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Original Article

Relationship between silent brain infarction and chronic kidney disease

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Abstract

Background. The presence of silent brain infarction (SBI) increases the risk of symptomatic stroke and dementia. The association between SBI and chronic kidney disease (CKD) has not been clarified. Moreover, little is known about what factors are related to SBI in CKD patients and whether the prevalence of SBI differs in CKD stage or cause of CKD.

Methods. This is a cross-sectional study. A total of 375 subjects—335 with CKD and 40 with essential hypertension—were included. All subjects underwent magnetic resonance imaging (MRI) of the brain to detect SBI. Glomerular filtration rate (GFR) was estimated using Modification of Diet in Renal Disease equation, and cardiovascular risk factors were examined.

Results. The prevalence of SBI was 56.5% in all subjects. Among causes of CKD, hypertensive nephrosclerosis had a strong association with SBI. According to the estimated GFR (eGFR) stage, the more severe the stage of eGFR, the higher the prevalence of SBI (age-adjusted odds ratio [95% confidence interval] for eGFR 30–59, 15–29 and <15 versus ≥60 mL/min/1.73 m^2: 1.34 [0.68–1.99], 1.94 [1.30–2.57] and 2.51 [1.91–3.10]). In multivariate logistic analysis, eGFR was related to SBI independently, in addition to age and blood pressure ($P = 0.025$). However, other traditional and non-traditional risk factors were not.

Conclusion. There was an independent association between eGFR and SBI. CKD patients should receive active detection of SBI and more intensive preventive management, especially for hypertension, should be needed in CKD patients to prevent SBI.

Keywords: chronic kidney disease; glomerular filtration rate; hypertension; magnetic resonance imaging; silent brain infarction

Introduction

Silent brain infarction (SBI) is defined as a cerebral infarction that is evident on brain imaging but is not associated with a clinical symptom [1]. In most cases, SBI is found as a lacunar infarction that is a small, deep cerebral infarction caused by occlusion of small penetrating cerebral arteries [2]. Therefore, SBI is categorized as small vessel disease and thus differs from other cardiovascular disease, such as ischaemic heart disease (IHD), aortic dissection and atherothrombotic cerebral infarction, because they are categorized as large vessel disease. SBI is seen on magnetic resonance imaging (MRI) both in patients with an overt stroke and in healthy elderly persons. It has been reported that the prevalence of SBI in the general population was from 8% to 28%, with the differences mainly explained by age [1]. The presence of SBI can predict clinical overt stroke [3,4] or reduced cognitive function [5,6]. It has been demonstrated that risk factors for SBI are not necessarily the same as those for clinical stroke [1,7], and several studies have consistently found that advanced age [3,4,8,9] and hypertension [3,8,9] are the most common risk factors for SBI.

Chronic kidney disease (CKD) has been shown to be an independent risk factor for cardiovascular disease [10–12], and cardiovascular disease is a leading cause of morbidity and mortality in CKD patients [13,14]. Similarly, several reports have indicated that CKD is associated with a high prevalence of stroke [10,11,15–19]. However, the association between CKD and SBI has not been clarified, and little is known about what factors are related to SBI in CKD patients.

The purpose of this study is to determine the prevalence and risk factors of SBI in CKD patients with a wide range of glomerular filtration rate (GFR) and to examine the strength

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of association between the prevalence of SBI and GFR stages.

Subjects and methods

Subjects

To determine the implications of CKD for the prevalence of SBI, we examined 335 elderly patients with CKD (stages 1–5) and 40 elderly patients with essential hypertension (EHT). A total of 375 subjects were enrolled, and all subjects attended the Department of Internal Medicine of Yokohama City University Medical Center, Japan, between August 2004 and October 2007. Exclusion criteria were subjects having a past history of stroke or transient ischaemic attacks (TIA), receiving renal replacement therapy (RRT) or having a past history of RRT and not in agreement with our study.

GFR was estimated using the Modification of Diet in Renal Disease (MDRD) equation, as follows [20]:

$$\mathrm{eGFR}\,(\mathrm{mL/min/1.73\,m^2}) = 175 \times \mathrm{SCr}\,(\mathrm{mg/dL})^{-1.154} \times \mathrm{age}\,(\mathrm{years})^{-0.203} \times 0.742\,(\text{if female}).$$

CKD was defined as either kidney damage or eGFR <60 mL/min/1.73 m^2 for 3 or more months [21]. Kidney damage was defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies [21]. CKD staging was based on eGFR. We classified eGFR into the following ranges: ≥ 60 mL/min/1.73 m^2 (stage 1 or 2), 30–59 mL/min/1.73 m^2 (stage 3), 15–29 mL/min/1.73 m^2 (stage 4) and <15 mL/min/1.73 m^2 (stage 5), according to the Kidney Disease Outcomes Quality Initiative stages [21]. All subjects with EHT had no kidney damage as described above, and their eGFR were not <60 mL/min/1.73 m^2.

The ethical committee of Yokohama City University Medical Center approved the protocol, and written informed consent was obtained from all subjects.

Silent brain infarction

All subjects underwent MRI of the brain. We performed axial T1-, T2- and proton-density-weighted scans on 1.5-T MRI scanners (Siemens AVANTO, Germany). The slice thickness was 6 mm with an interslice gap of 1.5 mm. We defined SBI as a focal area ≥ 3 mm and <20 mm in diameter in both T1- and T2-weighted scans that was visible as a low-intensity area on the T1-weighted image and as a high-intensity area on the T2-weighted image. Proton-density scans were used to distinguish infarctions from dilated perivascular spaces. Two trained physicians who had not been notified of any clinical information assessed the MR images independently. Their evaluation had an inter-reader intraclass correlation of 0.99.

We determined history of stroke and TIA by self-reporting, and by checking the medical records of all subjects, independent of their MRI outcome. We defined SBI as evidence on MRI of one or more infarctions, without a history of a stroke or TIA.

Risk factors

At the baseline examination, each subject completed a self-administered questionnaire covering their medical history, drugs received at least over the last year, smoking habit and alcohol intake. Trained interviewers at the screening checked the questionnaire, and the study physicians performed a physical examination of each subject and rechecked their medical history to improve the accuracy of the information.

Smoking habit was classified as current, past and never. With smokers, the Brinkmann index (cigarettes $\times$ year) was calculated. Alcohol intake was converted to grams of ethanol per day. We checked history of IHD, diabetes mellitus and hypertension. IHD was defined as either angina, history of myocardial infarction, coronary artery bypass surgery or percutaneous transluminal coronary angioplasty. Diabetes mellitus was defined according to the criteria recommended by the American Diabetes Association [22], in addition to a medical history of diabetes mellitus. Hypertension was diagnosed when blood pressure (BP) was $\geq$140/90 mmHg or patients were receiving antihypertensive treatments. BP was measured at least three times, after 5 min of rest, by trained observers using a standard mercury sphygmomanometer with the subject in the sitting position. The mean data were used for analysis.

Blood samples were collected after an overnight fast for the determination of serum creatinine, haemoglobin, fibrinogen, total protein, albumin, triglycerides, total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), calcium concentration, phosphate concentration, parathyroid hormone (PTH) and high-sensitivity C-reactive protein (hs-CRP). These specimens were assayed within 1 h. Serum creatinine concentration was measured by an enzymatic method. Serum calcium concentration was corrected for the serum albumin concentration, and the calcium–phosphate product was calculated. PTH measurements were based on an intact molecule assay. Proteinuria (g/day) was checked by collecting 24-h urine in CKD patients.

Statistical analysis

The SAS software package was used to perform all statistical analyses. All data are expressed as mean $\pm$ SD. eGFR was classified into four categories, and baseline characteristics were compared among eGFR categories. The mean values of selected conditions were examined using chi-squared statistics for categorical variables and one-way ANOVA of variance for continuous variables. Differences in the prevalence of SBI between eGFR categories, causes of CKD and nature of antihypertensive drugs were tested by logistic regression analysis. Age- or multivariable-adjusted odds ratios and 95% confidence intervals were also estimated by the use of multiple logistic regression analysis. Differences between the two groups, patients with SBI and those without, were analysed by means of unpaired Student's *t*-test. Chi-squared test was used to calculate the *P*-value for

Table 1. Demographic and clinical characteristics by the eGFR category

		Estimated GFR (mL/min/1.73 m^2)				
	Overall	≥60	30–59	15–29	<15	*P*-value
Number of patients	375	101	76	84	114	
Number of patients with SBI	212	38	43	53	78	
Men (%)	60.3	45.5	72.4	66.7	60.5	<0.001
Age (year)	63.5 ± 14.0	56.0 ± 13.7	67.4 ± 12.5	65.7 ± 12.8	65.9 ± 13.7	<0.001
Body mass index (kg/m^2)	24.1 ± 4.1	24.7 ± 4.7	24.1 ± 4.3	24.1 ± 3.9	23.7 ± 3.6	NS
Hypertension (%)	87.7	79.2	85.5	89.3	95.6	<0.01
Diabetes mellitus (%)	37.1	16.8	27.6	53.6	49.1	<0.001
History of ischaemic heart disease (%)	17.1	3.0	21.1	23.8	21.1	<0.001
Smoking habit						
Current (%)	22.7	24.2	29.7	25.0	16.5	NS
Past (%)	33.1	25.3	29.7	39.3	39.1	NS
Never (%)	44.2	50.5	40.6	35.7	44.4	NS
Brinkmann index (cigarettes × year)	457.0 ± 648.3	299.6 ± 463.3	515.2 ± 594.8	556.9 ± 678.6	477.3 ± 766.9	0.04
Alcohol intake						
Ethanol 0 g/day (%)	47.0	42.1	38.7	51.8	53.1	NS
Ethanol 0–20 g/day (%)	19.9	32.6	18.7	15.7	13.4	0.01
Ethanol >20 g/day (%)	33.1	25.3	42.6	32.5	33.5	NS
Systolic blood pressure (mmHg)	144.3 ± 26.9	138.3 ± 22.1	141.9 ± 24.3	144.4 ± 29.9	151.1 ± 28.8	<0.01
Diastolic blood pressure (mmHg)	77.3 ± 18.4	80.8 ± 16.3	77.5 ± 17.4	76.4 ± 19.7	74.9 ± 19.6	NS
Total cholesterol (mg/dL)	196.9 ± 55.3	213.6 ± 60.1	197.5 ± 51.8	195.9 ± 51.5	182.8 ± 52.5	<0.001
Triglycerides (mg/dL)	154.2 ± 94.1	151.5 ± 85.5	163.4 ± 102.5	171.1 ± 99.8	138.0 ± 89.3	NS
High-density lipoprotein cholesterol (mg/dL)	50.9 ± 18.2	59.8 ± 21.5	52.3 ± 17.4	46.7 ± 15.1	46.2 ± 15.2	<0.001
Low-density lipoprotein cholesterol (mg/dL)	115.5 ± 45.5	129.1 ± 47.3	113.7 ± 43.9	115.0 ± 44.7	106.3 ± 40.5	<0.01
Estimated GFR (mL/min/1.73 m^2)	40.1 ± 34.6	90.4 ± 19.6	41.4 ± 8.4	21.6 ± 4.5	8.2 ± 2.9	<0.001
Proteinuria (g/day)	1.8 ± 2.8	0.9 ± 2.5	1.6 ± 3.4	2.1 ± 2.5	2.4 ± 2.8	<0.01
Haemoglobin (g/dL)	11.2 ± 2.6	13.7 ± 1.7	12.0 ± 2.0	10.5 ± 1.8	8.9 ± 1.6	<0.001
Fibrinogen (mg/dL)	446.2 ± 132.9	400.8 ± 150.3	441.5 ± 127.8	441.7 ± 114.9	473.6 ± 132.5	0.01
Albumin (g/dL)	3.7 ± 0.7	4.0 ± 0.9	3.8 ± 0.6	3.5 ± 0.7	3.5 ± 0.6	<0.001
Hs-CRP (mg/dL)	0.243 ± 0.392	0.138 ± 0.142	0.238 ± 0.270	0.254 ± 0.388	0.330 ± 0.560	<0.01
Calcium (mg/dL)	9.2 ± 0.8	9.6 ± 0.5	9.4 ± 0.5	9.3 ± 0.8	8.8 ± 1.0	<0.001
Phosphate (mg/dL)	4.2 ± 1.4	3.4 ± 0.6	3.4 ± 0.6	3.9 ± 0.9	5.5 ± 1.6	<0.001
Calcium × phosphate product (mg^2/dL^2)	38.3 ± 11.9	33.1 ± 6.2	31.9 ± 5.8	36.2 ± 7.8	48.4 ± 14.2	<0.001
Intact PTH (pg/mL)	172.7 ± 231.1	49.9 ± 30.2	77.5 ± 64.0	123.3 ± 63.3	275.8 ± 316.4	<0.001

Values are expressed as mean ± SD or percentage.
GFR, glomerular filtration rate; PTH, parathyroid hormone.

categorical variables. Variables associated with SBI in univariable analysis were entered into a multivariable model using logistic regression methods to determine the power of each variable for predicting SBI. We performed multilinear regression analysis of factors related to the number of SBI. $P < 0.05$ was considered statistically significant in all analyses.

Results

Clinical and demographic details of our study are presented in Table 1.

Of 375 patients, 226 were men and 149 were women. The mean age was 63.5 ± 14.0 years (range, 27–89 years), and the mean eGFR was 40.1 ± 34.6 mL/min/1.73 m^2. SBI was present in 212 (56.5%) patients.

Of 335 CKD patients, 274 were diagnosed with CKD because of their eGFR, and 61 were diagnosed with CKD because of their kidney damage despite that their eGFR were ≥60 mL/min/1.73 m^2. Causes of CKD were chronic glomerulonephritis ($n = 89$; 26.6%), diabetes mellitus ($n = 114$; 34.0%), hypertensive nephrosclerosis ($n = 81$; 24.2%), polycystic kidney disease ($n = 14$; 4.2%) and others ($n = 37$; 11.0%). And 46.1% of patients with chronic gromerulonephritis, 57.9% of patients with diabetes mellitus, 74.1% of patients with hypertensive nephrosclerosis and 57.1% of patients with polycystic kidney disease had SBI. The prevalence of SBI in patients with hypertensive nephrosclerosis was twofold higher than that with non-hypertensive nephrosclerosis CKD patients after adjustment for age and eGFR (odds ratio [95% confidence interval]: 2.14 [1.54–2.74]).

According to the eGFR category, 38 of 101 patients (37.6%) with eGFR ≥60 mL/min/1.73 m^2, 43 of 76 patients (56.6%) with eGFR 30–59 mL/min/1.73 m^2, 53 of 84 patients (63.1%) with eGFR 15–29 mL/min/1.73 m^2 and 78 of 114 patients (68.4%) with eGFR <15 mL/min/1.73 m^2 had SBI. Age- and multivariable-adjusted odds ratios by the eGFR category for the prevalence of SBI were estimated (Table 2). This showed that the more severe the category of eGFR, the higher the prevalence of SBI. These relationships remained substantially unchanged even after adjustment for other traditional cardiovascular risk factors, such as hypertension, diabetes mellitus and hyperlipidaemia.

Figure 1 shows the odds ratio of the prevalence of SBI categorized by eGFR and systolic BP (sBP). In both patients with sBP ≥140 mmHg and those with sBP <140 mmHg,

Table 2. Association between the eGFR category and the prevalence of SBI

Estimated GFR (ml/min/1.73 m^2)	Odds ratio (95% confidence interval)	
	Age-adjusted	Multivariable-adjusted[a]
≥60	1.00	1.00
30–59	1.34 (0.68–1.99)	1.41 (0.74–2.09)
15–29	1.94 (1.30–2.57)	2.27 (1.58–2.95)
<15	2.51 (1.91–3.10)	2.62 (1.97–3.27)

[a]The analysis was adjusted for age, the presence of hypertension, diabetes mellitus and hyperlipidaemia.

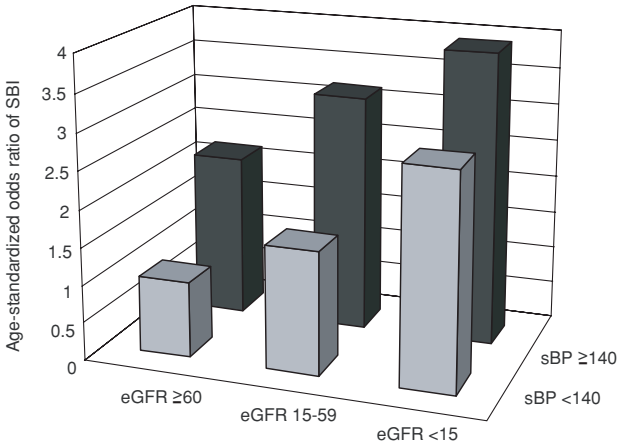

Fig. 1. Age-standardized odds ratio of SBI, categorized by eGFR and systolic BP (sBP) (eGFR ≥60, 15–59, <15 mL/min/1.73 m^2) and (sBP ≥140, <140 mmHg). Numbers of patients in each column were 58, 77 and 37 (left to right) for the near side (sBP <140 mmHg) and 43, 83 and 77 (left to right) for the far side (sBP ≥140 mmHg). The odds ratio of SBI for each column versus ≥60 mL/min/1.73 m^2 and sBP <140 mmHg was 1.00, 1.63 and 2.86 (left to right) for the near side (sBP <140 mmHg) and 2.17, 3.17 and 3.90 (left to right) for the far side (sBP ≥140 mmHg).

the prevalence of SBI increased as eGFR decreased. Patients with sBP <140 mmHg had a lower prevalence of SBI compared to those with sBP ≥140 mmHg in all eGFR categories. However, the influence of sBP became smaller as the eGFR category worsened.

Next, we analysed the patients by dividing them into two groups: those with SBI and those without SBI. Table 3 shows the baseline characteristics of the patients in these two groups. According to Table 3, age, prevalence of hypertension, history of IHD, Brinkmann index and sBP were higher whereas TC, HDL, LDL, eGFR and haemoglobin were lower in patients with SBI. Other traditional risk factors for cardiovascular disease, such as male sex, alcohol intake and diabetes mellitus, were not different in the two groups. In this study, we also investigated the relationships between SBI and non-traditional risk factors, such as proteinuria, anaemia, fibrinogen, albumin, hs-CRP and mineral metabolism of calcium and phosphate. Among these factors, only haemoglobin was different in the two groups; however, the difference was not significant after adjustment for eGFR. In relation to mineral metabolism of calcium and phosphate, we also investigated the association between SBI and the use of vitamin D (alfacalcidol and calcitriol) by comparing the prevalence ratio of these drugs between the two groups, but found no difference. Multivariable logistic analysis of factors that had a statistically significant relationship with SBI by univariable analysis revealed that eGFR had a graded association with the prevalence of SBI, in addition to age and sBP (Table 4).

Furthermore, we analysed the association between SBI and antihypertensive drugs. For each drug, we found no association with SBI. However, we found the following association by focusing on angiotensin (AT) II formation of each drug. We divided the patients receiving antihypertensive treatments into two groups: those receiving only drugs potentially increasing AT II (AT II type I receptor antagonists, diuretics and long-acting dihydropyridine calcium antagonists) and those receiving both drugs potentially increasing AT II and drugs potentially decreasing AT II (AT-converting enzyme inhibitors, beta-blockers and long-acting non-dihydropyridine calcium antagonists). The prevalence of SBI in the latter was statistically higher than that in the former after adjustment for age, sBP and eGFR (odds ratio [95% confidence interval]: 1.75 [1.21–2.29]).

To enhance the causal association of eGFR with SBI, analysis of the relationship between the number of SBI and eGFR was performed (Table 5). There was a significant negative correlation between the number of SBI and eGFR.

Discussion

Our study demonstrated the strength of association between SBI and eGFR.

There has been rapidly growing interest in the relationship between CKD and cardiovascular disease. However, little information has been available on the relationship between kidney and brain compared to kidney and heart. In cerebral disease, SBI is asymptomatic, but is important as a predictor of stroke and dementia. To prevent these disorders and keep a good quality of life, the control of risk factors for SBI is necessary. In this regard, our report, showing the association between CKD and SBI, would be meaningful.

There are two types of cerebral small vessel disease: SBI and white matter lesions (WML). Recently, it has been shown that eGFR was associated with WML [23,24]. However, the association between SBI and eGFR has not been clarified. Ikram *et al*. showed that there was no significant association between SBI and eGFR, despite showing a significant association between WML and eGFR [23]. However, the prevalence in severe stage CKD patients has not been sufficiently examined, and uraemia-related factors were not fully analysed because the study population had relatively good renal function (mean eGFR 54.8 mL/min/1.73 m^2). On the other side, in patients with more severe CKD, Kobayashi *et al*. showed that the prevalence of SBI in patients with creatinine clearance (CCr) <40 mL/min/1.73 m^2 was significantly higher than that in those with CCr ≥40 mL/min/1.73 m^2 ($n = 51$) [25]. However, their results were not adjusted for age and BP. Therefore, it remains unclear whether the high prevalence of SBI in CKD patients depends on age and/or BP, which are common strong risk factors for SBI and increase

Table 3. Characteristics of patients with and without SBI

	With SBI	Without SBI	*P*-value
Number of patients	212	163	
Men (%)	62.7	57.0	NS
Age (year)	67.7 ± 11.1	58.1 ± 15.5	<0.0001
Body mass index (kg/m^2)	23.9 ± 3.6	24.4 ± 4.6	NS
Hypertension (%)	94.8	78.5	<0.0001
Diabetes mellitus (%)	37.7	36.2	NS
History of ischaemic heart disease (%)	21.2	11.7	0.027
Smoking habit			
Current (%)	24.8	20.0	NS
Past (%)	33.0	33.1	NS
Never (%)	42.2	46.9	NS
Brinkmann index (cigarettes × year)	532.6 ± 714.0	359.1 ± 537.5	0.011
Alcohol intake			
Ethanol 0 g/day (%)	46.8	46.9	NS
Ethanol 0–20 g/day (%)	17.1	23.7	NS
Ethanol >20 g/day (%)	36.1	29.4	NS
Systolic blood pressure (mmHg)	148.4 ± 27.8	138.9 ± 24.9	<0.001
Diastolic blood pressure (mmHg)	78.2 ± 20.1	76.2 ± 16.1	NS
Total cholesterol (mg/dL)	190.6 ± 52.1	205.2 ± 58.3	0.012
Triglycerides (mg/dL)	157.7 ± 99.5	149.6 ± 86.5	NS
High-density lipoprotein cholesterol (mg/dL)	48.5 ± 16.0	54.2 ± 20.5	<0.01
Low-density lipoprotein cholesterol (mg/dL)	110.4 ± 41.7	122.4 ± 47.4	0.017
Estimated GFR (mL/min/1.73 m^2)	32.6 ± 30.5	49.7 ± 37.2	<0.0001
Proteinuria (g/day)	1.5 ± 2.2	2.1 ± 3.5	NS
Haemoglobin (g/dL)	10.8 ± 2.4	11.7 ± 2.7	<0.001
Fibrinogen (mg/dL)	443.2 ± 126.4	451.2 ± 143.2	NS
Albumin (g/dL)	3.7 ± 0.7	3.7 ± 0.8	NS
Hs-CRP (mg/dL)	0.253 ± 0.387	0.232 ± 0.399	NS
Calcium (mg/dL)	9.2 ± 0.8	9.3 ± 0.8	NS
Phosphate (mg/dL)	4.2 ± 1.3	4.1 ± 1.5	NS
Calcium × phosphate product (mg^2/dL^2)	38.6 ± 11.5	37.3 ± 12.4	NS
Intact PTH (pg/mL)	161.8 ± 154.0	188.8 ± 312.3	NS

Values are expressed as mean ± SD or percentage.
GFR, glomerular filtration rate; PTH, parathyroid hormone.

Table 4. Multivariable logistic regression analysis for the prevalence of SBI

	Odds ratio	95% confidence interval	*P*-value
Estimated GFR (mL/min/1.73 m^2)	0.989	0.979–0.998	0.025
Age (year)	1.054	1.034–1.074	<0.0001
Systolic blood pressure (mmHg)	1.016	1.006–1.026	<0.001
History of ischaemic heart disease	0.949	0.300–1.598	NS
Brinkmann index (cigarettes × year)	1.000	0.804–1.196	NS
Haemoglobin (g/dL)	1.083	0.952–1.214	NS
Total cholesterol (mg/dL)	0.997	0.993–1.001	NS

Table 5. Multilinear regression analysis of factors related to number of SBI

	Standard regression coefficient	*t*	*P*-value
Estimated GFR (mL/min/1.73 m^2)	−0.110	−2.118	0.035
Age (year)	0.310	6.073	<0.0001
Systolic blood pressure (mmHg)	0.098	1.981	0.048

as eGFR declines, or whether other uraemia-related factors play a role in SBI in CKD patients. In addition, their sample was too small to reach a conclusion on the relationship between CKD and SBI, and patients with diabetes mellitus, which is a major cause of CKD, were excluded from their study.

In the present study, we confirmed that BP and age were related to SBI in CKD patients, similar to the general population. Moreover, we revealed that eGFR was also associated with SBI independent of age and BP. In addition, we analysed and compared all-cause CKD patients to show the prevalence of SBI in each group of CKD patients and revealed that patients with hypertensive nephrosclerosis had a higher prevalence of SBI. It has been clarified that the prevalence of cardiac disease increases as the eGFR stage progresses [10–12]. We showed that this association is also applied to SBI. These findings may indicate that there is a cerebro-renal association, similar to the cardio-renal association.

Yamamoto *et al*. showed that patients with multiple lacunar infarctions had a higher risk for cardiovascular disease than patients with a single lacunar infarction [26]. Another group showed that the number of lacunae was related to the degree of brain atrophy [27]. Therefore, we also performed analysis of the relationship between the number of SBI and eGFR. The results revealed that a decline of eGFR was

associated with not only the prevalence of SBI but also the number of SBI independently.

Furthermore, we investigated the cause of the high prevalence of SBI in CKD patients. Reduced kidney function is associated with increased levels of inflammatory factors [28,29], enhanced coagulability [29], anaemia [30] and calcium–phosphate abnormality. Moreover, CKD patients often have proteinuria. Thus, we investigated these non-traditional factors: hs-CRP, albumin, fibrinogen, haemoglobin, mineral metabolism of calcium and phosphate and proteinuria. However, we could not find any influence of these factors on the prevalence of SBI. These results suggest that these factors do not play a major role in SBI alone and other non-traditional factors or the combination of multiple non-traditional risk factors affect the prevalence of SBI in CKD patients. However, more studies are needed to clarify why eGFR associates with SBI independently. For traditional factors, it has been cleared that smoking, dyslipidaemia and diabetes mellitus are risk factors for stroke in addition to advanced age and hypertension, and CKD patients often share these risk factors. Although no relationship was seen between these factors and SBI in our study, the strict control of multiple cardiovascular risk factors including these factors may be necessary in CKD patients to prevent cerebral dysfunction.

Meanwhile, hypertension and sBP associated with SBI very strongly in CKD patients. We investigated the prevalence of SBI, categorized by eGFR and sBP. The results revealed that not only the prevalence of SBI increased as the eGFR category worsened, but also the prevalence of SBI was markedly lower in patients whose hypertension was appropriately treated. In addition, patients with hypertensive nephrosclerosis had higher prevalence of SBI than those with other causes of CKD. This indicates that there is a link between vascular disease of the kidney and brain, and hypertension is important as a cause of the high prevalence of SBI in CKD patients. Blood vessels in the kidney and brain were reported to be highly susceptible to fluctuations in BP and flow because the vascular beds of both the kidney and brain have very low resistance and are passively perfused at high flow throughout systole and diastole [31]. Interestingly, this mechanism is present only in the kidney and brain, and it causes small-vessel injury in these organs. Therefore, BP control may be especially important to prevent small-vessel disease of the kidney and brain in CKD patients, and our results support this report.

We also considered whether the prevalence of SBI was different in the nature of antihypertensive treatments. Experimental data in rodents have documented that activation of AT_2 receptor of AT II may exert anti-ischaemic mechanisms in the brain [32–35]. In addition, the meta-analysis of randomized clinical trials have hypothesized that drugs increasing AT II are more stroke protective than drugs decreasing AT II [36]. In our study, most patients were treated with combined antihypertensive drugs. Furthermore, most of them received at least one of the drugs potentially increasing AT II. Thus, we analysed the association between SBI and AT II formation by dividing patients receiving antihypertensive treatments into two groups: those receiving only drugs potentially increasing AT II and those receiving both drugs potentially increasing AT II and drugs potentially decreasing AT II. By using multivariable logistic regression analysis, we showed that the prevalence of SBI in the latter was statistically higher than that in the former even after adjustment for factors that were associated with SBI independently in our study. Our results may support the hypothesis that drugs increasing AT II have a protective effect on brain ischaemia.

However, our study has several limitations. Firstly, it was cross-sectional, and therefore, a prospective study concerning the development of SBI may warrant the results. Secondly, we chose EHT patients as controls to consider whether eGFR associated with SBI independently, because most CKD patients had hypertension, which was a strong risk factor for SBI. Thus, we did not adopt the age-matched healthy subjects in the present study. However, it is an important and interesting point to gather and compare CKD patients to the age-matched healthy volunteer. We would like to reveal this problem in the future study. Finally, GFR was estimated by the MDRD equation. The equation we used is widely accepted. However, it may not be accurate across racial groups because of difference among races in creatinine generation. In order to compensate the MDRD equation, we re-analysed our data using the MDRD equation modified for Japanese [37] and the Cockcroft–Gault equation for CCr [38] and confirmed that the results were the same as those using the MDRD equation (data not shown). This reproducibility would guarantee the results of our study.

Despite these limitations, we described the graded association between eGFR and SBI in patients with a wide range of eGFR and reported the prevalence of SBI according to eGFR stage and cause of CKD. Moreover, we showed the importance of CKD as a predictor not only of SBI but also of the number of SBI.

In conclusion, CKD associates with SBI independently. Furthermore, the prevalence of SBI and the number of SBI increased markedly as eGFR decreased. Our findings suggest that CKD patients should be considered as a high-risk population for SBI, which is a risk for stroke and dementia, and be recommended for more intensive preventive management, including active detection of SBI and strict treatment of multiple cardiovascular risk factors, especially hypertension.

Conflict of interest statement. None declared.

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