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Microalbuminuria Is Independently Associated With Deep or Infratentorial Brain Microbleeds in Hypertensive Adults

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BACKGROUND
Brain microbleeds (BMBs) detected on gradient echo T2*-weighted magnetic resonance imaging (GE-MRI) may be pathophysiologically linked to ischemic cerebral small-vessel disease (SVD) and increased risk of future hemorrhagic stroke. Chronic kidney disease (CKD) has been associated with the presence of BMBs in stroke patients. However, the relationship between CKD markers and BMBs in stroke-free populations is unknown.

METHODS
Two hundred and eighty-five hypertensive subjects (mean age 68.6 years) without neurological symptoms were enrolled from a hospital-based outpatient clinic and all participants underwent GE-MRI. We calculated urinary albumin/creatinine ratio (UACR) from morning spot urine and the estimated glomerular filtration rate (eGFR) in serum samples. Multivariate logistic regression analysis was used to evaluate the association between these kidney biomarkers and the presence and location of BMBs, controlling for age, sex, use of antihypertensive or antithrombotic drugs, and MRI findings.

RESULTS
BMBs were observed in 48 (16.8%) patients. Median UACRs were significantly higher in patients with deep or infratentorial BMBs than in patients with pure lobar BMBs (54 vs. 17 mg/g creatinine, $P = 0.04$). No significant differences were found between eGFR levels and the location of BMBs. Microalbuminuria (UACR >30–≤300 mg/g creatinine), but not low eGFR level was significantly associated with higher prevalence of deep or infratentorial BMBs (odds ratio (OR): 3.16, 95% confidence interval (CI): 1.34–7.44, $P = 0.009$) even after adjustment for potential confounding factors.

CONCLUSIONS
Microalbuminuria is closely associated with the prevalence of deep or infratentorial BMBs in hypertensive patients. Our findings provide new insights into the association between risk factors and the distribution of BMBs.

Keywords: *blood pressure; brain microbleeds; chronic kidney disease; estimated glomerular filtration rate; hypertension; microalbuminuria*

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Gradient echo T2*-weighted magnetic resonance imaging (GE-MRI), which is a very sensitive technique for the detection of cerebral hemorrhage, has been attracting attention with the focus on millimeter-sized microbleeds in the brain parenchyma. Pathophysiologically, brain microbleeds (BMBs) may be associated with ischemic small-vessel disease (SVD), which includes lacunar infarcts (LIs) and white matter lesions (WMLs). Several reviews concerning the epidemiology, pathogenesis, and clinical significance of BMBs have been published.[1–5] According to these reviews, aging, male sex, hypertension, smoking, white matter hyperintensities on brain MRI, a history of ischemic stroke, and intracerebral hemorrhage are potential factors that are related to BMBs. Interestingly, an association between risk factors and the prevalence of BMBs differ with the distribution of BMBs in the Rotterdam Scan Study.[6,7]

Chronic kidney disease (CKD) has received attention as a marker of microangiopathy[8,9] as well as a risk factor for cardiovascular disease.[10,11] CKD is most commonly defined by a reduction in the glomerular filtration rate (GFR) or the presence of proteinuria. A previous study has indicated that low GFR levels are associated with subclinical markers of ischemic cerebral SVD, independent of cardiovascular risk factors.[9] Microalbuminuria is a marker for generalized vascular endothelial dysfunction and is associated with an increased incidence of cardiovascular events.[12–16] In addition, microalbuminuria is found to be a risk factor for ischemic cerebral SVD in community-based elderly subjects.[17] However, the relationship between CKD marker and BMBs in patients without a history of stroke or transient ischemic attack (TIA) is still unknown. An association between the presence of BMBs and

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future stroke, particularly in hemorrhagic stroke, has been observed in several prospective studies,[18,19] suggesting that reducing the incidence of BMBs would prevent the onset of hemorrhagic stroke. Therefore, the objective of the present study was to assess whether kidney biomarkers are related to the presence and location of BMBs in hypertensive patients without a history of stroke or TIA.

METHODS

Study population. From January 2007 to October 2010, we identified 650 consecutive hypertensive outpatients 50 years of age or older with neurological complaints (i.e., headache or dizziness) who agreed to undergo an MRI evaluation at our hospital. Hypertension was defined as >140/90 mm Hg at three different times or the taking antihypertensive medications. The exclusion criteria included prior history of stroke or TIA, severe dementia, thrombocytopenia, severe renal dysfunction (creatinine value ≥2.0 mg/dl) or dialysis. Because we aimed to study patients who most likely had ischemic SVD, patients with a potential cardioembolic source or large-vessel cerebrovascular disease defined as internal carotid, middle cerebral, or basilar intracranial artery stenosis >50% were also excluded. Finally, 285 hypertensive patients (123 men and 162 women, mean age 68.6 ± 8.9 years) without neurological symptoms were enrolled in the present study (**Figure 1**). All participants underwent GE-MRI. Informed consent was obtained from all participants, and the study protocol was approved by the Ethics Committee of Chubu Rosai Hospital. In addition, this study was conducted in accordance with the principles of the Declaration of Helsinki.

Measurement of the GFR and albuminuria. Each patient's estimated glomerular filtration rate (eGFR) was calculated from the following new three-variable Japanese equation:[20] eGFR (ml/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ × 0.739 (if female). A low eGFR level was defined as <60 ml/min/1.73 m^2, which shows a moderate stage of CKD. Urinary albumin excretion was expressed as the albumin/creatinine ratio in a urine sample taken in the morning. Urinary albumin creatinine ratio (UACR) was calculated from urinary albumin, which was estimated using the latex agglutination method and urinary creatinine concentration. Normoalbuminuria was defined as an UACR ≤30 mg/g creatinine, microalbuminuria was defined as an UACR between 30 and 300 mg/g creatinine, and macroalbuminuria was defined as an UACR >300 mg/g creatinine.

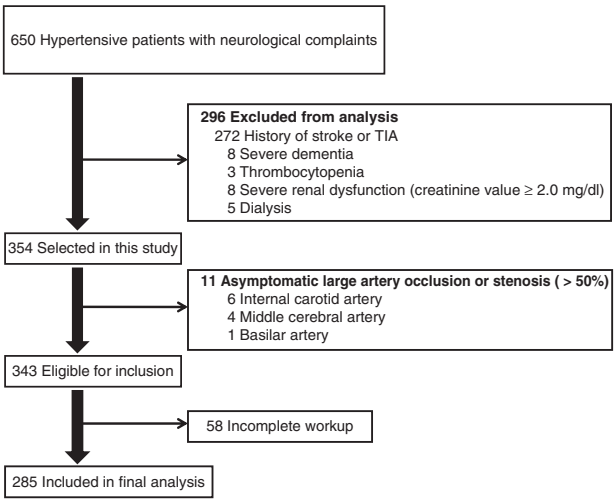

Figure 1 | Flow chart of patient inclusion. TIA, transient ischemic attack.

MRI. All the MRI examinations were performed on a Signa Horizon 1.5T (GE Healthcare, Milwaukee, WI). The imaging protocol consisted of T1-weighted spin-echo (inversion recovery; repetition time/echo time ((TR/TE) = 2380/27.4 ms), T2-weighted fast spin-echo (TR/TE = 4017/103 ms), fluid-attenuated inversion-recovery (TR/TE = 8002/146 ms), and T2*-weighted gradient echo (TR/TE = 500/15 ms, flip angle 20°) sequences in the axial plane with a slice thickness of 5 mm and a 2 mm interslice gap. BMBs were defined as punctate or round hypointensities of 2–10 mm diameter on T2*-weighted images. We made reference to the rating scale proposed by Cordonnier *et al.*[21] The location of BMBs was divided into three categories as follows: lobar type (cortex, subcortical white matter), deep type (basal ganglia, thalamus, internal or external capsule) and infratentorial type (brain stem, cerebellum). Symmetrical hypointensities in the globus pallidum, which most likely represented calcification or iron deposition, and the flow void artifact of the pial blood vessels were disregarded. The number of asymptomatic LIs and the severity of WMLs on MRI findings were also examined. We defined LIs as focal hyperintense areas that were larger than 3 mm in diameter on T2-weighted images, hypointense areas on T1-weighted images, and areas of hypointensity surrounded by a hyperintense rim on fluid-attenuated inversion-recovery images. Lesions less than 3 mm in diameter or with a signal intensity similar to that of cerebrospinal fluid on fluid-attenuated inversion-recovery images were excluded because of the high possibility of enlarged perivascular spaces, even if hyperintensity on T2-weighted images and hypointensity on T1-weighted images were determined. The numbers of asymptomatic LIs were indicated according to three categories: zero, one to three, and more than three lesions. Multiple LIs were defined as more than three lesions. The severity of WMLs was graded separately for periventricular and subcortical areas. Periventricular WMLs were classified as grade 1–3 as follows: grade 1 (mild); pencil-thin lining, grade 2 (moderate); smooth halo, grade 3 (severe); large confluence. Subcortical WMLs were classified according to the following 3 grade: grade 1 (mild); punctuate foci, grade 2 (moderate); beginning confluence, grade 3 (severe); diffuse confluence, in accordance with the Fazekas scale.[22,23] A grade ≥2 was regarded as advanced periventricular or subcortical WMLs. Two trained neurologist and radiologist who were blinded to laboratory and clinical information assessed the presence and location of BMBs. Each value of inter-rater reliability for the MRI findings, expressed as Cohen κ, was within the range of 0.67–0.84. **Figure 2** illustrates an example of a brain MRI that showed both BMBs and

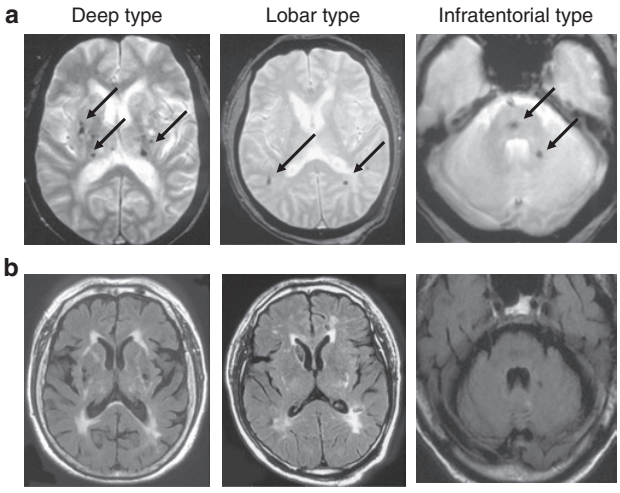

Figure 2 | An illustration of the brain magnetic resonance imaging (MRI) of the three participants who showed different types of brain microbleed (BMB) location. (**a**) BMBs (black arrows) were observed as signal losses in the basal ganglia, thalamus, deep white matter, and cerebellum on T2*-weighted gradient echo MRI. (**b**) Fluid-attenuated inversion-recovery images revealed multiple lacunar infarcts and periventricular white matter lesions.

ischemic small-vessel lesions (LIs and WMLs) according to the different BMB location.

Assessment of cardiovascular risk factors. Diabetes mellitus was defined as a fasting serum glucose level ≥126 mg/dl, hemoglobin A_{1c} levels ≥6.5%, or the use of antidiabetic drugs. Dyslipidemia was defined as a fasting serum low-density lipoprotein cholesterol level ≥140 mg/dl and/or a fasting serum triglyceride levels ≥150 mg/dl and/or a fasting serum high-density lipoprotein cholesterol level <40 mg/dl and/or the use of oral lipid-lowering drugs. Smoking status was defined as current use. Left ventricular hypertrophy was diagnosed on the basis of an electrocardiogram or chest X-ray that was conducted in the past 3 years. In the present study, patients with previous myocardial infarction, angina pectoris, or peripheral artery disease were not excluded.

Assessment of therapeutic drugs. The therapeutic drugs assessed for an association with the prevalence of BMBs were antihypertensives (calcium-channel blockers (CCBs), angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, antiplatelets (acetylsalicylic acid: aspirin, ticlopidine, clopidogrel, cilostazol), oral anticoagulants (warfarin), and HMG-CoA reductase inhibitors (statins). Antihypertensive drugs were administered to about 60% of the patients. Renin–angiotensin system inhibitors (angiotensin receptor blockers or angiotensin-converting enzyme inhibitors) were used more than CCBs in patients that were positive for proteinuria. No significant difference in systolic blood pressure was found between patients who were administered either CCBs or renin–angiotensin system inhibitors prior to the administration of these therapeutic agents. The most commonly used CCBs were nicardipine and nilvadipine, which are relatively strong brain blood vessel dilators, and amlodipine, which has a strong antihypertensive function. Antiplatelet drugs were administered to patients without a history of stroke or TIA if they had ischemic heart disease, peripheral artery disease, or multiple plaques in carotid ultrasonography. The selection of the type of antiplatelet drugs was left to the discretion of the attending physicians. Anticoagulants were administered to only one patient with previous myocardial infarction. Lipid-lowering drugs were also taken in many patients with dyslipidemia, and pravastatin and atoruvastatin were commonly used. In this study, the treatment duration was at least 1 year when GE-MRI was performed.

Statistical analysis. Statistical analysis was performed using the unpaired *t*-test or Mann–Whitney U test to compare continuous variables and the χ^2 test or the Fisher's exact test was used to assess categorical variables. A one-way analysis of variance with Scheffe *post hoc* correction was used to compare kidney biomarkers according to the different location of BMBs. UACR levels were analyzed as log-transformed values because of skewed distributions. Logistic regression analysis was used to evaluate the association between kidney biomarkers and the presence and location of BMBs. To assess independent factors associated with the location of BMBs, variables with $P < 0.05$ in univariate analysis were entered into a multivariate logistic regression analysis. All tests were two-tailed and a P value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS 11.0J software (SPSS, Chicago, IL).

RESULTS

The characteristics of the study population according to UACR levels are summarized in **Table 1**. Patients with microalbuminuria or macroalbuminuria (UACR >30 mg/g creatinine) compared with those without albuminuria (UACR ≤30 mg/g creatinine) were more likely to be older, and to have diabetes, use of antihypertensive drugs, antithrombotic drugs, lipid-lowering drugs, and BMBs. The characteristics of the study population with and without BMBs are summarized in **Table 2**. BMBs were observed in 48 of 285 participants (16.8%). Of the 218 identified BMBs, 57 (26.1%) were located in the basal ganglia, 34 (15.6%) in the thalamus, 38 (17.4%) in the brainstem (mostly in the pons), 23 (10.6%) in the cerebellum, 43 (19.7%) in the subcortical white matter, and 23 (10.6%) in the cortex. Age, the frequency of use of antihypertensive drugs (mainly CCBs) or antithrombotic drugs, multiple LIs, and advanced WMLs were significantly higher in patients with BMBs than in those without.

UACRs were significantly higher in patients with BMBs than in those without BMBs (48 (18–98) vs. 15 (8–32) mg/g creatinine, $P < 0.0001$). UACRs were also significantly higher in patients with deep or infratentorial BMBs than in those with pure lobar BMBs (54 (24–112) vs. 17 (10–36) mg/g creatinine, $P = 0.04$). In contrast, no significant differences were found between eGFR levels and the location of BMBs (**Figure 3**).

Table 1 | Characteristics of the study population stratified by UACR levels

	UACR ≤30 (*n* = 205)	UACR >30 (*n* = 80)	*P* value
Age (year)	67.7 ± 8.9	70.9 ± 8.5	0.006
Sex, male, *n* (%)	88 (42.9)	35 (43.8)	0.90
Diabetes mellitus, *n* (%)	89 (43.4)	48 (60.0)	0.01
Dyslipidemia, *n* (%)	93 (45.4)	42 (52.5)	0.28
Current smoker, *n* (%)	35 (17.1)	21 (26.3)	0.08
Left ventricular hypertrophy, *n* (%)	77 (37.6)	36 (45.0)	0.25
Systolic blood pressure (mm Hg)	136 ± 17	138 ± 18	0.55
Diastolic blood pressure (mm Hg)	77 ± 11	75 ± 11	0.07
Fasting blood glucose (mg/dl)	123.1 ± 32.9	147.1 ± 58.4	<0.0001
Hemoglobin A_{1c} (%)	6.0 ± 1.1	6.7 ± 1.6	0.001
Serum creatinine (mg/dl)	0.74 ± 0.18	0.84 ± 0.36	0.003
UACR (mg/g creatinine)	11.0 (6.0–18.0)	58.0 (37.5–122.3)	<0.0001
UACR >300 mg/g creatinine, *n* (%)	0	7 (8.8)	—
eGFR (ml/min/1.73 m^2)	70.7 ± 15.9	63.3 ± 22.3	0.002
eGFR <60 ml/min/1.73 m^2, *n* (%)	44 (21.5)	27 (33.8)	0.03
Use of antihypertensive drugs, *n* (%)	111 (54.1)	55 (64.7)	0.03
Angiotensin receptor blockers, *n* (%)	65 (31.7)	31 (38.8)	0.26
Angiotensin-converting enzyme inhibitors, *n* (%)	38 (18.5)	18 (22.5)	0.45
Calcium-channel blockers, *n* (%)	70 (34.1)	34 (42.5)	0.19
Use of antithrombotic drugs, *n* (%)	35 (17.1)	24 (30.0)	0.02
Use of lipid-lowering drugs, *n* (%)	56 (27.3)	32 (40.0)	0.04
Prior IHD, *n* (%)	10 (4.9)	7 (8.8)	0.22[a]
Prior PAD, *n* (%)	3 (1.5)	2 (2.5)	0.55[a]
Multiple LIs, *n* (%)	25 (12.2)	17 (21.3)	0.053
Advanced WMLs, *n* (%)	45 (22.0)	24 (30.0)	0.15
BMBs, *n* (%)	26 (12.7)	22 (27.5)	0.003

Values are represented as mean ± s.d. or median (interquartile range 25–75%). The comparisons of two groups are evaluated by unpaired *t*-test or Mann–Whitney U test. The χ^2 test for independence was performed where appropriate.
[a]Fisher's exact test.
BMBs, brain microbleeds; eGFR, estimated glomerular filtration rate; IHD, ischemic heart disease; LIs, lacunar infarcts; PAD, peripheral artery disease; UACR, urinary albumin/creatinine ratio; WMLs, white matter lesions.

The prevalence of deep or infratentorial BMBs was significantly higher in patients with microalbuminuria (UACR >30–≤300 mg/g creatinine) than in those without. These associations remained robust even after adjustment for age, sex, and eGFR levels. In contrast, no significant relationship was found between the presence of microalbuminuria and pure lobar BMBs. However, there was no significant relationship between low eGFR levels (<60 ml/min/1.73 m^2) and the location of BMBs (Table 3). Logistic regression analysis showed that multiple LIs (odds ratio (OR) : 4.16, 95% confidence interval (CI) : 1.52–11.40, $P = 0.006$), advanced WMLs (OR: 5.11, 95% CI: 1.97–13.29, $P = 0.001$), and microalbuminuria (OR: 3.16, 95% CI: 1.34–7.44, $P = 0.009$) were independently associated with the presence of deep or infratentorial BMBs (Table 4). No significant differences were found between low eGFR levels and the presence of deep or infratentorial BMBs in multivariate logistic analysis (OR: 0.59, 95% CI: 0.22–1.56, $P = 0.29$).

DISCUSSION

This cross-sectional hospital-based study demonstrates that, in hypertensive patients without a history of stroke or TIA, microalbuminuria is independently associated with the prevalence of deep or infratentorial BMBs, but not with pure lobar BMBs. In the population-based Rotterdam Scan Study,[6,7] risk factors for BMBs differed with their location. Cardiovascular risk factors were associated with the incidence of deep or infratentorial BMBs, but not with pure lobar BMBs. Our findings are in agreement with those of this study and also provide new insights into the association between risk factors and BMB location.

The hemodynamic similarities have been observed in the vascular beds in the brain and kidney.[24] Therefore, it is important to consider hemodynamic similarities of vascular beds as a factor for the association between BMBs and CKD. A previous report has suggested that juxtamedullary afferent arterioles are small and short vessels that are exposed to high pressure and must maintain a strong vascular tone to provide a large pressure gradient in a short distance.[25] Ito *et al.*[26] have hypothesized that albuminuria may be an early sign of vascular damages in strain vessels, such as the perforating arteries and juxtamedullary afferent arterioles. Because perforating branches in the brain have a similar vessel structure, there is the possibility of an association between the appearance of microalbuminuria and the occurrence of BMBs in the basal ganglia and brainstem. Furthermore, past epidemiological research has found that a higher incidence of cardiovascular disease is accompanied with an increase in urinary albumin concentrations in community-based subjects without hypertension or diabetes.[27] Therefore, active interventions that prevent the appearance of urinary albumin before the incidence of lifestyle diseases (i.e., ischemic heart disease, stroke) may be important in reducing their occurrence. Microalbuminuria increased the risk of ischemic stroke,[13–15] and more recently, Bouchi *et al.*[28] reported that the appearance of microalbuminuria has a greater influence on the incidence of stroke than a decrease in eGFR in patients with type 2 diabetes. Moreover, in a cross-sectional study of 236 subjects who had ischemic stroke and TIA in the past 22 months, proteinuria was strongly associated with the frequency and number of BMBs.[29] Although research findings suggest that the appearance of microalbuminuria is

Table 2 | Characteristics of the study population with and without BMBs

	All patients ($n = 285$)	With BMBs ($n = 48$)	Without BMBs ($n = 237$)	P value
Age (year)	68.6 ± 8.9	71.6 ± 8.3	68.0 ± 8.9	0.01
Sex, male, *n* (%)	123 (43.2)	21 (43.8)	102 (43.0)	0.93
Diabetes mellitus, *n* (%)	137 (48.1)	19 (39.6)	118 (49.8)	0.20
Dyslipidemia, *n* (%)	135 (47.4)	20 (41.7)	115 (48.5)	0.39
Current smoker, *n* (%)	56 (19.6)	9 (18.8)	47 (19.8)	0.86
Left ventricular hypertrophy, *n* (%)	113 (39.6)	24 (50.0)	89 (37.6)	0.11
Systolic blood pressure (mm Hg)	137 ± 18	141 ± 20	136 ± 17	0.07
Diastolic blood pressure (mm Hg)	76 ± 11	77 ± 11	76 ± 11	0.58
Fasting blood glucose (mg/dl)	129.8 ± 43.0	134.8 ± 52.8	128.9 ± 40.9	0.41
Hemoglobin A_{1c} (%)	6.2 ± 1.3	6.1 ± 1.1	6.3 ± 1.4	0.55
eGFR (ml/min/1.73 m^2)	68.6 ± 18.3	66.4 ± 16.4	69.0 ± 18.6	0.37
UACR (mg/g creatinine)	18.0 (9.0–39.3)	48.0 (18.0–97.8)	15.0 (8.0–32.0)	<0.0001
Microalbuminuria, *n* (%)	80 (28.1)	22 (45.8)	58 (24.5)	0.003
Use of antihypertensive drugs, *n* (%)	166 (58.2)	39 (81.3)	127 (53.6)	0.008
Angiotensin receptor blockers, *n*(%)	96 (33.7)	20 (41.7)	76 (32.1)	0.20
Angiotensin-converting enzyme inhibitors, *n* (%)	56 (19.6)	10 (20.8)	46 (19.4)	0.82
Calcium-channel blockers, *n* (%)	104 (36.5)	25 (52.1)	79 (33.3)	0.01
Use of antithrombotic drugs, *n* (%)	59 (20.7)	16 (33.3)	43 (18.1)	0.02
Use of lipid-lowering drugs, *n* (%)	88 (30.9)	14 (29.2)	74 (31.2)	0.17
Prior IHD, *n* (%)	17 (6.0)	4 (8.3)	13 (5.5)	0.45[a]
Prior PAD, *n* (%)	5 (1.8)	2 (4.2)	3 (1.3)	0.16[a]
Multiple LIs, *n* (%)	42 (14.7)	21 (43.8)	21 (8.9)	<0.0001
Advanced WMLs, *n* (%)	69 (24.2)	29 (60.4)	40 (16.9)	<0.0001

Values are represented as mean ± s.d. or median (interquartile range 25–75%). The comparisons of two groups are evaluated by unpaired *t*-test or Mann–Whitney U test. The χ^2 test for independence was performed where appropriate.
[a]Fisher's exact test.
BMBs, brain microbleeds; eGFR, estimated glomerular filtration rate; IHD, ischemic heart disease; LIs, lacunar infarcts; PAD, peripheral artery disease; UACR, urinary albumin/creatinine ratio; WMLs, white matter lesions.

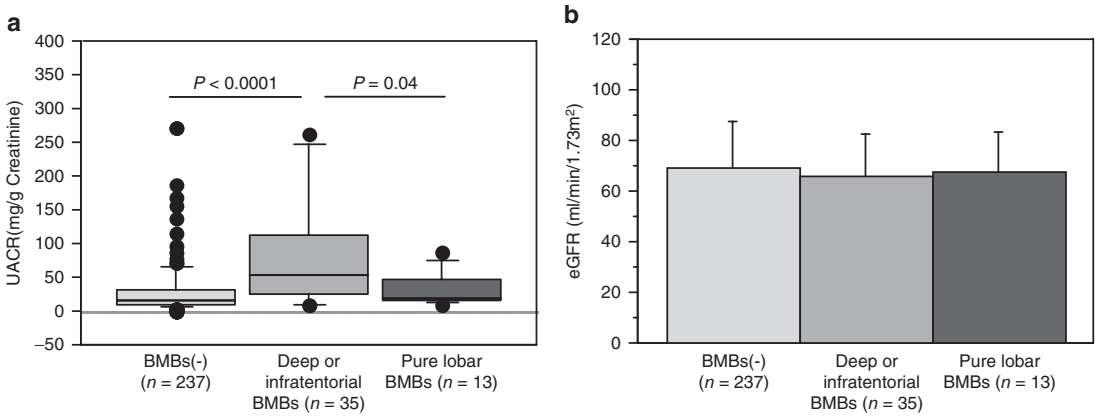

Figure 3 | Graphic representation of kidney biomarkers according to the location of brain microbleeds (BMBs). (**a**) Bars represent median values. Boxes are the interquartile ranges, and whiskers represent the range excluding statistical outliers. Dot plots of seven patients with macroalbuminuria are excluded from this figure. (**b**) Bars represent the standard deviation. eGFR, estimated glomerular filtration rate; UACR, urinary albumin/creatinine ratio.

associated with generalized vascular endothelial dysfunction and that it increases vascular endothelial permeability,[30] studies on this topic in the brain are still lacking. An association of multiple lacunar infarcts and advanced WMLs with BMBs was in agreement with the findings of other research but we observed for the first time that microalbuminuria was an independent risk factor for deep or infratentorial BMBs in hypertensive patients.

Table 3 | UACR and eGFR levels in relation to presence of BMBs in different location

	Any BMBs ($n = 48$)		Deep or infratentorial BMBs ($n = 35$)		Pure lobar BMBs ($n = 13$)	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
	OR (95%CI)	OR (95%CI)[a]	OR (95%CI)	OR (95%CI)[a]	OR (95%CI)	OR (95%CI)[a]
UACR[b]						
≤30 ($n = 205$)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
>30–≤300 ($n = 73$)	2.78 (1.45–5.34)*	2.55 (1.29–5.04)*	3.44 (1.64–7.21)*	3.31 (1.52–7.19)*	1.53 (0.45–5.17)	1.29 (0.37–4.48)
eGFR						
≥60 ($n = 214$)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
<60 ($n = 71$)	1.18 (0.58–2.38)	0.89 (0.41–1.91)	1.30 (0.58–2.89)	0.96 (0.40–2.29)	0.90 (0.24–3.36)	0.71 (0.17–2.85)

Values are represented as the odds ratio (OR) with 95% confidence interval (CI). Model 1, crude; Model 2 was adjusted for age and sex.
[a]Models of UACR are adjusted for eGFR. Models of eGFR are adjusted for UACR. [b]Seven patients with macroalbuminuria (UACR >300) were excluded from this analysis.
BMBs, brain microbleeds; eGFR, estimated glomerular filtration rate; UACR, urinary albumin/creatinine ratio.
*$P < 0.01$.

Table 4 | Factors associated with the presence of deep or infratentorial BMBs

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age (per 10 years)	1.68	1.08–2.59	0.02	1.01	0.58–1.77	0.96
Sex, male	0.88	0.43–1.82	0.74	1.39	0.55–3.49	0.49
Use of antihypertensive drugs	4.19	1.68–10.46	0.002	2.53	0.90–7.11	0.08
Use of antithrombotic drugs	3.01	1.42–6.39	0.004	0.87	0.32–2.36	0.78
Multiple LIs	10.89	4.89–24.24	<0.0001	4.16	1.52–11.40	0.006
Advanced WMLs	9.44	4.34–20.52	<0.0001	5.11	1.97–13.29	0.001
Microalbuminuria	3.44	1.64–7.21	0.001	3.16	1.34–7.44	0.009

Variables associated with the presence of deep or infratentorial BMBs by univariate analysis were entered into a multivariate logistic regression analysis. Values are represented as the odds ratio (OR) with 95% confidence interval (CI). Microalbuminuria was defined as an urinary albumin/creatinine ratio (UACR) between 30 and 300 mg/g creatinine.
BMBs, brain microbleeds; LIs, lacunar infarcts; WMLs, white matter lesions.

To our knowledge, only one study has explored an association between eGFR levels and the presence of BMBs. Cho *et al.*[31] reported a strong association between a decrease in eGFR and the appearance of BMBs in a study on 152 patients with acute ischemic stroke, however, they did not investigate an association with BMB location or presence of microalbuminuria. Our study failed to demonstrate a significant association between a decrease in eGFR and the prevalence and location of BMBs. Such discrepancies may be due to differences in the selection of baseline patient populations among the various studies. Another previous study indicated that albuminuria, but not eGFR, is associated with the carotid arterial remodeling process.[32] Therefore, further studies would be needed to confirm the relationship between microalbuminuria and cerebral small arterial remodeling. It is interesting to note that the prevalence of BMBs varies with different types of antihypertensive drug. Whether antihypertensive therapy has any effect on the prevalence and progression of BMBs is not fully understood. Therefore, further prospective large studies are needed to clarify whether there are any differences in BMB incidence rates in patients using different types of antihypertensive drug.

Certain methodological limitations of the present study should be addressed. First, albuminuria was evaluated from a single measurement of UACR. Second, although the results were adjusted for the use of renin–angiotensin system inhibitors because they easily affect urinary albumin levels, their usage periods varied among subjects, which could possibly have affected our results. Third, the small sample size of the pure lobar BMBs would have imposed limitations in multivariate analysis on an association between kidney markers and pure lobar BMBs.

In conclusion, microalbuminuria is strongly associated with an increased prevalence of deep or infratentorial BMBs in hypertensive patients without a history of stroke or TIA. Further prospective studies are required to specifically define whether a causal relationship between microalbuminuria and the development of BMBs exists in hypertensive patients.

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