

ORIGINAL ARTICLE

Chronic kidney disease, 24-h blood pressure and small vessel diseases are independently associated with cognitive impairment in lacunar infarct patients

Yasumasa Yamamoto¹, Tomoyuki Ohara¹, Yoshinari Nagakane¹, Eijiro Tanaka¹, Fukiko Morii¹, Takashi Koizumi¹ and Ichiro Akiguchi²

Although the relationships between chronic kidney disease (CKD) and cognitive impairment (CI) have been highlighted, the etiology of CI in CKD remains uncertain. Subjects comprised 224 consecutive patients with symptomatic lacunar infarction who underwent magnetic resonance imaging and ambulatory blood pressure monitoring (ABPM). Diurnal blood pressure (BP) patterns were categorized into three groups: dippers, non-dippers and risers. Lacunar infarcts (LIs), including both symptomatic and silent and diffuse white matter lesions (WMLs), were graded into three grades according to their degree. The results of kidney function were evaluated using estimated glomerular filtration rate (eGFR), categorized into three groups: stage 1, > 60; stage 2, 30–60; and stage 3, < 30 ml min⁻¹ per 1.73 m². There were 44 patients with CI. Confluent WMLs, including WML 2 and WML 3, were found in 36 patients (81.8%), and multiple lacunae including LI 2 and LI 3 were found in 30 patients (68.1%) with CI. Age > 75 years (odds ratio (OR), 5.5; *P* < 0.05), male sex (OR, 2.8; *P* < 0.05), non-dippers (OR, 6.3; *P* < 0.05) and risers (OR, 5.6; *P* < 0.05), eGFR 30–60 ml min⁻¹ per 1.73 m² (OR, 2.9; *P* < 0.05) and eGFR < 30 ml min⁻¹ per 1.73 m² (OR, 23.8; *P* < 0.01), WML grade 2 (OR, 5.1; *P* < 0.01) and WML grade 3 (OR, 45.2; *P* < 0.001) and LI grade 2 (OR, 3.2; *P* < 0.05) and LI grade 3 (OR, 6.4; *P* < 0.05) were independently associated with CI. Age > 75 years (OR, 4.1; *P* < 0.05), eGFR 30–60 ml min⁻¹ per 1.73 m² (OR, 3.7; *P* < 0.05) and eGFR < 30 ml min⁻¹ per 1.73 m² (OR, 8.7; *P* < 0.05) were independently associated with WML grade 3. Extensive small vessel diseases, CKD and non-dipping status were independently associated with CI. CKD appears to mainly contribute to vascular CI, whereas possibilities of overlapping with other mechanisms such as degenerative CI cannot be excluded. Strict night time BP control and renoprotective treatment may be warranted to prevent CI.

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INTRODUCTION

Chronic kidney disease (CKD) is a growing public health problem¹ and is emerging as an independent risk factor for not only cardiovascular events, but also stroke, cerebral small vessel diseases such as white matter lesions (WMLs) and lacunar infarcts (LIs)^{2–4} and cognitive impairment (CI).^{5–11} An increased burden of cerebrovascular disease has been considered to explain the etiology of CI.^{5–13} Up to now, however, only a few studies have applied structural brain imaging on the association between CKD and CI,¹³ leaving the etiology of CI in CKD uncertain.

On the other hand, elevated blood pressure (BP) has been established as the most important risk factor for cerebral small vessel disease.^{14,15} Moreover, 24-h ambulatory BP monitoring (ABPM) correlates more closely with hypertensive target organ damage than casual office BP readings.^{16–19}

The present study aimed to thoroughly elucidate associations between ABPM, cerebral small vessel disease and CKD with CI in a cohort of patients with LIs. LIs are lesions caused by penetrating artery disease associated with risk factors, natural history and clinical manifestation, which are significantly different from those of other brain infarcts. Consequently, they have homogeneous characteristics that are relevant and worthy of study.

METHODS

Patient selection

Among admissions to the Department of Neurology at the Kyoto Second Red Cross Hospital between 2002 and 2005, 245 consecutive patients with symptomatic lacunar infarction were selected for this study. We defined symptomatic lacunar infarction as a relevant deep, single hyperintensity, ≤ 20 mm in diameter on axial slices from magnetic resonance imaging (MRI) with

¹Department of Neurology, Kyoto Second Red Cross Hospital, Haruobicho Kamigyoku, Kyoto, Japan and ²Department of Neurology, Takeda Hospital, Kyoto, Japan
Correspondence: Dr Y Yamamoto, Department of Neurology, Kyoto Second Red Cross Hospital, 355-5 Haruobicho Kamigyoku, Kyoto 6028026, Japan.
E-mail: yyamamoto@fig7.so-net.ne.jp

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diffusion-weighted imaging that corresponded to one of the lacunar syndromes. Patients who had a potential cardiac source of embolism and those who had >50% stenosis of the extracranial carotid or vertebral arteries as detected by color-coded Duplex sonography were excluded. Among the 245 patients, 224 patients underwent 24-h BP monitoring, without previous administration of antihypertensive agents for >2 weeks after ictus. This study was reviewed by the ethics committee and all patients gave their informed consent to participate in this study.

Conventional risk factors

Hypertension was defined as either previous or present use of antihypertensive agents or a systolic BP (SBP) >140 mm Hg and/or a diastolic BP >90 mm Hg for >2 weeks from ictus without administration of antihypertensive agents. Diabetes mellitus was defined as a fasting glucose level of >140 mg dl⁻¹ or use of antidiabetic medication. Dyslipidemia was defined as a fasting total cholesterol level of >220 mg dl⁻¹ and/or a fasting triglyceride level of >200 mg dl⁻¹ without administration of any antihyperlipidemic agents. Cigarette smoking was defined as regularly smoking at the time of stroke.

Magnetic resonance imaging

All patients underwent MRI and magnetic resonance angiography. MRI scans were performed using 1.5-T superconducting magnets (Gyrosan Intera

Achieva 1.5 Pulsar, Philips, Eindhoven, Netherlands). Each MRI was performed within 3 days after ictus. Diffusion-weighted scans (TR: 1861 ms/TE: 69 ms, echo planar imaging factor: 37), T2-weighted scans (TR: 3500 ms/TE: 100 ms) and FLAIR were obtained at a slice thickness of 7 mm.

Silent LIs were defined as small deep infarcts ≤15 mm in diameter on horizontal sections, with high intensity on T2-weighted and FLAIR imaging located within the basal ganglia, thalamus, internal capsule, corona radiata or pons. WMLs were defined as diffuse hyperintensities located in the periventricular and/or subcortical white matter on T2-weighted and FLAIR imaging. The number of lacunae were counted and graded as follows: grade 1, single lacunae; grade 2, two to five lacunae; and grade 3, more than five lacunae. Diffuse WMLs were graded referring to Schmidt's classification:²⁰ grade 1, absent or punctuate; grade 2, becoming confluent; and grade 3, confluent. Results of MRI were evaluated by two authors (YY and IA) who were blinded to both BP data and clinical findings.

Ambulatory blood pressure monitoring

Data for 24-h BP were recorded using a portable automatic recorder (ABPM TM-243, A&D CompanyTokyo, Japan) at 30-min intervals over a 24-h period from 1300 to 1300 hours the following day. The accuracy of the equipment had been previously established.²¹ ABPM was performed 2–4 weeks after symptomatic LI ictus without antihypertensive therapy. Average BP values were calculated as follows. Systolic and diastolic BP were averaged over

Table 1 Baseline characteristics in the three groups

	<i>Non-demented</i>	<i>MCI</i>	<i>P-value,</i> <i>non-demented vs. MCI</i>	<i>CI</i>	<i>P-value,</i> <i>non-demented vs. CI</i>
Number	159	21		44	
Age	68.3 ± 9.4	72.4 ± 7.5	0.058	74.0 ± 8.5	0.0003
Sex (male)	96 (60.3)	10 (47.6)	0.23	28 (63.6)	0.57
Hypertension	124 (77.9)	18 (85.7)	0.41	40 (90.9)	0.063
Diabetes mellitus	27 (16.9)	5 (23.8)	0.44	4 (9.09)	0.2
Dyslipidemia	41 (25.7)	8 (30.0)	0.23	12 (27.2)	0.84
Smoking	38 (23.8)	4 (19.0)	0.56	12 (27.2)	0.57
Casual SBP	145.2 ± 20.8	151.4 ± 19.3	0.12	151.3 ± 20.1	0.075
24-h SBP	142.9 ± 21.0	148.5 ± 21.2	0.24	151.0 ± 19.6	0.021
Nocturnal SBP dip	0.048 ± 0.082	0.043 ± 0.075	0.79	0.008 ± 0.071	0.0032
Casual DBP	82.1 ± 12.3	81.0 ± 13.3	0.68	83.6 ± 13.4	0.61
24-h DBP	80.1 ± 11.9	82.0 ± 14.2	0.5	79.8 ± 12.8	0.89
Nocturnal DBP dip	0.067 ± 0.092	0.053 ± 0.085	0.49	0.037 ± 0.082	0.052
Dipper	34 (21.3)	6 (6.8)		3 (6.8)	
Non-dipper	75 (47.1)	8 (38.0)	0.64	21 (47.7)	0.076
Riser	44 (27.6)	7 (33.3)	0.86	20 (45.5)	0.013
Extreme dipper	6 (3.7)	0	0.97	0	0.97
Proteinuria	24 (15.0)	10 (47.6)	0.0009	18 (40.9)	0.0003
eGFR (ml min ⁻¹ per 1.73 m ²)	64.5 ± 17.9	58.4 ± 22.2	0.16	49.5 ± 19.6	<0.0001
eGFR >90	12 (7.5)	2 (9.5)		1 (2.27)	
eGFR 60–89	81 (50.9)	7 (33.3)	0.44	10 (22.7)	0.78
eGFR 30–59	64 (40.2)	11 (52.3)	0.97	28 (63.6)	0.11
eGFR 15–29	2 (1.2)	0	0.97	4 (9.0)	0.97
eGFR <15	0	1 (4.7)		1 (2.2)	
<i>Lacunar infarcts</i>					
Grade 1	114 (71.6)	8 (38.0)		14 (31.8)	
Grade 2	35 (22.0)	11 (52.3)	0.0054	21 (47.7)	0.0002
Grade 3	6 (3.7)	2 (9.5)	0.081	9 (20.4)	<0.0001
<i>White matter lesions</i>					
Grade 1	119 (74.8)	6 (28.5)		8 (18.1)	
Grade 2	6 (27.2)	14 (66.6)	0.0012	18 (40.9)	0.0003
Grade 3	6 (3.3)	1 (4.7)	0.16	18 (40.9)	<0.0001
MMSE	29.5 ± 0.80	26.2 ± 0.73	<0.0001	19.5 ± 3.8	<0.0001

Abbreviations: CI, cognitive impairment; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; MCI, mild cognitive impairment; MMSE, mini-mental state examination; SBP, systolic blood pressure.
Values in parentheses are percentage.
P-values are calculated compared with non-demented group.

successive 30-min intervals for daytime (0600 to 2200 hours) and night time (2230 to 0530 hours) periods. The degree of nocturnal BP dip was calculated as follows: (average daytime value–average night time BP)/average daytime value.

Based on the BP dip, patients were categorized as dippers when the BP dip was >0.1 and patients were categorized as non-dippers when the BP dip was $0.1-0$. Furthermore, patients were categorized as extreme dippers when the BP dip was >0.25 and risers when the BP dip was <0 . According to the guideline, 24-h SBP average values were categorized into three groups: <125 mm Hg, $125-145$ mm Hg and >145 mm Hg.

Chronic kidney disease

The estimated glomerular filtration rate (eGFR) was calculated from the serum creatinine (Cr) value and age using the abbreviated Modification of Diet in Renal Disease equation modified by the Japanese coefficient,²² as follows: eGFR (ml min^{-1} per 1.73 m^2) = $0.741 \times 175 \times \text{age}^{-0.203} \times \text{Cr} (\text{mg dl}^{-1})^{-1.154}$ (if female,

$\times 0.742$). Then, eGFR was categorized into three groups: stage 1, >60 ; stage 2, $45-60$; and stage 3, $<45 \text{ ml min}^{-1}$ per 1.73 m^2 .

Based on Japanese CKD stage criteria, eGFR values were classified into five groups: ≥ 90 , $60-89$, $30-59$, $15-29$ and $<15 \text{ ml min}^{-1}$ per 1.73 m^2 .

Proteinuria was detected by qualitative analysis of proteinuria.

Evaluation of global cognitive impairment (GCI)

The cognitive ability of all patients was also evaluated using the mini-mental state examination (MMSE). As the standard MMSE cut score of 24 has been widely used, we diagnosed CI if MMSE score was ≤ 24 .²³ Moreover, as a cut score of 27 was proposed for mild CI (MCI), we diagnosed MCI if MMSE score was $25-27$.²⁴ We estimated MMSE of >27 as non-demented.

Statistical analysis

First, demographics, conventional risk factors, categorized eGFR, 24-h SBP average, diurnal BP pattern and the three categories for the degree of small vessel disease were compared between groups with MCI and CI and non-demented estimating non-demented group as reference. Continuous variables were expressed as mean \pm s.d., and categorized variables were given as the percentage of patients so affected. A comparison of clinical variables between groups was performed with the χ^2 -test for categorized variables and with Student's *t*-test for continuous variables. For groups with three graded small vessel disease, grade 1 was estimated as the reference.

The relationship between CKD and ABPM pattern were also investigated using the χ^2 -test.

Logistic regression analysis 1 was performed to investigate the factors contributing to groups with MCI and CI. As the number of extreme dippers was small and their characteristics were similar to dippers (Table 1), extreme dippers were incorporated into dippers. Similarly, eGFR <15 and $>90 \text{ ml min}^{-1}$ per 1.73 m^2 were incorporated into eGFR $15-30$ and

Table 2 The relationship between diurnal blood pressure pattern and categorized estimated glomerular filtration rate (eGFR)

	eGFR >60 113	eGFR 30–60 103	eGFR <30 8
<i>Dipper</i>			
49	26 (53.0)	22 (44.8)	1 (2.0)
<i>Non-dipper</i>			
104	54 (51.9)	45 (43.2)	5 (4.8)
<i>Riser</i>			
71	33 (46.4)	36 (50.7)	2 (2.8)

Table 3 Contributing factors for mild cognitive impairment

Mild cognitive impairment	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Age <65 years	1			1		
Age 65–75	1.72	0.50–5.92	0.38	1.63	0.44–6.06	0.46
Age >75	2.13	0.60–7.55	0.24	2.01	0.51–7.98	0.31
Sex (male)	0.59	0.23–1.48	0.26	0.9	0.33–2.46	0.84
Hypertension	1.69	0.47–6.08	0.41			
Diabetes mellitus	1.52	0.51–4.52	0.44			
Dyslipidemia	1.77	0.68–4.57	0.23			
Dipper	1					
Non-dipper	0.71	0.23–2.19	0.55			
Riser	1.06	0.32–3.42	0.92			
24-h SBP <125 mm Hg	1					
24-h SBP 125–145 mm Hg	1.91	0.37–9.82	0.43			
24-h SBP >145 mm Hg	2.26	0.47–10.72	0.304			
eGFR >60	1					
eGFR 30–60	1.77	0.69–4.53	0.22			
eGFR <30	5.16	0.42–62.71	0.19			
WML 0–1	1			1		
WML 2	7.93	2.83–22.17	<0.0001	5.51	1.84–16.44	0.0022
WML 3	3.96	0.39–39.50	0.24	3.15	0.29–33.86	0.34
LI 1	1			1		
LI 2–5	4.12	1.54–11.01	0.0047	2.77	0.95–8.09	0.061
LI >5	4.07	0.72–22.90	0.11	3.09	0.49–19.50	0.22

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; LI, lacunar infarct; OR, odds ratio; SBP, systolic blood pressure, WML, white matter lesion. OR and 95% CIs of various covariates for the mild cognitive impairment group.

60–90 ml min⁻¹ per 1.73 m², respectively. The odds ratio (OR) and 95% confidence intervals of covariates for the groups with MCI and CI were calculated. Covariates included were conventional risk factors (yes or no) and categorized groups, such as 24-h SBP average (125–145 and 145 mm Hg vs. <125 mm Hg), ABPM pattern (non-dippers and risers vs. dippers), eGFR (eGFR <30 and 30–60 vs. eGFR >60 ml min⁻¹ per 1.73 m²), WML and LI (grade 2 and grade 3 vs. grade 1). ABPM pattern was adjusted for categorized 24-h SBP average. Covariates shown to be significant in univariate analysis were subsequently examined using multivariate analysis.

Logistic regression analysis 2 was performed to explore the association of the aforementioned covariates with extensive small vessel disease using logistic regression analysis, estimating grade 1 for LI and WML as a reference. The ORs for multiple lacunae (grade 2 and grade 3 vs. grade 1) and confluent WMLs (grade 2 and grade 3 vs. grade 1) were calculated. Logistic regression analysis was performed using Stat-View 5.0 software (SAS Institute, Cary, NC, USA). Probability values <0.05 were considered significant.

RESULTS

Baseline characteristics

CI was absent in 159 patients and MCI was present in 21 patients and CI in 44 patients (Table 1). Compared with the non-demented group I, the group with MCI showed higher incidence of proteinuria and more extensive small vessel disease, and the group with CI showed older age, higher 24-h SBP average, lower nocturnal SBP dip, lower eGFR and more extensive small vessel disease (Table 1). In the MCI group, confluent WMLs including WML grade 2 and WML grade 3 were found in 15 patients (71.3%), and multiple lacunae including LI grade 2 and LI grade 3 were found in 13 patients (61.8%). In the CI group, confluent WMLs were found in 36 patients (81.8%), and

multiple lacunae in 30 patients (68.1%). Statin was used for 78 patients (34.8%) and antiplatelet agents were prescribed for 214 patients (95.5%). There were no significant differences between groups (data not shown).

The relationship between CKD and diurnal BP pattern

There were no significant relationships between categorized CKD and diurnal BP pattern (Table 2).

Logistic regression analysis 1: factors Associated with MCI and CI. The OR and 95% confidence intervals of covariates for MCI and CI are displayed in Tables 3 and 4. The covariate significantly associated with MCI after multivariate analysis was WML grade 2 (OR, 5.5; *P*<0.05). The covariates significantly associated with CI after multivariate analysis were age >75 years (OR, 5.5; *P*<0.05), male sex (OR, 2.8; *P*<0.05), non-dippers (OR, 6.3; *P*<0.05) and risers (OR, 5.6; *P*<0.05), eGFR 30–60 ml min⁻¹ per 1.73 m² (OR, 2.9; *P*<0.05) and eGFR <30 ml min⁻¹ per 1.73 m² (OR, 23.8; *P*<0.01), WML grade 2 (OR, 5.1; *P*<0.01) and WML grade 3 (OR, 45.2; *P*<0.001) and LI grade 2 (OR, 3.2; *P*<0.05) and LI grade 3 (OR, 6.4; *P*<0.05).

Logistic regression analysis 2: factors associated with extensive small vessel disease. The OR and 95% confidence intervals of covariates for confluent WMLs and multiple lacunae are displayed in Tables 5 and 6. In multivariate analysis, age >75 years (OR, 2.3; *P*<0.05), female sex (OR, 0.53; *P*<0.05) and hypertension (OR, 5.46; *P*<0.05) were significantly associated with WML grade 2, and age >75 years (OR, 4.1; *P*<0.05), eGFR 30–60 ml min⁻¹ per 1.73 m² (OR, 3.7; *P*<0.05)

Table 4 Contributing factors for cognitive impairment

Cognitive impairment	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Age < 65 years	1			1		
Age 65–75	1.65	0.58–4.67	0.33	1.62	0.42–6.22	0.48
Age > 75	4.43	1.67–11.79	0.0028	5.55	1.48–20.74	0.01
Sex (male)	1.14	0.57–2.29	0.69	2.82	1.02–7.75	0.043
Hypertension	2.82	0.94–8.43	0.063			
Diabetes mellitus	0.48	0.16–1.48	0.205			
Dyslipidemia	1.07	0.50–2.29	0.84			
Dipper	1			1		
Non-dipper	3.73	1.04–13.28	0.041	6.37	1.16–34.80	0.032
Riser	6.01	1.67–21.95	0.0061	5.6	1.00–31.21	0.049
24-h SBP < 125 mm Hg	1					
24-h SBP 125–145 mm Hg	1.5	0.43–5.15	0.51	2.58	0.44–15.03	0.29
24-h SBP > 145 mm Hg	2.73	0.88–8.44	0.81	3.74	0.72–19.48	0.11
eGFR > 60	1			1		
eGFR 30–60	3.69	1.71–7.96	0.0008	2.95	1.10–7.95	0.031
eGFR <30	21.13	3.65–122.2	0.0007	23.88	2.32–245.67	0.0076
WML 0–1	1			1		
WML 2	7.65	3.06–19.08	<0.0001	5.13	1.73–15.21	0.0032
WML 3	53.55	15.77–181.83	<0.0001	45.26	9.75–210.07	<0.0001
LI 1	1			1		
LI 2–5	4.5	2.08–9.71	0.0001	3.27	1.19–9.66	0.031
LI >5	10.46	3.37–32.51	<0.0001	6.47	1.43–29.22	0.015

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; LI, lacunar infarct; OR, odds ratio; SBP, systolic blood pressure, WML, white matter lesion. OR and 95% CIs of various covariates for the cognitive impairment group.

Table 5 Contributing factors for multiple lacunae

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
<i>LI grade 2 vs. grade 1</i>						
Age < 65 years	1			1		
Age 65–75	0.87	0.42–1.79	0.71	0.71	0.32–1.52	0.37
Age > 75	0.71	0.34–1.49	0.37	0.59	0.26–1.31	0.19
Sex (male)	0.75	0.42–1.35	0.34	0.8	0.42–1.50	0.8
Hypertension	6.03	2.05–17.79	0.0011	4.75	1.46–15.23	0.0095
Diabetes mellitus	1.51	0.70–3.23	0.28			
Dyslipidemia	0.69	0.35–1.36	0.29			
Dipper	1			1		
Non-dipper	1.63	0.75–3.71	0.2	1.86	0.78–4.44	0.16
Riser	2.94	1.27–6.78	0.011	3.21	1.28–8.06	0.012
24-h SBP < 125 mm Hg	1					
24-h SBP 125–145 mm Hg	1.63	0.60–4.36	0.33	0.94	0.30–2.89	0.91
24-h SBP > 145 mm Hg	2.36	0.93–5.94	0.067	0.9	0.30–2.70	0.86
eGFR > 60	1			1		
eGFR 30–60	2.01	1.10–3.65	0.022	1.55	0.82–2.96	0.17
eGFR < 30	7.14	1.31–38.92	0.023	5.38	0.95–30.25	0.055
<i>LI grade 3 vs. grade 1</i>						
Age < 65	1			1		
Age 65–75	1.53	0.43–5.37	0.5	1.59	0.43–5.90	0.48
Age > 75	0.65	0.15–2.79	0.56	0.56	0.12–2.54	0.45
Sex (male)	1.13	0.39–3.25	0.81	1.5	0.50–4.51	0.46
Hypertension	2.7	0.58–12.39	0.2			
Diabetes mellitus	1.32	0.34–5.02	0.68			
Dyslipidemia	1	0.33–3.02	>0.99			
Dipper	1			1		
Non-dipper	5.34	0.65–43.84	0.11	5.06	0.59–43.21	0.13
Riser	8.94	1.06–75.23	0.043	8.5	0.96–74.68	0.053
24-h SBP < 125 mm Hg	1			1		
24-h SBP 125–145 mm Hg	0.72	0.15–3.49	0.68	0.49	0.092–2.63	0.4
24-h SBP > 145 mm Hg	1.28	0.32–5.04	0.72	0.87	0.20–3.75	0.85
eGFR > 60	1			1		
eGFR 30–60	3.25	1.07–9.91	0.037	4.1	1.30–12.86	0.015
eGFR < 30	8	0.61–104.01	0.112	7.67	0.53–110.03	0.133

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; LI, lacunar infarct; OR, odds ratio; SBP, systolic blood pressure. OR and 95% CIs of various covariates for the cognitive impairment group.

and eGFR < 30 ml min⁻¹ per 1.73 m² (OR, 8.7; *P* < 0.05) were significantly associated with WML grade 3. Hypertension (OR, 4.7; *P* < 0.001) and riser (OR, 3.2; *P* < 0.05) were significantly associated with LI grade 2, and eGFR < 30 to 60 ml min⁻¹ per 1.73 m² (OR, 4.1; *P* < 0.05) was significantly associated with LI grade 3.

DISCUSSION

In groups with MCI and CI, extensive small vessel diseases were frequently identified. Age > 75 years, male sex, non-dipping status, CKD represented by eGFR < 60 ml min⁻¹ per 1.73 m², extensive small vessel diseases were found to be independently associated with CI, whereas only extensive small vessel diseases (WML grade 2) were found to be independently associated with MCI. CKD was also independently associated with extensive small vessel diseases including WML grade 3 and LI grade 3.

The presence of extensive small vessel disease including severe WMLs (WML grade 3) and many lacunae (LI grade 3) were strongly associated with CI (ORs, 45.2 and 6.4, respectively) in multivariate analysis. Moreover, CKD was also independently asso-

ciated with severe WMLs and many lacunae. Accordingly, the significant relationship between CI and CKD in the present study is partly explicable by the hypothesis that extensive small vessel disease may represent an intermediate stage along the pathway from CKD to GCI.

On the other hand, CKD was independently associated with CI after adjusting for extensive small vessel diseases. Unexpectedly, adjustment for confluent WMLs only slightly attenuated the OR of CKD for CI. Moreover, the association of CKD with CI was stronger than that with extensive small vessel disease. There is a growing awareness that vascular dementia and degenerative dementia such as Alzheimer's disease share similar mechanisms and lesions.^{25–28} Accordingly, the possibility that factors other than extensive small vessel disease such as Alzheimer's disease are involved in the pathogenesis of CI in CKD cannot be excluded. In fact, cystatin C, an innovative measure of kidney function, is reported to colocalize with β -amyloid in the brains of patients with Alzheimer's disease.²⁶

Numerous cross-sectional and longitudinal reports have correlated CKD with GCI.^{5–13} The REGARDS (Reasons for Geographic and

Table 6 Contributing factors for confluent white matter lesions (WMLs)

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
<i>WML grade 2 vs. grade 1</i>						
Age < 65 years	1			1		
Age 65–75	1.61	0.74–3.50	0.22	1.57	0.70–3.50	0.26
Age > 75	2.35	1.06–5.22	0.034	2.35	1.03–5.38	0.041
Sex (male)	0.49	0.27–0.90	0.021	0.53	0.28–0.98	0.045
Hypertension	5.19	1.75–15.76	0.0029	5.4	1.79–16.26	0.0027
Diabetes mellitus	1.1	0.50–2.38	0.8			
Dyslipidemia	1.79	0.93–3.43	0.076			
Dipper	1					
Non-dipper	1.16	0.52–2.58	0.703			
Riser	2.18	0.95–5.01	0.065			
24-h SBP < 125 mm Hg	1					
24-h SBP 125–145 mm Hg	1.55	0.57–4.21	0.38			
24-h SBP > 145 mm Hg	2.11	0.83–5.34	0.11			
eGFR > 60	1					
eGFR 30–60	1.64	0.90–3.00	0.104			
eGFR < 30	2.56	0.49–13.43	0.26			
<i>WML grade 3 vs. grade 1</i>						
Age < 65	1			1		
Age 65–75	0.97	0.24–3.84	0.97	0.95	0.23–3.90	0.95
Age > 75	4.25	1.29–13.96	0.016	4.11	1.21–13.87	0.022
Sex (male)	0.6	0.25–1.45	0.26	0.7	0.27–1.77	0.45
Hypertension	1.25	0.43–3.62	0.67			
Diabetes mellitus	0.45	0.10–2.09	0.31			
Dyslipidemia	1.71	0.67–4.40	0.26			
Dipper	1					
Non-dipper	1.25	0.36–4.28	0.72			
Riser	2.42	0.69–8.50	0.16			
24-h SBP < 125 mmHg	1					
24-h SBP 125–145 mm Hg	0.95	0.25–3.59	0.94			
24-h SBP > 145 mm Hg	1.2	0.35–4.04	0.76			
eGFR > 60	1			1		
eGFR 30–60	3.87	1.42–10.54	0.008	3.79	1.36–10.55	0.01
eGFR < 30	8.55	1.19–61.52	0.032	8.76	1.11–68.86	0.038

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; SBP, systolic blood pressure. OR and 95% CIs of various covariates for the cognitive impairment group.

Racial Differences in Stroke) study showed that each 10 ml min⁻¹ per 1.73 m² decrease in eGFR was associated with an 11% increased prevalence of GCI.⁵ Buchman *et al.*⁸ prospectively studied 886 elderly without dementia and found that decreased eGFR at baseline was associated with a more rapid rate of cognitive decline. The INVADE study found a significant association between moderate-to-severe CKD at baseline and development of new GCI after following 3679 participants for 2 years (OR, 2.14).⁹ Moreover, the Rancho Bernardo study suggested that CKD makers are helpful to predict the future risk of dementia.¹³

A considerable number of reports have shown the relationship between CKD and small vessel disease independent of vascular risk factors.^{3,4} Decreased GFR is often attributable to renal small vessel disease including glomerular endothelium dysfunction and lipohyalinosis, which are associated with vascular risk factors.²⁹ As the vascular supplies to the kidney and brain are similar, renal small vessel disease may also be indicative of the presence of small vessel disease in the brain.³⁰ On the other hand, levels of an endogenous inhibitor of nitric oxide synthase, asymmetric dimethylarginine, are increased in patients

with impaired kidney function.³¹ Such factors could accelerate extensive small vessel diseases in patients with CKD. It may be safely said that hypertension, especially non-dipping patterns, may cause CKD and CKD may accelerate extensive small vessel diseases those are strongly associated vascular CI. The causal relationship between hypertension, CKD and small vessel disease should be explored further.

The non-dipping status, including non-dippers and risers, was also independently associated with CI. Alterations in autonomic nervous function³² and sodium-sensitive essential hypertension³³ have all been reported to be associated with the non-dipping status. It is uncertain whether non-dipping status represents the primary precipitant for development of CI or it represents the consequence of CI.^{4,35} It should also be noted that the non-dipping status remained significantly associated with CI after adjusting for CKD and extensive small vessel disease. In contrast with previous reports on hypertensive patients,³⁶ a significant relationship between non-dipping status and CKD was not found. It is suspected that patient controls with hypertension³⁶ and those with LIs exhibit different characteristics. Active treatment has

been reported to be associated with reduced risks of dementia and cognitive decline.²⁷ Strict night time BP control may be necessary to prevent the progression of CI in the LI cohort.

The present study showed several limitations. We relied on one serum Cr measurement and did not perform repeat measurements. This was a cross-sectional study and the causal relationship between CKD and GCI could not be determined. The number of patients was small. We were not able to test all cognitive domains, and instead used only the MMSE. Moreover, as we studied LI patients, the possible selection bias and possible influence of infarction on diurnal variation cannot be excluded.³⁴ On the other hand, the strengths of the present study included use of a homogeneous cohort of lacunar infarction, precise evaluation of small vessel disease and performance of ABPM.

In conclusion, the majority of patients with GCI in this cohort of patients with LIs may be classified as showing vascular CI correlated with extensive small vessel disease. On the other hand, CKD and hypertensive non-dipper status were associated with GCI independent of traditional vascular risk factors and extensive small vessel disease. Accordingly, CKD may correlate with diseases of GCI other than vascular GCI, such as degenerative GCI. Further studies focusing on the contribution of CKD to CI are warranted. To prevent subsequent progression of cognitive decline, the data indicate that careful consideration for night time BP control and renoprotective treatment may be helpful.

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