)	371 (86.1)	.553
Dyslipidemia, n (%)	25 (37.9)	182 (42.2)	.505
Diabetes mellitus, n (%)	15 (22.7)	111 (25.8)	.599
Pre-existing CVD, n (%)	14 (21.2)	110 (25.5)	.451
Stroke, n (%)	3 (4.5)	47 (10.9)	.110
Angina pectoris or myocardial infarction, n (%)	12 (18.2)	78 (18.1)	.987
Fasting glucose, mg/dL	103.2 ± 18.5	106.7 ± 27.0	.301
Total cholesterol, mg/dL	192.5 ± 28.0	189.1 ± 29.5	.379
High-density lipoprotein, mg/dL	57.4 ± 15.2	56.6 ± 14.6	.672
No. of office visits	10.0 ± 2.9	9.4 ± 3.1	.175

ACE, angiotensin converting enzyme; CVD, cardiovascular disease; WM, working memory.
Data are mean ± SD or number (percentage). Pre-existing CVD includes pre-existing angina pectoris, myocardial infarction, or stroke. *P*-values were obtained by unpaired *t*-test or chi-squared test.

enzyme inhibitor use, and higher numbers of office visits than those excluded (n = 28); other variables were similar between the included and excluded patients (Table S1). The mean age of the 497 patients was 83.2 ± 3.2 years, and 55.7% were women. Pre-existing CVD was observed in 24.9% (n = 124) of the patients (stroke, 50 patients; angina pectoris or myocardial infarction, 90 patients). The distribution of the simple visual WM test scores was as follows: 0 (n = 17, 3.4%), 1 (n = 49, 9.9%), 2 (n = 155, 31.2%), and 3 (n = 276, 55.5%).

Table 1 summarizes the differences in the demographic and clinical characteristics of the patients with and without WM impairment. The age of the patients with WM impairment (n = 66) was significantly higher than that of the patients without WM impairment (n = 431), and they tended to have lower body mass index values. There were no significant differences in the classes of antihypertensive medication use between the patients with and without WM impairment. The percentage of pre-existing CVD was not significantly different between the two groups (21.2% vs 25.5%, respectively; $P = .451$); nor was the percentage of stroke (4.5% vs 10.9%, respectively; $P = .110$). The average number of office visits, which indicates the number of times that visit-to-visit BP was measured during the follow-up period, was not significantly different between the groups (10.0 ± 2.9 vs 9.4 ± 3.1, respectively; $P = .175$).

3.2 | Blood pressure and BPV parameters

Table 2 shows the mean 24-hour ambulatory BP values and their short-term BPV parameters. The mean systolic and diastolic BP levels (including 24-hour ambulatory BP, morning BP, daytime BP, and nighttime BP) showed no significant differences between the patients with and without WM impairment. However, all of the short-term BPV parameters were significantly higher in the patients with WM impairment compared to those without.

Table 3 provides the office BP values at baseline and their long-term BPV parameters. The baseline office systolic and diastolic BP levels showed no significant differences between the groups with and without WM impairment. However, the SD_{SBP}, CV_{SBP}, and MMD_{SBP} values were all significantly higher in the patients with WM impairment compared to those without. Figure S1 shows the office BP variation during the follow-up period in patients with and those without WM impairment. The office BP levels remained similar in both groups during the follow-up period.

3.3 | Relative risk of WM impairment

To evaluate the relative risk of WM impairment, we used weighted SD_{SBP} and visit-to-visit SD_{SBP} as the short-term and the long-term BPV parameters, respectively, because the other respective parameters were significantly correlated with them (Table S2). The correlation between weighted SD_{SBP} and visit-to-visit SD_{SBP} was significant, but it was very weak ($r = .104$, $P = .021$). We divided the weighted SD_{SBP} and visit-to-visit SD_{SBP} values into quartiles, and used the references of weighted SD_{SBP} < 14.8 mm Hg (the lowest quartile of weighted SD_{SBP}) and visit-to-visit SD_{SBP} < 8.6 mm Hg (the lowest quartile of visit-to-visit SD_{SBP}), respectively.

Both the highest quartile of weighted SD_{SBP} (≥21.4 mm Hg) and that of visit-to-visit SD_{SBP} (≥14.5 mm Hg) presented a significantly

TABLE 2 Twenty-four ambulatory BP parameters of study cohort (n = 497)

Variable	With WM impairment (n = 66)	Without WM impairment (n = 431)	*P*-value
24-hr ambulatory SBP, mm Hg	131.0 ± 15.0	130.3 ± 14.6	.873
24-hr ambulatory DBP, mm Hg	71.5 ± 7.0	70.4 ± 7.3	.198
Morning SBP, mm Hg	140.2 ± 22.4	142.1 ± 20.4	.488
Morning DBP, mm Hg	79.7 ± 16.9	78.1 ± 13.0	.370
Daytime SBP, mm Hg	135.5 ± 15.2	135.4 ± 15.3	.014
Daytime DBP, mm Hg	74.3 ± 7.3	73.2 ± 7.7	.257
Nighttime SBP, mm Hg	123.2 ± 18.7	121.4 ± 16.7	.591
Nighttime DBP, mm Hg	66.6 ± 8.8	65.4 ± 8.5	.244
SD_{SBP}, mm Hg	22.6 ± 4.6	20.3 ± 5.6	.003
SD_{DBP}, mm Hg	13.4 ± 2.8	12.2 ± 3.3	.005
CV_{SBP}, %	17.3 ± 3.5	15.7 ± 4.2	.003
CV_{DBP}, %	18.8 ± 3.8	17.3 ± 4.7	.022
Weighted SD_{SBP}, mm Hg	20.3 ± 4.3	18.2 ± 4.9	.003
Weighted SD_{DBP}, mm Hg	12.2 ± 2.9	11.1 ± 3.1	.007

BP, blood pressure; CV, coefficient of variation; DBP, diastolic blood pressure; SBP, systolic blood pressure; WM, working memory.
Data are mean ± SD. *P*-values were obtained by logistic regression analysis adjusted by age.

TABLE 3 Visit-to-visit BP parameters of study cohort (n = 497)

Variable	With WM impairment (n = 66)	Without WM impairment (n = 431)	*P*-value
Office SBP, mm Hg	144.8 ± 22.8	139.6 ± 20.5	.068
Office DBP, mm Hg	75.6 ± 13.7	73.4 ± 13.3	.156
SD_{SBP}, mm Hg	13.5 ± 5.5	11.8 ± 4.6	.017
SD_{DBP}, mm Hg	7.8 ± 2.8	7.0 ± 2.8	.058
CV_{SBP}, %	9.7 ± 4.2	8.5 ± 3.1	.012
CV_{DBP}, %	10.8 ± 4.2	10.0 ± 4.1	.193
MMD_{SBP}, mm Hg	40.3 ± 15.5	35.4 ± 14.4	.032
MMD_{DBP}, mm Hg	23.3 ± 8.4	20.9 ± 9.0	.057

BP, blood pressure; CV, coefficient of variation; DBP, diastolic blood pressure; MMD, maximum and minimum blood pressure difference; SBP, systolic blood pressure; WM, working memory.
Data are mean ± SD. *P*-values were obtained by logistic regression analysis adjusted by age.

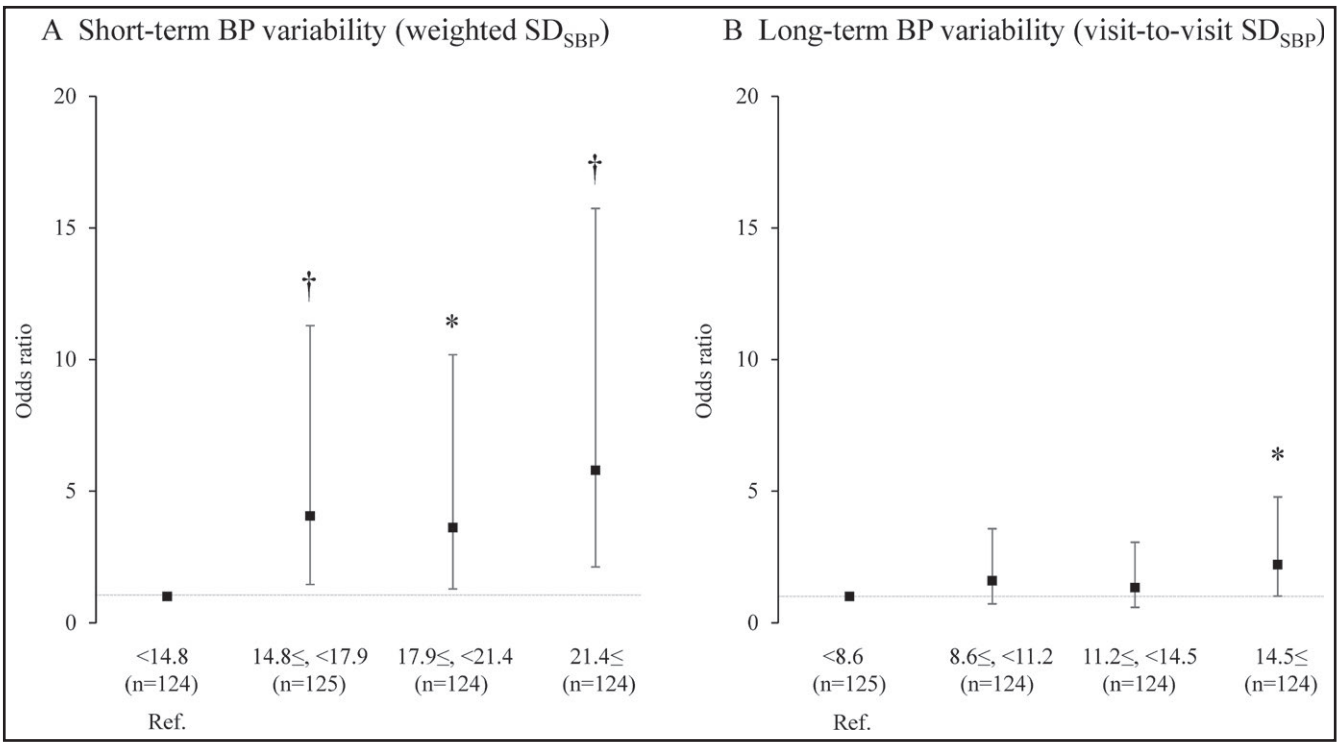

FIGURE 2 The relative risk of working memory impairment according to systolic BP variability quartiles, with OR and 95% CI values. Weighted SD_{SBP} < 14.8 mm Hg and visit-to-visit SD_{SBP} < 8.6 mm Hg were used as references (Ref.), respectively, and the bars represent ORs (95% CIs) with adjustment for age. A logistic regression analysis was used with adjustment for age. *P < .05, †P < .01

high relative risk of WM impairment compared to the references; the odds ratio (OR) of the highest quartile of weighted SD_{SBP} was 5.79, with the 95% confidence interval (CI) of 2.13-15.74 (P = .001). The OR of the highest quartile of visit-to-visit SD_{SBP} was 2.21, with the 95% CI of 1.02-4.78 (P = .045; Figure 2).

We next set the highest quartile of weighted SD_{SBP} and that of visit-to-visit SD_{SBP} as the high BPV group, and the other quartile of weighted SD_{SBP} (<21.4 mm Hg) and that of visit-to-visit SD_{SBP} (<14.5 mm Hg) as the low BPV group, respectively. The patients with both high weighted SD_{SBP} and high visit-to-visit SD_{SBP} showed the highest relative risk (OR 3.52, 95% CI 1.42-8.72, P = .007) of WM impairment compared to those with both low weighted SD_{SBP} and low visit-to-visit SD_{SBP} (Figure 3).

We calculated the parameters of diastolic BPV in the same way as those of systolic BPV. The correlation between weighted SD_{DBP} and visit-to-visit SD_{DBP} was not significant (r = .071, P = .117). The highest quartile of weighted SD_{DBP} (≥13.0 mm Hg) presented a significantly high relative risk and the highest quartile of visit-to-visit SD_{DBP} (≥8.8 mm Hg) showed a trend toward higher relative risk of WM impairment compared to the reference; the OR of the highest

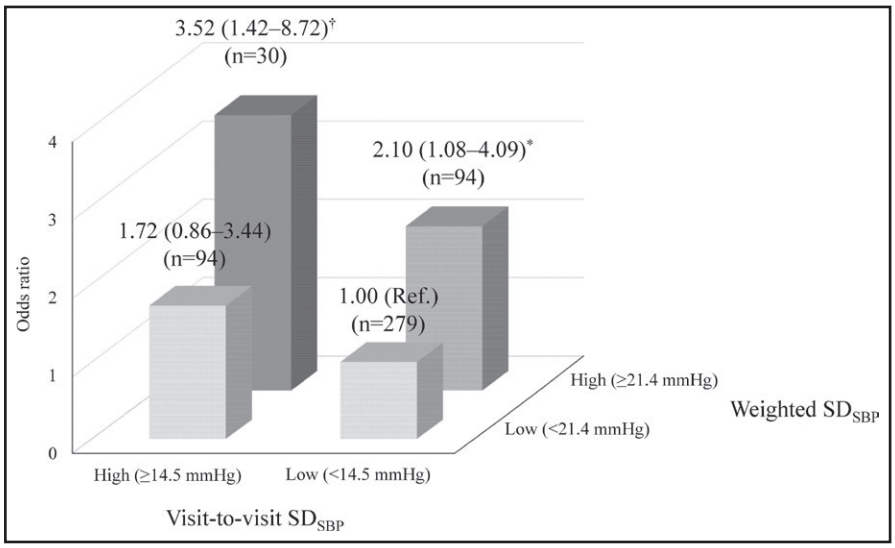

FIGURE 3 Relative risk of working memory impairment according to each systolic BP variability category group, with OR and 95% CI values. The findings for the group with both low weighted SD_{SBP} (<21.4 mm Hg) and visit-to-visit SD_{SBP} < 14.5 mm Hg were used as references (Ref.). A logistic regression analysis was used with adjustment for age. $^{*}P < .05$, $^{\dagger}P < .01$

quartile of weighted SD_{DBP} was 3.75, with a 95% CI of 1.53-9.19 ($P = .004$). The OR of the highest quartile of visit-to-visit SD_{DBP} was 1.95, with a 95% CI of 0.89-4.26 ($P = .096$; Figure S2). The patients with both high weighted SD_{DBP} and high visit-to-visit SD_{DBP} showed the highest relative risk (OR 2.94, 95% CI 1.20-7.20, $P = .019$) of WM impairment compared to those with both low weighted SD_{DBP} (<13.0 mm Hg) and low visit-to-visit SD_{DBP} (<8.8 mm Hg; Figure S3).

4 | DISCUSSION

The main findings of this study of elderly patients (≥80 years) are as follows. First, both the short-term and long-term blood pressure variability (BPV) parameters, not BP levels, were significantly higher in the patients with working memory (WM) impairment compared to those without. Second, the patients with both high weighted SD_{SBP} and visit-to-visit SD_{SBP} showed the highest relative risk of WM impairment. These findings indicate that exaggerated BPV may be associated with WM impairment in very elderly patients (ie, those aged ≥80 years). The assessment of both short-term and long-term BPV parameters could thus be important for identifying patients with WM impairment.

The novel finding of the present study was that the patients with WM impairment showed exaggeration of both short-term and long-term BPV compared to those without WM impairment, despite the lack of difference in BP levels between the two groups. Our results indicate that the initial increase in BPV, not the BP level, could be associated with the progression of WM impairment. The contribution of exaggerated BPV leading to cognitive dysfunction in the elderly has been reported. Two studies of Japanese hypertensive patients showed that exaggerated ambulatory BPV (SD) was related to cognitive dysfunction,[22,23] and Nagai et al[24] also showed that exaggerated visit-to-visit BPV (CV and MMD) were significantly associated with cognitive impairment independently of average BP levels in the elderly (mean age 80 years). Sabayan et al[25] reported that higher visit-to-visit BPV (SD) was associated with worse performances regarding selective attention, reaction time, general cognitive speed, and immediate and delayed memory, independently of average BP levels in the elderly (mean age 75 years) in a longitudinal study with 3.2 years of follow-up.

The present study is the first to reveal that individuals ≥80 years, with both exaggerated short-term and long-term BPV parameters, showed the highest relative risk of WM impairment. The underlying mechanisms differ between short-term and long-term BPV. Short-term BPV is affected by various types of intrinsic factors such as increased central sympathetic drive and reduced arterial and cardiopulmonary reflexes,[34] increased arterial stiffness,[35,36] humoral,[37] and genetic factors.[21] In contrast, long-term BPV was reported to be influenced by extrinsic factors such as compliance with and the improper administration of antihypertensive drugs, the type of antihypertensive drugs,[38] errors in office BP measurements, and seasonal BP changes.[37] In light of the very high ages of our study's patients, increases in both intrinsic and extrinsic factors for BPV might have more strongly affected the significant association with WM impairment compared to individuals <80 years.

In addition, the reports that both short-term and long-term BPVs are associated with each other, which leads to the progression of cerebral, cardiac, renal and vascular damage independently of mean BP levels[37,39] might support our results.

Ambulatory BP monitoring can provide a significant amount of BP information (including the mean BP level and its variability), which cannot be estimated by office BP monitoring. However, ABPM cannot be used routinely to assess BPV. Various types of BP monitoring should thus be performed, and the evaluation of the combination of different types of BPV parameters would be effective to detect WM impairment at an early stage.

An association between exaggerated BPV and cognitive dysfunction has been reported,[22-25] but whether exaggerated BPV may be causally related to cognitive dysfunction or simply a result of cognitive dysfunction remains unclear. Some studies have suggested that exaggerated BPV may contribute to cognitive dysfunction, since it has been demonstrated to have detrimental effects on the cerebral

perfusion and cerebral hemodynamic[40,41] as well as alter the neurovascular coupling.[42] On the other hand, there is also evidence that the autonomic dysregulation or neurodegeneration, both of which cause cognitive dysfunction, may lead to exaggerated BPV.[43-46] We were unable to establish causality based on our findings, but we found that exaggerated BPV and cognitive dysfunction were closely related to each other from the early stage of cognitive decline, and we considered that these factors might form a "vicious cycle."[39] To suppress this cycle at the early stage, various types of BPV should be evaluated in detail.

In this study, we evaluated the patients' WM function by using a simple visual WM test. There are various types of screening tests to evaluate WM function, but some are very difficult to use for screening in general practice. The simple visual WM test used in this study easily evaluated WM function even in elderly patients ≥80 years. As we also reported regarding this test (for which the association between the decrease in cognitive function and mortality was established), we observed that cognitive dysfunction assessed by this same simple visual WM test was an independent risk factor for total death and cardiovascular death in elderly ≥80 years,[47] which indicates that this simple test would be an effective method for evaluating both the cognitive function and mortality risk in the very elderly. Further studies are needed to validate the clinical implication of this simple test.

The major strength of this study includes the large number of patients ≥80 years in a general practice population. In addition, the patients had maintained their general intellect and activities of daily living without any signs of severe cognitive dysfunction or dementia. However, there are study limitations. First, we did not evaluate the patients' global cognitive function. Second, we used an extremely simple test for evaluating WM function. Further studies are needed to investigate the association between exaggerated BPV and WM impairment assessed by other tests, such as the California Verbal Learning Test,[48] Wechsler Memory Scale,[49] and Gollin Figures Test,[50] which have been confirmed to be valid and are widely used to assess cognitive function. Third, it is possible that the results of this study should not be extrapolated to individuals <80 years. Fourth, patients who had a pre-existing stroke event were included in this study. Finally, we did not assess the changes of antihypertensive medications during the follow-up period.

5 | CONCLUSIONS

In very elderly patients (≥80 years), both short-term and long-term BP variability parameters were significantly associated with working memory impairment, and the patients with both exaggerated short-term BP variability and exaggerated long-term BP variability showed the highest relative risk of working memory impairment. The BP variability parameters could be a significant indicator of working memory impairment. In very elderly patients, we should evaluate not only BP levels but also their variability for the detection of working memory impairment at an early stage.

CONFLICTS OF INTEREST

None.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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