Age-Specific Associations of Renal Impairment and Cerebral Small Vessel Disease Burden in Chinese with Ischaemic Stroke

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Background: Recent studies in Caucasians with transient ischaemic attack or ischaemic stroke have demonstrated significant age-specific associations between cerebral small vessel disease (SVD) burden on magnetic resonance imaging and renal impairment. We aimed to validate these findings in a large cohort of Chinese with ischaemic stroke. *Methods:* In 959 Chinese with ischaemic stroke who received a brain magnetic resonance imaging at the University of Hong Kong, we determined the age-specific associations of renal impairment (glomerular filtration rate < 60 mL/min/1.73 m^2) with neuroimaging markers of SVD as well as with the SVD score. *Results:* Although renal impairment was associated with the SVD score in univariate analysis in all patients (odds ratio 1.61, 95% confidence interval 1.24-2.09, $P < .0001$), these associations were attenuated after adjusting for age and sex ($P = .38$). Similar findings were noted in patients with ischaemic stroke due to SVD and non-SVD subtypes. However, in 222 of 959 patients aged <60, renal impairment was independently associated with an increasing microbleed (adjusted odds ratio 6.82, 2.26-20.59), subcortical (4.97, 1.62-15.24) periventricular white matter hyperintensity (3.96, 1.08-14.51) and global SVD burden (3.41, 1.16-10.04; all $P < .05$) even after adjusting for age, sex, and vascular risk factors. Nevertheless, there were no associations between renal impairment and individual neuroimaging markers of SVD nor with the SVD score in patients aged ≥60 after adjusting for age and sex (all $P > .05$). *Conclusions:* In Chinese with ischaemic stroke, renal impairment was independently associated with microbleed, white matter hyperintensity and global SVD burden in individuals aged <60, but not in those aged ≥60, suggesting that there may be shared susceptibilities to premature systemic disease.

Key Words: Cerebral small vessel disease—Chronic kidney disease—Magnetic—Resonance imaging—Renal impairment—Stroke

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Introduction

Renal impairment is associated with an increased risk of stroke,[1] the associations of which appear to be particularly strong amongst Asian populations.[2] As the microvasculature of the brain and the kidneys are similar anatomically and functionally,[3] and hence may be equally susceptible to vascular injury, there has been considerable interest in determining the relationships between renal impairment and cerebral small vessel disease (SVD).

Previous meta-analyses have revealed that amongst patients without stroke, renal impairment is associated with SVD on neuroimaging, as represented by presence of silent brain infarcts or white matter hyperintensity (WMH).[4] In neurologically healthy adults, renal impairment has also been associated with cerebral microbleed presence and burden.[5] In patients with ischaemic stroke, however, results have been conflicting where an association between renal impairment and neuroimaging markers of cererbral SVD or lacunar stroke subtypes have only been noted in some studies.[4,6-9]

Indeed, recent findings from a population-based study of Caucasians with transient ischaemic attack (TIA) and ischaemic stroke have revealed that the associations between renal impairment and SVD burden on magnetic resonance imaging (MRI) may be age-specific.[10] In this study, renal impairment was associated with SVD burden, but only in individuals aged <60 after adjusting for potential shared risk factors such as hypertension, suggesting that factors leading to premature susceptibility to a multisystem disease may be present.[10]

However, ethnic differences in underlying prevalence and burden of SVD is known to exist. While Chinese with ischaemic stroke have a higher burden of cerebral microbleeds, lacunes and overall SVD burden compared with Caucasians with TIA or ischaemic stroke,[11] the burden of enlarged perivascular spaces (PVSs) in Chinese appears to be lower.[12] We therefore aimed to determine and validate the age-specific associations of renal impairment and cerebral SVD burden in a large cohort of Chinese with ischaemic stroke.

Materials and Methods

We prospectively studied 1076 predominantly Chinese with a diagnosis of acute ischemic stroke who received a MRI scan incorporating a haemosiderin-sensitive sequence (susceptibility weighted imaging) at The University of Hong Kong (HKU) MRI Unit during March 1, 2008, to September 30, 2014.

All patients gave written informed consent, or assent was obtained from relatives of patients who were unable to provide consent. The study was approved by the local research ethics committee (Institutional Review Board of the University of Hong Kong).

We collected demographic data, atherosclerotic risk factors and details of hospitalisation of index event during face-to-face interview and cross-referenced these with primary care and hospital records. Blood tests for renal function were taken upon admission for ischaemic stroke and renal impairment was defined as a glomerular filtration rate (GFR) of <60 /mL/min/1.73 m^2 according to the Chronic Kidney Disease Epidemiology Collaboration equation for the Asian population.[13]

All patients were scanned using a 3-T MRI scanner Achieva (Philips Healthcare). Details of scan parameters can be found in the Supplementary Table. A senior neuroradiologist supervised the interpretation of the MR images. Microbleeds were defined as rounded, hypodense foci up to 10 mm in size and were differentiated from microbleed mimics.[14] The location and number of microbleeds were scored according to the Microbleed Anatomical Rating Scale,[15] and microbleed-burden graded as absent, 1, 2-4, and ≥5. The severity of white matter disease was determined according to the Fazekas scale.[16] Subcortical WMH was graded as 0 (absent), 1 (puntate foci), 2 (beginning confluence of foci), and 3 (large confluent areas); while periventricular WMH was graded as 0 (no WMH except for small triangular foci surrounding the frontal horns), 1 (periventricular hyperintensity surrounding the anterior and posterior horns ± discrete WMHs), 2 (extensive patchy WMHs and their early confluent stages), and 3 (confluent, completely surrounding lateral ventricles). MRI-visible enlarged basal ganglia (BG) PVSs were defined as small (<3 mm) punctate hyperintensities on T2 images based on a previously validated scale.[17] Burden of enlarged PVSs were stratified into 3 groups: <11, 11-20 and >20. Lacunes were defined as rounded or ovoid lesions, >3 and <20 mm in diameter, in the basal ganglia, internal capsule, thalamus, centrum semiovale, cerebellum, or brainstem, of cerebrospinal fluid signal density on T2 and FLAIR and no increased signal on diffusion-weighted imaging.[18]

The total SVD score was calculated for all patients where 1 point is allocated to each of the following: (1) presence of lacunes, (2) presence of microbleeds, (3) moderate-severe (>10) BG-PVSs, and (4) severe periventricular and/or moderate-severe deep WMH.[19]

The intrarater κ for 50 randomly selected scans was: lacunes −.82, microbleed burden (0, 1, 2-4, and ≥5) −.81, periventricular WMH burden (Fazekas grade 0, 1, 2, 3) −.69; subcortical WMH burden (Fazekas grade 0, 1, 2, 3) −.71; BG-PVS burden (<11, 11-20, >20) −.86.

Statistical Analysis

We compared the clinical and imaging characteristics of patients with and without renal impairment using *t* test for continuous variables and χ^2 test for categorical variables. Using ordinal regression, we determined the rela-

tionships of renal impairment with burden of microbleeds (0, 1, 2-4, ≥5), subcortical and periventricular WMH (Fazekas grade 0, 1, 2, 3) and enlarged BG-PVSs (<11, 11-20, ≥20) as well as the total SVD score (0, 1, 2, 3, 4), in a univariate model (model 1), model adjusted for age and sex (model 2) and model adjusted for age, sex, and vascular risk factors (hypertension, hyperlipidaemia, diabetes, atrial fibrillation, smoking history, model 3). We also used binary logistic regression to determine the relationships of renal impairment with presence of lacunes and cerebral microbleeds of strictly deep, strictly lobar and of mixed location, versus no lacunes or microbleeds as reference, in a univariate model and models described above. We stratified our analysis according to ischaemic stroke subtype (SVD vs non-SVD) as classified by the Trial of Org 10172 in Acute Stroke Treatment criteria,[20] and also by age (<60 vs ≥60).

All analyses were done with SPSS version 22.

Results

A total of 1076 patients with ischaemic stroke received a MRI stroke protocol at the HKU MRI Unit during the period March 1, 2008 to September 30, 2014. After excluding 117 patients who had incomplete imaging data or did not have renal function measured prior to MRI scan, 959 patients were included in the final analysis. Clinical and neuroimaging characteristics of the study population are shown in Table 1. The mean age of the study population

Table 1. *Clinical and imaging characteristics of the study population*

	All patients N = 959	Renal impairment N = 243	Normal renal function N = 716	*P*
Baseline clinical characteristics				
Mean (SD) age (years)	69 (12)	76 (9)	67 (12)	<.0001
Males (%)	576 (60.1)	149 (61.3)	427 (59.6)	.65
Hypertension (%)	628 (65.5)	194 (79.8)	434 (60.6)	<.0001
Diabetes (%)	270 (28.2)	95 (39.1)	175 (24.4)	<.0001
Hyperlipidaemia (%)	245 (25.5)	72 (29.6)	173 (24.2)	.11
Ever-smokers (%)	287 (29.9)	67 (27.6)	220 (30.7)	.37
Atrial fibrillation (%)	124 (12.9)	54 (22.2)	70 (9.8)	<.0001
TOAST classification				.007
Small vessel disease (%)	405 (42.2)	91 (37.4)	314 (43.9)	.084
Large artery atherosclerosis (%)	332 (34.6)	79 (32.5)	253 (35.3)	.44
Cardio-embolic (%)	114 (11.9)	44 (18.1)	70 (9.8)	.001
Undetermined (%)	42 (4.4)	9 (3.7)	33 (4.6)	.72
Others (%)	66 (6.9)	20 (8.2)	46 (6.4)	.38
Imaging characteristics				
N with DWI lesion (%)	750 (78.2)	183 (75.3)	567 (79.2)	.21
N with microbleeds (%)	434 (45.3)	124 (51.0)	310 (43.3)	.037
N with ≥5 microbleeds (%)	115 (12.0)	41 (16.9)	74 (10.3)	.008
N with strictly deep microbleeds (%)	60 (6.3)	11 (4.5)	49 (6.8)	.22
N with strictly lobar microbleeds (%)	153 (16.0)	44 (18.1)	109 (15.2)	.31
N with strictly infratentorial microbleeds (%)	37 (3.9)	4 (1.6)	33 (4.6)	.051
N with microbleeds of mixed location (%)	184 (19.2)	65 (26.7)	119 (16.6)	.001
N with periventricular WMH				<.0001
Grade 1 (%)	211 (22.0)	67 (27.6)	144 (20.1)	
Grade 2 (%)	74 (7.7)	32 (13.2)	42 (5.9)	
Grade 3 (%)	30 (3.1)	11 (4.5)	19 (2.7)	
N with subcortical WMH				.069
Grade 1 (%)	468 (48.8)	105 (43.2)	363 (50.7)	
Grade 2 (%)	274 (28.6)	73 (30.0)	201 (28.1)	
Grade 3 (%)	152 (15.8)	50 (20.6)	102 (14.2)	
N with enlarged basal ganglia PVSs				<.0001
<10 (%)	650 (67.8)	143 (58.8)	507 (70.8)	
10-20 (%)	241 (25.1)	70 (28.8)	171 (23.9)	
>20 (%)	68 (7.1)	30 (12.3)	38 (5.3)	
N with lacunes (%)	427 (44.5)	109 (44.9)	318 (44.4)	.94
Mean total SVD score	1.67 ± 1.15	1.90 ± 1.19	1.60 ± 1.12	<.0001

Abbreviations: DWI, diffusion weighted imaging; PVS, perivascular spaces; SVD, small vessel disease; WMH, white matter hyperintensity.

Table 2. *Relationships of renal impairment with individual neuroimaging markers and global burden of small vessel disease*

	Model 1 OR (95% CI)	*P*	Model 2 OR (95% CI)	*P*	Model 3 OR (95% CI)	*P*
Microbleed burden*	1.51 (1.15-1.99)	.003	1.31 (.98-1.75)	.073	1.30 (.96-1.75)	.087
Strictly deep microbleeds†	.65 (.33-1.26)	.20	.65 (.32-1.32)	.24	.67 (.33-1.38)	.28
Strictly lobar microbleeds†	1.23 (.84-1.81)	.29	1.22 (.81-1.84)	.35	1.22 (.80-1.87)	.35
Microbleeds of mixed location†	1.83 (1.30-2.59)	.001	1.47 (1.01-2.14)	.042	1.46 (1.00-2.14)	.050
Subcortical WMH burden*	1.41 (1.07-1.84)	.013	1.09 (.81-1.45)	.58	1.11 (.83-1.49)	.49
Periventricular WMH burden*	2.09 (1.57-2.80)	<.0001	1.27 (.92-1.73)	.14	1.30 (.94-1.75)	.087
Enlarged BG-PVS burden*	1.78 (1.33-2.40)	<.0001	1.00 (.72-1.38)	1.00	.99 (.71-1.38)	.96
Presence of lacunes†	1.02 (.76-1.36)	.91	1.06 (.77-1.46)	.72	1.04 (.75-1.43)	.83
Total SVD score*	1.61 (1.24-2.09)	<.0001	1.13 (.86-1.50)	.38	1.12 (.84-1.49)	.44

Model 1: unadjusted model; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, hypertension, hyperlipidaemia, diabetes mellitus, ever-smoking, and atrial fibrillation.

Abbreviations: BG, basal ganglia; CI, confidence interval; OR, odds ratio; PVS, perivascular space; SVD, small vessel disease; WMH, white matter hyperintensity.

*Ordinal regression.

†Binary logistic regression.

was 69 (12) years and 60% were men. Sixty six percent had a past history of hypertension. The mean GFR was 78 (24) mL/min/1.73 m^2. Patients with renal impairment were older [76 (9) vs 67 (12) years] and were more likely to have underlying hypertension (79.8% vs 60.6%), diabetes (39.1% vs 24.4%), and atrial fibrillation (22.2% vs 9.8%; all $P < .0001$).

There were no differences in proportion of patients with a diffusion-weighted imaging-positive lesion in patients with or without renal impairment ($P = .21$). However, patients with renal impairment were associated with a greater prevalence (51.0% vs 43.3%, $P = .037$) and burden (16.9% vs 10.3% with ≥5, $P = .008$) of microbleeds. There were no differences in prevalence of strictly deep or strictly lobar microbleeds, but patients with renal impairment were more likely to have microbleeds of mixed location (26.7% vs 16.6%, $P = .001$). Patients with renal impairment were also associated with a greater burden of periventricular WMH ($P < .0001$) as well as burden of enlarged BG-PVSs (12.3% vs 5.3% with >20, $P < .001$), but no differences in prevalence of subcortical WMH ($P = .069$) nor lacunes ($P = .94$) were noted in patients with or without renal impairment. Consequently, the mean total SVD score was greater in patients with renal impairment compared with patients without renal impairment [1.90 (1.19) vs 1.60 (1.12), $P < .0001$].

In univariate analysis of all patients, renal impairment was significantly associated with burden of microbleeds, WMH (subcortical and periventricular) and enlarged BG-PVSs (all $P < .05$, Table 2). However, all associations of renal impairment with SVD burden were attenuated after adjusting for age and sex (Table 2).

When patients were stratified according to the Trial of Org 10172 in Acute Stroke Treatment classification (Table 3), there were no significant associations between renal impairment and SVD burden in patients with ischaemic stroke due to SVD (n = 405/959) and non-SVD subtypes (n = 554/959), after adjusting for age and sex (all $P > .05$, Table 3). However, in patients with stroke due to non-SVD, renal impairment was associated with a reduced risk of strictly deep microbleeds (age and sex adjusted odds ratio [OR] .33, 95% confidence interval .12-.89, $P = .029$), but increased risk of microbleeds of mixed location (OR 1.94, 1.17-3.20, $P = .010$, Table 3).

In an analysis stratified by age, strong univariate associations were noted between renal impairment and burden of microbleeds, subcortical and periventricular WMH, and total SVD score in the 222 of 959 patients aged <60 (all $P < .05$, Table 4). These associations remained after adjusting for age and sex and also after adjusting for other vascular risk factors (Table 4). Patients with renal impairment were independently associated with an increasing microbleed (multivariate adjusted OR 6.82, 2.26-20.59, $P = .001$), subcortical WMH (4.97, 1.62-15.24, $P = .005$), and periventricular WMH burden (3.96, 1.08-14.51, $P = .038$) as well as an increasing total SVD score (3.41, 1.16-10.04, $P = .026$). No significant associations between renal impairment and enlarged BG-PVS burden nor presence of lacunes were noted. However, in patients aged ≥60, no relationships between renal impairment and an increasing burden of individual neuroimaging markers of SVD nor global SVD burden was noted after adjusting for age and sex (total SVD score: 1.03, .77-1.38, $P = .85$; $P_{het} = .036$; Table 5).

Discussion

In a large cohort of Chinese patients with ischaemic stroke, we noted that although renal impairment was strongly associated with a range of neuroimaging markers of SVD and an increasing global burden of SVD, these associations were all attenuated after adjusting for age and sex. The relationships between renal impairment and SVD burden however, remained in individuals aged <60,

Table 3. *Relationships of renal impairment with individual neuroimaging markers and global burden of small vessel disease, stratified by stroke subtype according to the TOAST classification*

	Small vessel disease (n = 405)				Non-small vessel disease (n = 554)			
	Model 1 OR (95% CI)	*P*	Model 2 OR (95% CI)	*P*	Model 1 OR (95% CI)	*P*	Model 2 OR (95% CI)	*P*
Microbleed burden*	1.60 (1.04-2.47)	.033	1.34 (.85-2.12)	.20	1.48 (1.04-2.11)	.029	1.28 (.87-1.88)	.20
Strictly deep microbleeds†	1.63 (.60-4.43)	.33	2.14 (.73-6.27)	.17	.35 (.13-.90)	.029	.33 (.12-.89)	.029
Strictly lobar microbleeds†	1.75 (.98-3.12)	.059	1.68 (.91-3.10)	.10	.96 (.57-1.61)	.88	.96 (.54-1.68)	.88
Microbleeds of mixed location†	1.35 (.79-2.31)	.28	1.03 (.58-1.83)	.92	2.43 (1.54-3.85)	<.0001	1.94 (1.17-3.20)	.010
Subcortical WMH burden*	1.17 (.76-1.80)	.47	.93 (.59-1.47)	.76	1.62 (1.14-2.30)	.007	1.15 (.78-1.68)	.48
Periventricular WMH burden*	2.48 (1.58-3.39)	<.0001	1.59 (.99-2.57)	.057	1.95 (1.33-2.86)	.001	1.05 (.69-1.61)	.80
Enlarged BG-PVS burden*	1.82 (1.15-2.89)	.011	.98 (.59-1.63)	.95	1.81 (1.23-2.66)	.003	1.01 (.66-1.54)	.96
Presence of lacunes†	1.41 (.88-2.26)	.15	1.36 (.83-2.24)	.23	.86 (.59-1.27)	.46	.89 (.58-1.35)	.58
Total SVD score*	1.98 (1.30-3.02)	.001	1.36 (.88-2.12)	.17	1.46 (1.04-2.04)	.027	1.00 (.69-1.43)	.99

Model 1: unadjusted model; Model 2: adjusted for age and sex.

Abbreviations: BG, basal ganglia; CI, confidence interval; OR, odds ratio; PVS, perivascular space; SVD, small vessel disease; TOAST, trial of org 10172 in acute stroke treatment.

*Ordinal regression.

†Binary logistic regression.

but not in those aged ≥60, and renal impairment was significantly associated with microbleed, subcortical, and periventricular WMH burden as well as the total SVD score, independent of other vascular risk factors in younger individuals. The relationships between renal impairment and SVD burden was however, not significantly different in patients with ischaemic stroke classified as small vessel occlusion or nonsmall vessel occlusion.

Table 4. *Relationships of renal impairment with individual neuroimaging markers and global burden of small vessel disease in patients age <60*

	Model 1 OR (95% CI)	*P*	Model 2 OR (95% CI)	*P*	Model 3 OR (95% CI)	*P*
Microbleed burden*	6.83 (2.33-20.07)	.0005	6.70 (2.27-19.73)	.001	6.82 (2.26-20.59)	.001
Strictly deep microbleeds†	1.03 (.13-8.48)	.98	1.07 (.13-8.85)	.95	.79 (.09-6.79)	.83
Strictly lobar microbleeds†	3.54 (1.00-12.58)	.051	3.57 (1.00-12.78)	.050	3.55 (.95-13.30)	.060
Microbleeds of mixed location†	3.54 (1.00-12.58)	.051	3.44 (.95-12.50)	.060	3.75 (.94-14.95)	.061
Subcortical WMH burden*	4.72 (1.60-13.96)	.005	4.43 (1.49-13.16)	.007	4.97 (1.62-15.24)	.005
Periventricular WMH burden*	4.20 (1.21-14.64)	.024	4.18 (1.20-14.66)	.025	3.96 (1.08-14.51)	.038
Enlarged BG-PVS burden*	.61 (.08-4.95)	.64	.58 (.07-4.70)	.61	.59 (.07-5.01)	.63
Presence of lacunes†	1.87 (.57-6.07)	.30	1.84 (.56-5.99)	.31	1.61 (.48-5.45)	.44
Total SVD score*	3.72 (1.29-10.74)	.015	3.50 (1.21-10.10)	.021	3.41 (1.16-10.04)	.026

Model 1: unadjusted model; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, hypertension, hyperlipidaemia, diabetes mellitus, ever-smoking, and atrial fibrillation.

Abbreviations: BG, basal ganglia; CI, confidence interval; OR, odds ratio; PVS, perivascular space; SVD, small vessel disease; WMH, white matter hyperintensity.

*Ordinal regression.

†Binary logistic regression.

Table 5. *Relationships of renal impairment with individual neuroimaging markers and global burden of small vessel disease, in patients aged ≥60*

	Model 1 OR (95% CI)	*P*	Model 2 OR (95% CI)	*P*
Microbleed burden*	1.26 (.94-1.69)	.12	1.16 (.86-1.58)	.33
Strictly deep microbleeds†	.67 (.32-1.39)	.28	.58 (.27-1.23)	.16
Strictly lobar microbleeds†	1.07 (.71-1.62)	.76	1.12 (.73-1.73)	.61
Microbleeds of mixed location†	1.59 (1.10-2.31)	.013	1.39 (.94-2.04)	.098
Subcortical WMH burden*	1.13 (.84-1.50)	.43	1.01 (.75-1.37)	.93
Periventricular WMH burden*	1.56 (1.15-2.11)	.004	1.19 (.87-1.64)	.28
Enlarged BG-PVS burden*	1.42 (1.04-1.93)	.027	1.02 (.73-1.41)	.93
Presence of lacunes†	.96 (.71-1.32)	.82	1.01 (.73-1.40)	.96
Total SVD score*	1.25 (.95-1.65)	.12	1.03 (.77-1.38)	.85

Model 1: unadjusted model; Model 2: adjusted for age and sex.

Abbreviations: BG, basal ganglia; CI, confidence interval; OR, odds ratio; PVS, perivascular space; SVD, small vessel disease; WMH, white matter hyperintensity.

*Ordinal regression.

†Binary logistic regression.

Our findings are consistent with those from a cohort consisting predominantly of Caucasians with TIA and minor ischaemic stroke.[10] Despite underlying differences in prevalence and burden of neuroimaging markers of SVD in both cohorts,[10-12] the associations between an increasing SVD score in individuals aged <60 were similar after adjusting for age, sex, and vascular risk factors (Oxford Vascular Study: OR 3.11, 1.21-7.98; HKU: 3.41, 1.16-10.04). Associations between an increasing SVD score with renal impairment were similarly attenuated at older ages in both cohorts.[12] Our findings therefore suggest that the observations noted by Liu et al[10] may be generalisable in the Chinese population.

Indeed, our results and those from Liu et al[10] are consistent with those from a recent rigously conducted systematic review and meta-analysis on the associations between cerebral SVD and renal function.[4] Although no specific associations between renal impairment and lacunar stroke was noted in all studies, this meta-analysis did identify a striking four-fold increase in risk of renal impairment in young indviduals (age 15-49) with lacunar stroke, compared with other stroke subtypes.[4,21] In contrast, in studies of patients with mean age of ≥70, no significant associations between renal impairment and stroke subtypes were noted.[4] Similar age-specific associations between renal impairment and WMH were identified in the nonstroke populations, where the associations between renal impairment and WMH was greater in cohorts of average age 50-60 (OR 3.19, 1.69-6.01) compared with those of average age >70 (1.53, 1.31-1.79).[4]

The reasons underlying these consistent age-specific associations between renal impairment and SVD, however, remains uncertain. Indeed, our findings suggest that certain "at-risk" individuals may possibly have an underlying genetic susceptibility, leading to a premature multisystem vasculopathic process affecting the small vessels. Recent multiancestory genome-wide association studies have, for example, identified a number of new loci associated with stroke due to SVD or related pathologies such as WMH on MRI.[22] Individuals with these (or yet-to-be-identified) genetic polymorphisms may well be susceptible to a multiorgan vasculopathic process affecting both renal function and the cerebral small vessels.

Other than validating findings from other cohorts, our findings also reinforces the importance of regular monitoring of renal function in young individuals with cerebral SVD. Similarly, a high suspicion of concomitant cerebral SVD should be present in young patients with renal impairment. Vascular risk factors, in particular blood pressure, should be treated aggressively in these individuals to prevent deterioration of their renal function and/or underlying cerebral SVD.

Our study is however, limited by the following aspects. First, we based the definition of renal impairment on a serum-creatinine-derived equation,[13] from a single renal function measurement taken upon hospitalisation after ischaemic stroke. Such a measurement may be affected by acute inflammation or dehydration secondary to stroke and may potentially overdiagnose renal impairment. We did not base the diagnosis of renal impairment on premorbid renal function,[10] which may have been a more accurate representative of the patients' renal function. Second, unlike other studies, we did not determine the relationships of SVD with proteinuria, another widely used surrogate marker to reflect renal function. We also did not measure cystatin C, which may be a more sensitive marker of renal impairment in individuals who have a creatinine-based GFR between 45 and 59 mL/min/1.73 m^2. Third, in this cross-sectional study, we were not able to determine whether changes in renal function with time corresponded with changes in the burden of SVD. Fourth, although we adjusted for known confounding factors, residual confounding could not be excluded, and unlike other studies,[10] we did not adjust for long-term premorbid mean blood pressure.

In conclusion, in a large cohort of Chinese with ischaemic stroke, we noted that independent to age, sex, and vascular risk factors, cerebral SVD burden was significantly associated with renal impairment in patients aged <60, but these associations were attenuated in individuals of aged ≥60.

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Supplementary Materials

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