Prognostic Relationships between Microbleed, Lacunar Infarction, White Matter Lesion, and Renal Dysfunction in Acute Ischemic Stroke Survivors

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Background: It is well known that renal dysfunction and cerebral small-vessel disease (SVD), including microbleed, lacunar infarction, and white matter lesion (WML), are associated with poor prognosis after ischemic stroke. However, the prognostic relationship between renal dysfunction and SVD has not been well evaluated in acute ischemic stroke survivors. Therefore, in this study, we evaluated the prognostic relationships between estimated glomerular filtration rate (eGFR) and cerebral SVD after acute ischemic stroke. *Methods:* We retrospectively reviewed the clinical and radiological data of acute ischemic stroke survivors with decreased eGFR (<60 mL/min/1.73 m^2, n = 128) and controls (eGFR ≥60 mL/min/1.73 m^2, n = 128). The presence of SVD was evaluated according to magnetic resonance imaging performed on admission. Mortality data were obtained from medical chart reviews and telephone interviews. *Results:* Patients with silent lacunar infarction, WML, or microbleed had lower eGFR than patients without such lesions (60.4 ± 34.8 versus 87.5 ± 28.4 mL/min/1.73 m^2, 60.5 ± 37.1 versus 73.9 ± 33.3 mL/min/1.73 m^2, and 57.6 ± 33.3 versus 73.9 ± 32.9 mL/min/1.73 m^2, respectively). In addition, the multivariate adjusted odds ratio for the presence of SVD increased inversely with eGFR. Three-year survival was lower in patients with renal dysfunction and each type of SVD. The presence of WML was an independent risk factor for cardiovascular death. *Conclusions:* Renal impairment was associated with the presence of SVD in acute ischemic stroke survivors. Both renal impairment and the presence of SVD were predictors of poor poststroke survival. **Key Words:** Chronic renal disease—stroke—cerebral small-vessel disease—mortality.

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Received July 12, 2016; revision received September 9, 2016; accepted September 22, 2016.

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1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2016.09.037

Introduction

A close relationship exists between renal dysfunction and risk of stroke. Moreover, chronic kidney disease (CKD) increases poststroke mortality,[1,2] and patients with lower estimated glomerular filtration rates (eGFRs) have poorer survival after acute stroke.[3]

The relationship between cerebrovascular disease and CKD is thought to be based on small-vessel disease (SVD). Although the mechanisms have not been firmly established, the pathophysiological explanation may be based on the similarity of the vascular beds in the brain and kidney.[2] A previous Japanese study postulated a "strain vessel hypothesis" to explain the close inter-relationships of the small arteries of the brain, heart, and kidneys.[4]

SVD of the brain, including silent lacunar infarction, microbleed, and white matter lesion (WML), is clinically related to impaired cognitive function, dementia, and stroke.[5-7] Additionally, studies have correlated the extent of lacunar infarction, microbleed, and WML with renal dysfunction.[8-13] However, few studies have reported the relationship between the type of SVD and renal dysfunction or evaluated the relationships of SVD and renal dysfunction with mortality in acute ischemic stroke survivors. Therefore, in the present study, we investigated whether the severity of CKD is associated with the prevalence of cerebral SVD in acute ischemic stroke survivors. Furthermore, we studied the 3-year survival rate after acute ischemic stroke based on presence of SVD and CKD.

Methods

Patients

We retrospectively reviewed the data of patients aged over 30 years who were admitted to the Department of Neurology at Chungnam National University Hospital with acute ischemic stroke between February 2012 and April 2013. In all admitted patients with stroke, the presence of vascular risk factors, including diabetes, hypertension, dyslipidemia, smoking, history of coronary heart disease, previous stroke, and peripheral artery disease, was assessed. At the time of admission, neurological examination, brain magnetic resonance imaging (MRI), and workup for underlying risk factors and comorbid cardiovascular diseases were performed. Workup included complete blood count, chemistry profile, lipid profile, electrocardiography, echocardiography, and estimation of pulse wave velocity (PWV). Ankle–brachial index (ABI) was also determined as a measure of peripheral artery disease.

During the study period, 1256 patients were admitted with acute ischemic stroke. We excluded those who did not undergo brain MRI or were suspected of having acute renal injury or decreased eGFR due to severe dehydration. Finally, 1138 patients were enrolled in the study. The study design and protocol were reviewed and approved by the Ethics Committee of Chungnam National University Hospital (IRB No. 2015-11-041).

Measurement of eGFR

Initial renal function was evaluated based on eGFR using the Modification of Diet in Renal Disease formula at the time of admission. eGFR classification was based on Kidney Disease: Improving Global Outcomes criteria. Of the 1138 patients enrolled in the study, 128 showed moderate to severe renal dysfunction (eGFR <60 mL/min/1.73 m^2). Of the remaining 1010 patients with intact renal function (eGFR ≥60 mL/min/1.73 m^2), we selected 128 age- and sex-matched controls.

MRI Analysis

Patients underwent MRI using a 1.5-T scanner (Signa Excite, GE Healthcare, Milwaukee, Illinois, USA) at the time of admission. Sequences included axial diffusion-weighted images, T1-weighted images, T2-weighted images, and gradient echo images.

Silent lacunar infarction was rated visually as a focal lesion of more than 3 but less than 20 mm in maximum diameter, characterized by hypointensity on T1-weighted images with corresponding hyperintensity on T2-weighted images.[14] Severity of WML was assessed based on the Fazekas scale.[15] Periventricular white matter hyperintensity (WMH) extending into the deep white matter (Fazekas grade 3) and confluence or early confluence of deep WMH (Fazekas grades 2-3) were considered to represent the presence of WML.[16] Microbleed was defined as small (<5 mm) round foci showing low signal intensity on gradient echo images.[14] The presence of each type of SVD and the grade of WML were interpreted by 2 experienced neurologists (J.W.S. and H.S.J.), and interrater reliability was measured. To assess intrarater reliability, 1 neurologist re-evaluated the images 2 weeks later.

Mortality Analysis

We obtained survival data from medical chart reviews and telephone interviews with patient caregivers in December 2015. For mortality analysis, patients who died of cerebral edema due to large cardioembolic infarction during admission or of significant causes other than a cardiovascular event, such as trauma or advanced cancer, were excluded. Of 256 patients, 232 were included in the mortality analysis.

Statistical Analysis

Age, sex, vascular risk factors, stroke subtype on admission, ejection fraction on echocardiography, PWV, and ABI were compared between patients with eGFRs less than 60 mL/min/1.73 m^2 and those with eGFRs of 60 mL/min/1.73 m^2 or higher. The relationships between those risk factors, including kidney function, and the presence of each type of SVD were evaluated. Chi-square test was used to compare categorical variables, while the Student *t*-test was used to compare continuous variables. Logistic regression analysis was performed to estimate the relationships between severity of renal dysfunction and each type of SVD. The Kaplan–Meier method and log-rank test were used to evaluate mortality according to renal function with or without SVD. SPSS version 22 for Windows (SPSS Inc., Chicago, IL) was used for data analysis, and a *P* value less than .05 was considered significant.

Results

The demographic features of the study participants are presented in Table 1. Among the 256 total patients (mean

Table 1. *Demographic features of the patients*

Characteristics	Total (N = 256)	eGFR of 60 or higher (n = 128)	eGFR lower than 60 (n = 128)	*P* value
Age (year)	73.3 ± 9.9	73.4 ± 9.8	7.3 ± 10.1	.965
Sex, M : F	156 (61):100 (39)	78 (61):50 (39)	78 (61):50 (39)	1.000
Cerebrovascular risk factors				
Hypertension	192 (75)	79 (61)	113 (88)	<.001
Diabetes	90 (35)	28 (22)	62 (48)	<.001
Smoking (ever-smoker)	49 (19)	21 (16)	28 (22)	.211
Dyslipidemia	79 (31)	32 (25)	47 (37)	.058
Previous stroke	63 (25)	26 (20)	37 (29)	.146
Coronary heart disease	37 (15)	10 (8)	27 (21)	.004
Stroke subtype				.537
TIA	40 (16)	23 (18)	17 (13)	
Large artery atherosclerosis	68 (27)	29 (23)	39 (30)	
Cardioembolism	60 (23)	31 (24)	29 (23)	
Small-vessel occlusion	62 (24)	29 (23)	33 (26)	
Others	8 (7)	11 (9)	7 (6)	
Undetermined	8 (3)	5 (4)	3 (2)	
eGFR (mL/min/1.73 m^2)	69.4 ± 35.6	97.3 ± 27.1	41.5 ± 15.6	<.001
EF on EchoCG (%)	56.8 ± 10.3	57.6 ± 9.5	56.0 ± 10.9	.211
Pulse wave velocity (cm/s)	2225.6 ± 748.2	2177.4 ± 677.2	2275.1 ± 815.3	.349
Ankle–brachial index	1.1 ± .2	1.1 ± .1	1.0 ± .2	.008

Abbreviations: EchoCG, echocardiography; EF, ejection fraction; eGFR, estimated glomerular filtration rate; F, female; M, male; TIA, transient ischemic attack.

Values are given as n (percentage).

age, 73.3 ± 9.9 years; 61% male), those with eGFRs less than 60 mL/min/1.73 m^2 more frequently had hypertension ($P < .001$), diabetes ($P < .001$), and coronary heart disease ($P = .004$) than those with eGFRs of 60 mL/min/1.73 m^2 or higher (n = 128). ABI was lower in the low eGFR group than in the high eGFR group (1.0 ± .2 versus 1.1 ± .1, $P = .008$).

Risk Factors for SVD

Risk factors for each type of SVD are presented in Table 2. Patients with lacunar infarction (n = 172) were older ($P = .007$), more frequently had hypertension ($P < .001$), diabetes ($P = .030$), and previous stroke ($P = .002$), and had lower eGFR (60.4 ± 34.8 versus 87.5 ± 28.4 mL/min/1.73 m^2, $P < .001$) than patients without lacunar infarction. Patients with WML (n = 89) were older ($P = .002$), more frequently had hypertension ($P = .002$) and previous stroke ($P = .021$), and had lower eGFR (60.5 ± 37.1 versus 73.9 ± 33.3 mL/min/1.73 m^2, $P = .004$) than patients without WML. Patients with microbleed (n = 42) more frequently had hypertension ($P = .018$) and had lower eGFR (57.6 ± 33.3 versus 73.9 ± 32.9 mL/min/1.73 m^2, $P = .001$) than patients without microbleed. Among the other factors, PWV and ABI were related to the presence of lacunar infarction and WML (Table 2).

In multivariate analysis, age and eGFR were independently related to the presence of SVD (Table 3). According to the stage of CKD, the most severe stage showed the highest prevalence of SVD (Table 3). The odds ratio (OR) for lacunar infarction increased inversely with eGFR (OR, 10.3; 95% confidence interval [CI], 2.0-54.3; $P = .006$ for eGFR = 30-59 mL/min/1.73 m^2; OR, 10.9; 95% CI, 2.0-59.0; $P = .006$ for eGFR < 30 mL/min/1.73 m^2). The OR for WML also increased inversely with eGFR (OR, 2.9; 95% CI, .9-9.3; $P = .072$ for eGFR = 30-59 mL/min/1.73 m^2; OR, 3.8; 95% CI, 1.1-12.5; $P = .031$ for eGFR < 30 mL/min/1.73 m^2). Similar results were found with regard to microbleed (OR, 2.9; 95% CI, 1.1-8.0; $P = .039$ for eGFR = 30-59 mL/min/1.73 m^2; OR, 3.7; 95% CI, 1.3-10.6; $P = .016$ for eGFR < 30 mL/min/1.73 m^2). Hypertension, diabetes, previous stroke, PWV, and ABI were not related to SVD after adjusting for age and eGFR (Table 3).

Cardiovascular Mortality According to Type of SVD and eGFR

Overall, 69 of 234 patients died during the 3-year follow-up period (overall mortality rate, 29.4%). In the low eGFR group, 42 patients (36%) died, whereas in the high eGFR group, 27 patients (23%) died. Cumulative survival curves using the Kaplan–Meier log-rank test also showed lower survival in the low eGFR group than in the high eGFR group ($P = .020$) (Fig 1, A).

In the analysis according to the type of SVD, the presence of each type of SVD and low eGFR were significantly

Table 2. *Risk factors for small-vessel disease*

Factors	Lacunar infarction (+) n = 172	Lacunar infarction (−) n = 82	*P* value	White matter lesion (+) n = 89	White matter lesion (−) n = 164	*P* value	Microbleed (+) n = 42	Microbleed (−) n = 106	*P* value
Age	74.5 ± 9.5	70.9 ± 10.6	.007	75.9 ± 8.0	71.9 ± 10.6	.002	74.1 ± 9.9	73.0 ± 32.9	.464
Sex, male	106 (62)	48 (59)	.680	53 (60)	101 (62)	.788	42 (64)	106 (60)	.370
Hypertension	140 (82)	51 (62)	.001	74 (83)	117 (71)	.025	56 (84)	125 (71)	.018
Diabetes	68 (40)	22 (27)	.030	36 (40)	52 (33)	.272	26 (39)	59 (34)	.450
Smoking	33 (19)	16 (20)	.547	7 (8)	42 (26)	<.001	11 (17)	34 (19)	.713
Dyslipidemia	56 (33)	23 (28)	.473	29 (33)	50 (31)	.777	21 (32)	51 (29)	.752
Previous stroke	52 (30)	10 (12)	.002	29 (33)	33 (20)	.021	20 (30)	37 (21)	.091
Previous CHD	28 (16)	9 (11)	.342	14 (16)	23 (14)	.424	11 (17)	24 (14)	.544
eGFR (mL/min/1.73 m^2)	60.4 ± 34.8	87.5 ± 28.4	<.001	60.5 ± 37.1	73.9 ± 33.3	.004	57.6 ± 33.3	73.9 ± 32.9	.001
EF on EchoCG (%)	56.6 ± 10.1	57.0 ± 10.8	.768	57.6 ± 8.0	56.3 ± 11.4	.274	56.0 ± 10.5	57.2 ± 10.2	.417
Pulse wave velocity (cm/s)	2292.3 ± 797.4	2079.1 ± 615.8	.058	2374.0 ± 874.2	2141.5 ± 659.3	.032	2223.0 ± 859.4	2218.9 ± 718.4	.973
Ankle–brachial index	1.06 ± .16	1.10 ± .14	.069	1.03 ± .16	1.20 ± 1.45	.009	1.05 ± .15	1.09 ± .15	.104

Abbreviations: CHD, coronary heart disease; EchoCG, echocardiography; EF, ejection fraction; eGFR, estimated glomerular filtration rate.
Values are given as n (percentage).

Table 3. *Multiple logistic regression analysis of the risk factors of small-vessel disease*

Risk factors	Lacunar infarction OR	Lacunar infarction 95% CI	*P* value	White matter lesion OR	White matter lesion 95% CI	*P* value	Microbleed OR	Microbleed 95% CI	*P* value
Age	.950	.912-.989	.013	.945	.909-.984	.005	.988	.957-1.019	.429
Hypertension	1.472	.682-3.179	.325	.984	.454-2.130	.967	1.476	.663-3.285	.340
Diabetes	1.061	.480-2.347	.884	—	—	—	—	—	—
Previous stroke	3.026	1.088-8.413	.034	1.900	.886-4.075	.099	1.447	.744-2.813	.276
eGFR (mL/min/1.73 m^2)									
90 or higher (reference)	—	—	—	—	—	—	—	—	—
60-89	1.903	.364-9.951	.446	1.370	.475-3.951	.560	1.265	.523-3.058	.717
30-59	10.306	1.953-54.392	.006	2.910	.909-9.315	.072	2.899	1.054-7.973	.039
Lower than 30	10.851	1.997-58.963	.006	3.764	1.131-12.527	.031	3.681	1.276-10.623	.016
Pulse wave velocity	1.000	.999-1.000	.554	1.000	.999-1.000	.323	—	—	—
Ankle–brachial index	.868	.070-10.719	.912	4.198	.500-35.240	.186	—	—	—

Abbreviations: CI, confidential interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.

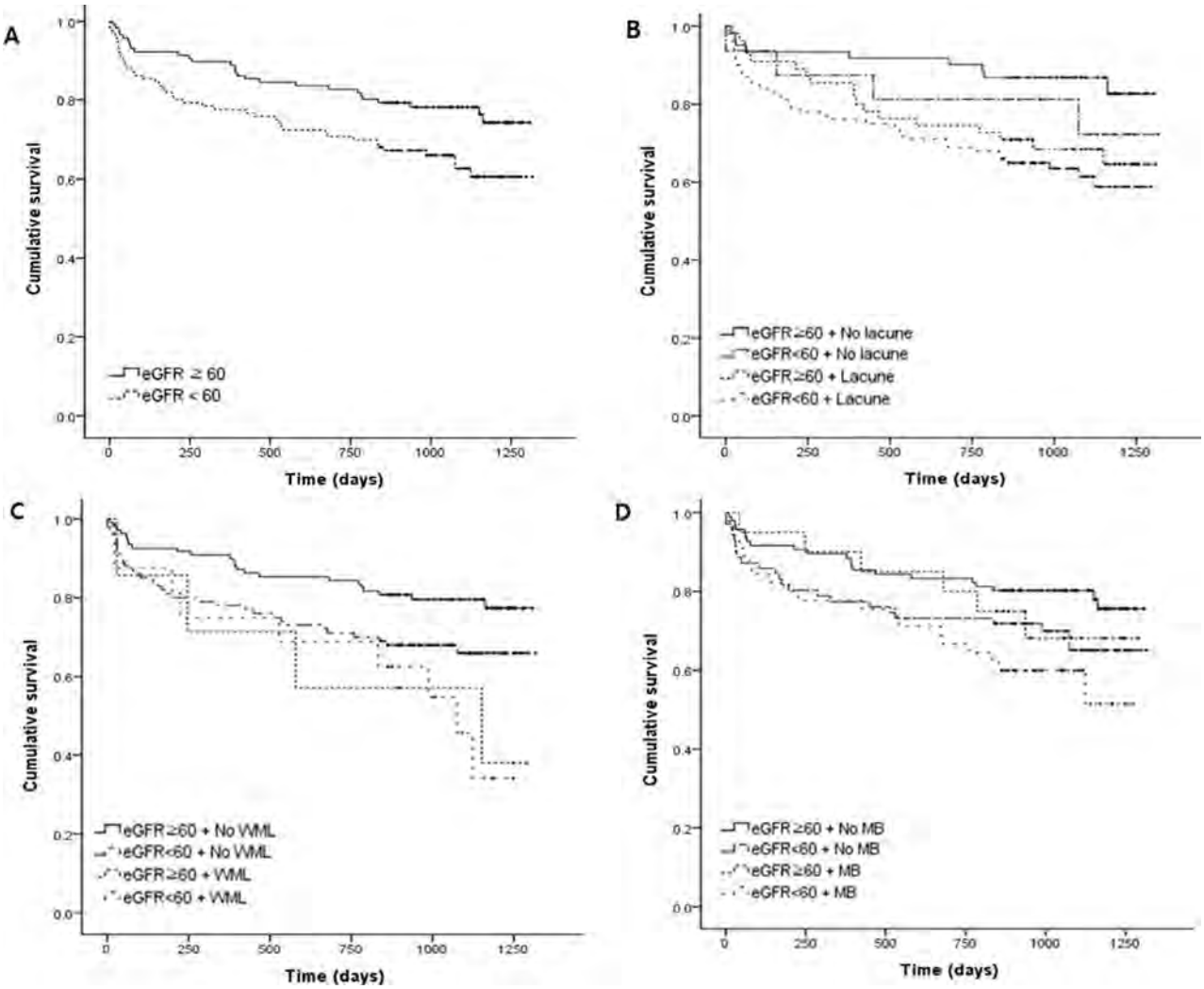

Figure 1. *Mortality rate according to eGFR, type of cerebral small-vessel disease, and presence of chronic kidney disease. (A) The survival according to eGFR, (B) the survival according to eGFR and lacune infarction, (C) the survival accoridng to eGFR and WML, (D) the survival according to eGFR and MB. Abbreviations: eGFR, estimated glomerular filtration rate; MB, microbleed; WML, white matter lesion.*

related to survival. Patients with both low eGFR and lacunar infarction showed lower survival than patients with lacunar infarction or low eGFR alone, whereas patients with high eGFR and no lacunar infarction showed the highest survival ($P < .001$) (Fig 1, B). Similarly, patients with both low eGFR and WML showed lower survival than patients with WML or low eGFR alone, whereas patients with high eGFR and no WML showed the highest survival ($P < .001$) (Fig 1, C). Additionally, patients with both low eGFR and microbleed showed lower survival than patients with microbleed or low eGFR alone, whereas patients with high eGFR and no microbleed showed the highest survival ($P = .012$) (Fig 1, D).

Among the risk factors, age, diabetes, eGFR, ABI, and the presence of each type of SVD were related to mortality (Table 4). After adjusting for age and eGFR, which were highly related to SVD, the presence of WML was the only factor related to mortality (OR, 2.9; 95% CI, 1.1-7.7; $P = .035$) (Table 4).

Discussion

In our study, we found that patients with SVD, including silent lacunar infarction, WML, and microbleed, had lower eGFR than patients without such lesions. In addition, patients with lower eGFR and each type of SVD had higher mortality than patients with higher eGFR and each type of SVD after acute ischemic stroke.

The brain and kidneys have similarly structured vascular beds. The juxtamedullary afferent arterioles in the kidneys and the perforating arteries in the brain are both exposed to high-volume blood flow[17] and perfuse vital nephrons and brainstem structures, respectively. Furthermore, microalbuminuria is associated with both cerebrovascular disease and kidney damage, and is used as an early marker of "strain vessel" damage caused by high vascular pressure.[4] Cerebral SVD, including lacunar infarction, WML, and microbleed, primarily affects the small arteries, arterioles, venules, and capillaries of the

Table 4. *Univariate and multivariate analyses of the factors related to cardiovascular mortality*

Factors	Univariate analysis			Multivariate analysis		
	Death (n = 69)	Survival (n = 165)	*P* value	OR	95% CI	*P* value
Age	77.1 ± 9.6	71.6 ± 9.9	<.001	—	—	—
Sex, male	41 (59)	103 (62)	.667	—	—	—
Hypertension	13 (19)	43 (26)	.238	—	—	—
Diabetes	38 (55)	111 (67)	.077	.820	.400-1.683	.589
Previous stroke	17 (24)	38 (23)	.791	—	—	—
Coronary heart disease	12 (17)	22 (13)	.422	—	—	—
Atrial fibrillation	21 (30)	34 (21)	.106	—	—	—
eGFR (<60 mL/min/1.73 m^2)	42 (61)	27 (39)	.031	—	—	—
EF on EchoCG (%)	54.1 ± 13.7	58.3 ± 7.9	.022	.973	.940-1.007	.120
Pulse wave velocity (cm/s)	2343.0 ± 856.4	2164.6 ± 721.2	.149	—	—	—
Ankle–brachial index	1.03 ± .17	1.10 ± .14	.005	.122	.012-1.232	.074
Lacunar infarction	56 (81)	99 (60)	.002	2.058	.853-4.967	.108
White matter lesion (Fazekas grades 2-3)	13 (19)	11 (7)	.005	2.876	1.078-7.670	.035
Presence of microbleeds	25 (36)	40 (24)	.062	1.044	.478-2.277	.914

Abbreviations: CI, confidential interval; EchoCG, echocardiography; EF, ejection fraction; eGFR, estimated glomerular filtration rate; OR, odds ratio; SVD, small-vessel disease.

For the analysis of survival, patients who died of causes other than cardiovascular disease were excluded.

Among the relating factors in the univariate analysis, age and kidney function were excluded for the multiple logistic regression analysis to avoid a confounding effect with SVD.

Values are given as n (percentage).

subcortical structures of the brain.[18] There have been several studies demonstrating the associations between cerebral SVD, CKD, and microalbuminuria.

Previous studies have shown that nitric oxide level is decreased in patients with CKD, which contributes to progressive renal failure.[19] Nitric oxide is also a key player in regulating blood flow in the brain and delivering metabolic substrates.[20] Hassan et al demonstrated that the level of NO_x, an inactive metabolite of nitric oxide, was lower in patients with SVD.[21] Therefore, decreased nitric oxide level may play an important role in both renal and brain dysfunctions. However, additional molecular biology studies are needed to confirm the association between CKD and SVD.

There have been many studies to evaluate the relationship between CKD and each type of SVD. The Northern Manhattan Study showed that patients with CKD demonstrated an increased volume of WMH.[8] In the same study, Khatri et al found that each 1-mg/dL increase in serum creatinine was positively associated with the volume of WMH. In another study, Wada et al reported that patients with lower eGFR tended to have more lacunar infarctions and higher grades of WML. Wada et al also found that patients with CKD had a 1.9 times greater chance of lacunar infarction and a 1.5 times greater chance of WML compared with controls.[9]

The presence of microbleed has also been shown to be related to kidney function. In 1 study, lower eGFR was associated with a 3 times greater risk of microbleed.[12] In other studies, eGFR was independently related to the presence of microbleed, age, sex, and blood pressure.[22] Moreover, in patients with recent intracerebral hemorrhage, the presence and the number of microbleeds were related to CKD.[23]

In the present study, we found that the presence of each type of SVD gradually increased according to the presence and stage of CKD. Our results agree with those of previous studies showing that the severity of CKD was related to the presence of SVD. However, we found that all 3 types of SVD were related to severity of CKD in a cohort of acute ischemic stroke survivors.

We also found poor survival in patients with impaired renal function and SVD during the 3 years following acute ischemic stroke. Oksala et al demonstrated that the survival curves for eGFR and WML were almost superimposable, and suggested that the pathogeneses of SVD leading to CKD and WML were similar. However, Oksala et al also showed that patients with severe WML had similar survival as patients with good and poor renal functions; in other words, severe WML was associated with poor survival independent of renal function.[24] This finding suggests that WML may be a potent predictor of mortality independent of eGFR.

In addition, we found that WML was the most relevant factor among the 3 types of SVD with regard to 3-year survival according to multifactorial analysis. To our knowledge, there has been no study to evaluate which type of SVD is most significantly related to survival in patients with CKD. Although it is unclear why WML is a more significant risk factor than lacunar infarction and microbleed, some possible reasons are as follows: The cutoff

value for the presence of lacunar infarction or microbleed that correlates with mortality cannot be easily determined. Therefore, in the present study, the presence of lacunar infarction or microbleed was determined using a validated scoring method based on the burden of SVD.[16] Using those criteria, the presence of SVD pathology was defined by 1 or more lesions. As a result, more than two thirds of the patients (67.7%) in our cohort had silent lacunar infarction. However, silent lacunar infarction is often found in healthy elderly individuals without cardiovascular risk factors.[25] Moreover, in a previous study, first-ever lacunar stroke was associated with low stroke recurrence and mortality.[26] In other words, isolated or few silent lacunar infarctions cannot be a strong risk factor for long-term mortality. On the other hand, microbleed is largely known to be related to increased mortality. However, the relationship of microbleed with mortality has been reported to be dose dependent.[27] In that study, presence of only 1 microbleed showed no increased risk of mortality, whereas presence of more than 1 microbleed showed a 6-fold risk of stroke-related death compared with having no microbleed.[27] In another study, the presence of 3 or more microbleeds was associated with increased risk of mortality.[28] However, a small number of microbleeds can be observed after traumatic brain injury[29] and in healthy elderly individuals.[30] Therefore, similar to lacunar infarction, isolated or few microbleeds cannot be a strong risk factor for long-term mortality. In the current study, the presence of WML was defined as Fazekas grade 3 in periventricular WMH or Fazekas grades 2-3 in deep WMH.[16] To compare the definitions of the presence of lacunar infarction or microbleed, patients with more severe WML were differentiated. As a result, WML was the most relevant factor among the 3 types of SVD with regard to 3-year survival.

A limitation of our study is its retrospective, single-center design. A prospective study involving a larger cohort and additional studies regarding the molecular and genetic mechanisms of vascular disease are required to elucidate the cerebrorenal connection found in the present study.

Conclusions

Our study showed that low eGFR is a clinical marker and independent risk factor for cerebral SVD, such as lacunar infarction, WML, and microbleed. Furthermore, our data demonstrated that the severity of renal dysfunction was closely associated with the severity of SVD in acute ischemic stroke survivors. In addition, both renal impairment and the presence of SVD were predictors of poor poststroke survival.

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