

# Imaging Pattern and Outcome of Stroke in Patients With Systemic Lupus Erythematosus: A Case-control Study

Lap Kiu Tsoi<sup>1</sup> , Chi Chiu Mok<sup>2</sup>, Bik Ling Man<sup>1</sup> , and Yat Pang Fu<sup>1</sup> 

**ABSTRACT.** *Objective.* To evaluate the outcome of stroke in patients with systemic lupus erythematosus (SLE).

*Methods.* Patients who fulfilled  $\geq 4$  American College of Rheumatology criteria for SLE and had a history of stroke from 1997 to 2017 were identified. The functional outcome of stroke [assessed by the modified Rankin Scale (mRS) at 90 days], mortality, stroke complications, and recurrence were retrospectively studied and compared with matched non-SLE patients with stroke.

*Results.* Forty SLE patients and 120 non-SLE patients with stroke (age at stroke  $44.7 \pm 13.7$  yrs, 87.5% women) were studied. Ischemic type of stroke (90% vs 63%,  $P = 0.001$ ) and extensive infarction (69.4% vs 18.7%,  $P < 0.001$ ) were more common in SLE than non-SLE patients. Border zone infarct and multiple infarcts on imaging were significantly more prevalent in SLE patients. Patients with SLE were more functionally dependent than controls at 90 days poststroke. Logistic regression showed that SLE was significantly associated with a poor stroke functional outcome independent of age, sex, past stroke, atherosclerotic risk factors, and the severity of stroke (OR 5.4, 95% CI 1.1–26.0,  $P = 0.035$ ). Stroke mortality at 30 days was nonsignificantly higher in SLE than non-SLE patients, but all-cause mortality (37.5% compared to 8.3%,  $P < 0.001$ ), recurrence of stroke (30% compared to 9.2%,  $P = 0.002$ ), and poststroke seizure (22.5% compared to 3.3%,  $P = 0.001$ ) were significantly more common in SLE patients after an observation of  $8.4 \pm 6.1$  years. SLE was independently associated with all-cause mortality and stroke recurrence over time.

*Conclusions.* Stroke in patients with SLE is associated with a poorer outcome than matched controls in terms of functional recovery, recurrence, and mortality.

*Key Indexing Terms:* atherosclerosis, cerebrovascular, complication, morbidity, systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disorder that predominantly affects younger women. Neuropsychiatric (NP) manifestations of SLE are heterogeneous and among the most prevalent manifestations of the disease<sup>1</sup>. Studies have reported 12–94% of patients with SLE had NP manifestations, which could be independent of serological and clinical disease activity in other systems<sup>2</sup>. Nineteen NP syndromes of SLE have been defined by the American College of Rheumatology (ACR), with standardized nomenclature and reporting criteria<sup>3</sup>. In our local Chinese patients with SLE, the most frequent NP manifestations are seizure disorder and cerebrovascular disease<sup>4</sup>.

Cerebrovascular accident (stroke) is uncommon in the younger population but carries substantial functional impairment to patients and economic burden to the society<sup>5</sup>. Patients with SLE are at 2- to 3-fold increased risk of developing all types

of stroke<sup>6,7</sup> compared to the general population and may require prolonged hospitalization, leading to higher cost of illness<sup>8</sup>.

Accelerated atherosclerosis due to increased prevalence of traditional Framingham risk factors and the immune-mediated processes related to the SLE activity is associated with increased stroke risk in patients with SLE<sup>9,10</sup>. Younger age, male sex, hyperlipidemia, smoking, hypertension (HTN), homocysteine level, and the use of steroids were reported to be risk factors for stroke in patients with SLE, while the use of hydroxychloroquine (HCQ) is protective<sup>9,10,11,12</sup>. Cohort studies have identified the antiphospholipid (aPL) antibodies as an additional risk factor for vascular events, including stroke, in SLE<sup>13,14</sup>.

Although the incidence and risk factors of stroke in patients with SLE have been well reported<sup>6,7,8</sup>, little is known about the imaging pattern of stroke, its functional recovery, and complications. Therefore, the objective of our current study was to evaluate the functional outcome of stroke and its long-term complications in a group of Chinese patients with SLE.

## MATERIALS AND METHODS

We conducted a single-center, matched cohort study to compare the outcomes of stroke in SLE and non-SLE patients who were admitted to our hospital over a 20-year period. The stroke pattern, short-term functional outcome of stroke at 90 days, 30-day mortality, stroke recurrence, and complications were evaluated.

*Study population.* Adult patients (age  $\geq 18$  yrs) who were admitted to our acute medical wards for stroke between years 1997 and 2017 were identified

<sup>1</sup>L.K. Tsoi, MB, MRCP, B.L. Man, MD, MRCP, Y.P. Fu, MB, FRCP, Division of Neurology, Department of Medicine, Tuen Mun Hospital;

<sup>2</sup>C.C. Mok, MD, FRCP, Division of Rheumatology, Department of Medicine, Tuen Mun Hospital, Hong Kong.

The authors declare no conflicts of interest.

Address correspondence to Dr. C.C. Mok, Department of Medicine, Tuen Mun Hospital, Hong Kong. Email: ccmok2005@yahoo.com.

Full Release Article. For details see Reprints and Permissions at jrheum.org.

Accepted for publication August 7, 2020.

from our hospital database using the International Classification of Diseases, 9th revision (ICD-9) codes for stroke (430–435). Exclusion criteria were (1) absence of imaging findings, (2) diagnosis of retinal artery occlusion, (3) diagnosis of cerebral venous thrombosis, and (4) history of rheumatic diseases other than SLE or hematological disorders (e.g., leukemia, protein C/S deficiency). Patients who had the ICD-9 code for SLE were first identified. In case the diagnosis of stroke was doubtful after medical record review in the SLE patients, they were excluded from analysis. Three age- and sex-matched non-SLE patients admitted in the same time period were randomly selected as controls from the remaining pool. Likewise, when the diagnosis of stroke was doubtful in a non-SLE control, another patient was randomly selected for replacement. Our study was approved by the Research and Ethics Committee of Tuen Mun Hospital (NTWC/CREC/17093).

**Data collection.** Demographic data and traditional risk factors for stroke such as HTN, diabetes mellitus (DM), hyperlipidemia, atrial fibrillation, previous stroke, use of antithrombotic medications, and history of chronic rheumatic heart disease or heart valve replacement surgery were collected. The severity of stroke within 24 hours of onset was assessed by the National Institute of Health Stroke Scale (NIHSS)<sup>15</sup>. An NIHSS score of  $\geq 6$  was defined as moderate/severe stroke. Dyslipidemia was defined by the atherogenic index of plasma (AIP), which was calculated by the logarithm of the serum triglyceride to high-density lipoprotein (HDL) cholesterol level<sup>16</sup>. An elevated AIP value  $> 0.21$  was regarded as high risk for vascular events<sup>17</sup>. Chronic kidney disease (CKD) was defined according to the National Kidney foundation criteria<sup>18</sup> when the calculated estimated glomerular filtration rate was  $< 60$  mL/min/1.73 m<sup>2</sup> for  $> 3$  months (i.e., stage 3a or below). All data were collected retrospectively by medical record review.

The type of clinical stroke was classified into ischemic (including minor stroke or transient ischemic attack) or hemorrhagic. Ischemic stroke was classified as involving the anterior or posterior circulation with reference to brain imaging (magnetic resonance imaging or computed tomography scan). The pattern of ischemic stroke was divided into several categories as follows: (1) no infarct changes, (2) small single cortical or subcortical lacunar infarct (size 2–15 mm), (3) border zone infarct from any of the major cerebral vessel (anterior cerebral, middle cerebral, or posterior cerebral artery), (4) multiple ( $\geq 2$ ) infarcts involving multiple ( $\geq 2$ ) major cerebral vessel territory or multiple ( $\geq 2$ ) subbranch artery within the same major cerebral vessel, and (5) large territorial infarct (1 single major cerebral vessel  $>$  two-thirds involvement of the vessel territory). Category 2 was determined by measuring the size of infarct on brain scan. To define categories 3 and 4, we referred to the description from previous radiological studies<sup>19,20</sup> for anterior circulation stroke, and the New England Medical Center Posterior Circulation Registry by Caplan, *et al*<sup>21</sup> for posterior circulation stroke. Categories 1 and 2 were regarded as having light vascular burden, while categories 3, 4, and 5 were regarded as heavy vascular burden (i.e., extensive ischemic stroke). In patients with hemorrhagic stroke, the location and etiology of hemorrhage were recorded.

The following additional data were obtained from SLE patients during stroke presentation: age of SLE diagnosis, time from SLE diagnosis to first stroke, SLE Disease Activity Index 2000 (SLEDAI-2K) score<sup>22</sup>, use of immunosuppressants [glucocorticoids (GC) and HCQ], renal involvement according to the ACR criteria<sup>23</sup>, and the presence of antiphospholipid syndrome (APS), which was defined according to the updated classification criteria in 2006<sup>24</sup>.

**Disease activity assessment of SLE.** Disease activity of SLE was assessed by the SLEDAI-2K, which is a global clinical index for the assessment of SLE disease activity in the preceding 10 days<sup>22</sup>. High SLE disease activity was arbitrarily defined when the SLEDAI-2K score was  $\geq 12$ .

**Assessment for functional recovery after stroke.** The modified Rankin Scale (mRS) measures the degree of disability or dependence in patients with stroke or other neurological diseases<sup>25</sup>. It consists of an ordinal scale ranging from 0 to 6. The mRS was used to assess for the functional outcome post-stroke in this study.

**Outcomes of interest.** The primary outcome of interest was the 90-day functional recovery after stroke (assessed by the mRS). The mRS was dichotomized into scores 0–2, which represented functional independence, and 3–6, which represented functional dependence. Secondary outcomes included all-cause 30-day and long-term mortality, stroke complications (epilepsy, need for long-term feeding tube insertion, aspiration pneumonia), need for neurosurgical intervention (such as craniectomy, craniotomy, Burr hole procedure, ventricular shunt insertion), and stroke recurrence.

**Statistical analyses.** Unless otherwise stated, values in this study were expressed as mean  $\pm$  SD. Continuous variables of 2 groups were compared by the Student *t*-test or Mann-Whitney U test (when data did not follow a normal distribution). Categorical variables were compared by the chi-square test. Missing data (mainly lipid and glucose data in around 10% of patients) were replaced by the group mean. Factors associated with a poor functional outcome at 90 days poststroke were studied by logistic regression. Survival analysis for all-cause mortality and stroke recurrence was performed by the Kaplan-Meier curve, with time 0 referred to as the time of stroke. The log-rank test was used to compare the survival between the 2 groups. Cox regression was used to evaluate the factors associated with all-cause mortality and stroke recurrence. The following covariates were put into the regression models: age, sex, smoking status, presence of DM, HTN, chronic kidney disease or atrial fibrillation, history of previous stroke, NIHSS score, dyslipidemia, history of previous of stroke of any types, stroke class (ischemic or hemorrhagic), and use of antithrombotic treatment. Statistical significance was defined as a *P* value of  $< 0.05$ , 2-tailed. All data were analyzed using the SPSS program (26.0 for Windows).

## RESULTS

**Clinical characteristics of the patients studied.** A total of 40 SLE and 120 age- and sex-matched non-SLE Chinese patients were studied (Table 1). Baseline demographic data were similar between the 2 groups, except for a higher proportion of SLE patients using antithrombotic therapy before the stroke episode. The median NIHSS score was significantly higher in SLE patients than controls (4.0 vs 2.0,  $P = 0.01$ ), and more SLE patients had moderate/severe stroke (NIHSS score  $\geq 6$ ; 27.5% vs 10.8%,  $P = 0.01$ ).

**Traditional atherosclerotic risk factors.** Patients with SLE had a significantly higher fasting serum triglyceride but lower serum HDL cholesterol and glucose levels than non-SLE controls (Table 1). The calculated AIP score was also significantly higher. Moderate/severe chronic renal impairment (CKD stage 3a or below) was more common in patients with SLE than controls.

**Stroke in SLE patients.** Twenty-five (65%) SLE stroke patients had renal involvement. The median SLEDAI-2K at onset of stroke was  $18.0 \pm 9.3$ . Nine (22.5%) and 25 (62.5%) patients, respectively, were using HCQ and GC before the current stroke. Sixteen (40%) patients had positive aPL antibodies: lupus anticoagulant (LAC;  $n = 3$ , 19%), moderate/high titers of IgG anticardiolipin antibodies (aCL;  $n = 8$ , 50%), and both ( $n = 5$ , 31%). Ten of these patients were anticoagulated before the stroke episodes were studied because of previous stroke or other indications. Five patients with positive LAC were anticoagulated before or during the episode of stroke being studied such that the test was not repeated due to technical interference with warfarin. Hence, they were regarded as having probable APS.

**Imaging patterns of stroke.** The radiological features of our patients are summarized in Table 2. Ischemic stroke was more common in SLE than non-SLE patients (90.0% vs 62.5%,

Table 1. Demographic characteristics and vascular risk factors of the SLE patients and controls studied.

	SLE Stroke, n = 40	Controls, n = 120	Total, n = 160	P
Age at stroke, yrs	44.7 ± 13.7	44.7 ± 13.7	44.7 ± 13.7	> 0.99
Women	35 (87.5)	105 (87.5)	140 (87.5)	> 0.99
NIHSS				
Range	0–32	0–32	0–32	
Median, IQR	4 (0–4)	2 (2–7.75)	3 (1–4.25)	0.01
< 6	25 (62.5)	105 (87.5)	130 (81.3)	0.01
≥ 6	11 (27.5)	13 (10.8)	24 (15)	
Unknown	4 (10)	2 (1.7)	6 (3.7)	
Comorbidities				
Diabetes mellitus	2 (5.0)	18 (15.0)	20 (12.5)	0.10
Hypertension	14 (35.0)	43 (35.8)	57 (35.6)	0.92
Atrial fibrillation	2 (5.0)	4 (3.3)	6 (3.8)	0.63
Smoking status				
Active smokers	6 (15.0)	13 (10.8)	19 (11.9)	0.77
Ex-smokers	2 (5.0)	7 (5.8)	9 (5.6)	
Nonsmokers	32 (80.0)	100 (83.3)	132 (82.5)	
Chronic RHD	0 (0.0)	6 (5.0)	6 (3.8)	0.15
Heart valve replacement	0 (0.0)	1 (0.8)	1 (0.6)	0.56
Previous stroke	6 (15.0)	7 (5.8)	13 (8.1)	0.07
Moderate to severe CKD <sup>a</sup>	5 (12.5)	2 (1.7)	7 (4.38)	0.004
Vascular risk factors during stroke				
Fasting glucose, mmol/L	5.12 ± 0.69	6.05 ± 1.98	5.81 ± 1.79	0.004
Serum total cholesterol, mmol/L	4.97 ± 1.38	5.05 ± 1.09	5.03 ± 1.16	0.70
Serum triglyceride, mmol/L	2.02 ± 1.32	1.54 ± 0.94	1.66 ± 1.17	0.01
Serum HDL, mmol/L	1.15 ± 0.43	1.36 ± 0.38	1.31 ± 0.40	0.004
Serum LDL, mmol/L	2.94 ± 1.10	2.98 ± 0.93	2.97 ± 0.97	0.83
AIP	0.48 ± 0.86	0.0023 ± 0.69	0.12 ± 0.76	0.001
Mild (< 0.11)	15 (37.5)	77 (64.2)	92 (57.5)	0.43
Moderate (0.11–0.21)	3 (7.5)	10 (8.3)	13 (8.1)	
Severe (> 0.21)	22 (55.0)	33 (27.5)	55 (34.4)	
Use of antithrombotic before stroke <sup>b</sup>	9 (22.5)	9 (7.5)	18 (11.3)	0.009

Data are expressed in mean ± SD or n (%) unless otherwise specified. <sup>a</sup> Defined as CKD stage 3a or above (eGFR < 60 mL/min/1.73 m<sup>2</sup>). <sup>b</sup> Included antiplatelet agents and anticoagulants. AIP: atherogenic index of plasma; CKD: chronic kidney disease; GFR: glomerular filtration rate; HDL: high-density lipoprotein; IHD: ischemic heart disease; LDL: low-density lipoprotein; NIHSS: National Institute of Health Stroke Scale; PVD: peripheral vascular disease; RHD: rheumatic heart disease; SLE: systemic lupus erythematosus.

$P = 0.001$ ). A significantly higher proportion of SLE patients had border zone infarct (27.8% vs 12.0%,  $P < 0.001$ ) and multiple infarcts (33.3% vs 4.0%,  $P < 0.001$ ). In patients with ischemic stroke, more SLE patients had extensive disease on imaging than non-SLE patients (69.4% vs 18.7%,  $P < 0.001$ ). Patients with more extensive infarct had a significantly higher NIHSS score than those without (median score  $4.0 \pm 6.6$  vs  $2.0 \pm 1.6$ ,  $P = 0.001$ ). In SLE patients with more extensive infarct, the SLEDAI-2K score was nonsignificantly higher than those with less extensive lesions ( $20.8 \pm 10.4$  vs  $13.6 \pm 3.7$ ,  $P = 0.054$ ).

**Functional outcome at 90 days poststroke.** Table 3 shows the clinical outcomes of stroke in our patients. At 90 days poststroke, the mean mRS scores were significantly higher in SLE than control patients. The proportion of patients with functional dependence (mRS score 3–6) was significantly higher in SLE patients (32.5% vs 8.3%,  $P < 0.001$ ). A nonsignificantly higher 30-day poststroke mortality was also observed in the SLE group (7.5% vs 2.5%,  $P = 0.15$ ).

Logistic regression showed that SLE (OR 5.4, 95% CI 1.1–26.0,  $P = 0.04$ ), history of previous stroke (OR 12.1, 95% CI 1.9–76.0,  $P = 0.008$ ), and higher stroke severity (NIHSS  $\geq 6$ ;

OR 15.1, 95% CI 3.8–60.3,  $P < 0.001$ ) were independently associated with a poorer functional outcome (mRS 3–6) at 90 days poststroke (Table 4).

In patients with SLE, a separate logistic regression did not demonstrate that high SLE disease activity at stroke onset was significantly associated with a poorer outcome, after adjustment for age, sex, traditional cardiovascular risk factors, NIHSS score, previous stroke, and the aPL antibodies (either LAC or aCL; data not shown). The proportion of patients with poor outcome at 90 days was not significantly different between patients with and without definite/probable APS (31.2% vs 33.3%,  $P = 0.89$ ).

**Long-term mortality.** The mean duration of follow-up after stroke in the SLE and non-SLE patients was  $9.4 \pm 8.2$  and  $8.0 \pm 5.0$  years, respectively. The mortality rate was  $0.8 \pm 2.8$  and  $0.3 \pm 1.9$  per patient-year in SLE and non-SLE patients, respectively. Significantly more SLE than control patients had succumbed (of any causes; 37.5% vs 8.3%,  $P < 0.001$ ). More SLE patients died of stroke or its recurrence than non-SLE patients (15.0% vs 3.3%,  $P = 0.008$ ; Table 3). No significant difference in other causes of death was found between the 2 groups.

Table 2. Radiological findings of the SLE and non-SLE stroke patients studied.

	SLE Stroke, n = 40	Non-SLE Stroke, n = 120	Total, n = 160	P
<b>Stroke subtypes</b>				
Ischemic stroke	36 (90.0)	75 (62.5)	111/160 (69.4)	0.001
Hemorrhagic stroke	4 (10.0)	45 (37.5)	49/160 (30.6)	
<b>Stroke location</b>				
Anterior circulation stroke	24/36 (66.7)	30/75 (40.0)	54/111 (48.6)	0.03
Posterior circulation stroke	5/36 (13.9)	15/75 (20.0)	20/111 (18.0)	
No infarct	7/36 (19.4)	30/75 (40.0)	37/111 (33.3)	
<b>Infarct lesion pattern</b>				
None	7/36 (19.4)	33/75 (44.0)	40/111 (36.0)	< 0.001
Small single-cortical or subcortical lacunar (2–15 mm)	4/36 (11.1)	28/75 (37.3)	32/111 (28.8)	
Border zone	10/36 (27.8)	9/75 (12.0)	19/111 (17.1)	
Multiple	12/36 (33.3)	3/75 (4.0)	15/111 (13.5)	
Large territorial	3/36 (8.3)	2/75 (2.7)	5/111 (4.5)	
Extensive infarct	25/36 (69.4)	14/75 (18.7)	39/111 (35.1)	< 0.001
<b>Hemorrhage type/location</b>				
SAH	2/4 (50.0)	21/45 (46.7)	23/49 (46.9)	0.03
Lobar	1/4 (25.0)	10/45 (22.2)	11/49 (22.4)	
BG	0/4 (0.0)	10/45 (22.2)	10/49 (20.4)	
Cerebellar	0/4 (0.0)	3/45 (6.7)	3/49 (6.1)	
Subdural	1/4 (25.0)	0/45 (0.0)	1/49 (2.0)	
IVH	0/4 (0.0)	1/45 (2.2)	1/49 (2.0)	
<b>Hemorrhage etiology</b>				
Aneurysm	2/4 (50.0)	20/45 (44.4)	22/49 (44.9)	0.15
AVM	0/4 (0.0)	13/45 (28.9)	13/49 (26.5)	
Hypertension	0/4 (0.0)	7/45 (15.6)	7/49 (14.3)	
Warfarin	1/4 (25.0)	1/45 (2.2)	2/49 (4.1)	
Uncertain	1/4 (25.0)	3/45 (6.7)	4/49 (8.2)	

Data are expressed in n/N (%) unless otherwise specified. AVM: atrioventricular malformation; BG: basal ganglia; IVH: intraventricular hemorrhage; SAH: subarachnoid hemorrhage; SLE: systemic lupus erythematosus.

Table 3. Outcomes and complications of stroke in SLE and non-SLE patients.

	SLE, n = 40	Non-SLE, n = 120	Total, n = 160	P
Mean 90-day mRS scores	1.7 ± 2.0	0.9 ± 1.4	1.1 ± 1.6	0.004
90-day mRS (3–6)	13 (32.5)	10 (8.3)	23 (14.4)	< 0.001
30-day mortality	3 (7.5)	3 (2.5)	6 (3.75)	0.15
All-cause mortality at end of follow up	15 (37.5)	10 (8.3)	25 (15.6)	< 0.001
<b>Mortality due to index or recurrent stroke at the end of follow-up</b>				
	6 (15.0)	4 (3.3)	10 (6.3)	0.008
<b>Cause of death</b>				
Infection	4/15 (26.7)	3/10 (30.0)	7/25 (28.0)	0.56
Index stroke or recurrent stroke	6/15 (40.0)	4/10 (40.0)	10/25 (40.0)	
Malignancy	3/15 (20.0)	0/10 (0.0)	3/25 (12.0)	
<b>Stroke recurrence</b>				
Stroke recurrence	12 (30.0)	11 (9.2)	23 (14.4)	0.002
Stroke recurrence within 90 days	4 (10.0)	5 (4.2)	9 (5.6)	0.18
Stroke recurrence rate (per patient-yr)	0.7 ± 2.6	0.2 ± 1.2	0.4 ± 1.7	0.11
Mean follow-up duration	9.4 ± 8.2	8.0 ± 5.0	8.4 ± 6.1	0.33
<b>Complications (within 30 days)</b>				
Epilepsy	8 (22.5)	4 (3.3)	12 (7.5)	0.001
Neurosurgical intervention	3 (7.5)	33 (27.5)	36 (22.5)	0.009
Aspiration	2 (5.0)	2 (1.7)	4 (2.5)	0.24
Use of feeding tube	2 (5.0)	1 (0.8)	3 (1.9)	0.09

Data are expressed in mean ± SD or n (%). mRS: modified Rankin Scale; SLE: systemic lupus erythematosus.

Table 4. Independent risk factors for a poorer stroke outcome (90-day mRS 3–6).

	All Patients, n = 160 OR (95% CI)	P
SLE	5.4 (1.1–26.0)	0.04
Age at stroke, per yr	1.0 (1.0–1.1)	0.59
Male sex	0.9 (0.1–11.1)	0.93
Previous stroke	12.1 (1.9–76.0)	0.008
Hypertension	0.9 (0.2–5.1)	0.94
Diabetes mellitus	2.8 (0.3–23.9)	0.36
Active smoker	0.5 (0.1–3.2)	0.45
AIP > 0.21	1.5 (0.4–6.1)	0.57
Atrial fibrillation	1.0 (0.03–29.5)	0.99
Ischemic stroke	2.7 (0.3–23.9)	0.36
NIHSS $\geq$ 6	15.1 (3.8–60.3)	< 0.001
Moderate to severe CKD <sup>a</sup>	0.9 (0.1–10.8)	0.92

<sup>a</sup> Defined as CKD stage 3a or below (eGFR < 60 ml/min/1.73 m<sup>2</sup>). AIP: atherogenic index of plasma; CKD: chronic kidney disease; mRS: modified Rankin Scale; NIHSS: National Institute of Health Stroke Scale; SLE: systemic lupus erythematosus.

The cumulative survival rates for SLE and non-SLE stroke patients were 45.2% and 84.9%, respectively, at 15 years ( $P < 0.001$ ) after stroke (Figure 1). Cox regression showed that SLE was an independent risk factor for all-cause mortality after adjusting for other confounding factors as shown in Table 5 (HR 39.4, 95% CI 5.2–297,  $P < 0.001$ ). Among patients with SLE, there was no difference in mortality between those with and without the definite/probable APS (25.0% vs 45.8%,  $P = 0.18$ ).

**Stroke complications and recurrence.** A significantly higher proportion of SLE patients had poststroke epilepsy than non-SLE patients (22.5% vs 3.3%,  $P = 0.001$ ; Table 3). In patients with SLE, 7 developed generalized tonic-clonic seizure (GTCS), and 1 developed partial seizure with secondary generalization. In non-SLE patients, 3 developed GTCS, and 1 developed partial seizure with secondary generalization. Non-SLE were more likely than SLE patients to receive neurosurgical intervention after stroke (27.5% vs 7.5%,  $P = 0.009$ ). Other complications had similar frequencies in the 2 groups.

The 90-day stroke recurrence was not significantly different between SLE and non-SLE patients (10.0% vs 4.2%,  $P = 0.18$ ). However, significantly more SLE patients had recurrence of stroke (ischemic or hemorrhagic) at long-term follow-up (30% vs 9.2%,  $P = 0.002$ ). The rate of stroke recurrence was  $0.73 \pm 2.63$  and  $0.2 \pm 1.2$  per patient-year, respectively, in SLE and non-SLE patients. The cumulative stroke recurrence rates for SLE and non-SLE patients were 40.5% and 14.3%, respectively, at 10 years ( $P = 0.001$ ). There was no significant difference in the median time for stroke recurrence between the 2 groups ( $2.3 \pm 3.4$  yrs in SLE vs  $1.2 \pm 4.4$  yrs in non-SLE patients,  $P = 0.44$ ). Cox regression demonstrated that SLE was a risk factor for stroke recurrence independent of age, sex, history of stroke, initial NIHSS score, various atherosclerotic risk factors, and the type of stroke (HR 4.0, 95% CI 1.3–12.5,  $P = 0.018$ ; data not shown).

Among patients with SLE, there was no significant difference between those with and without definite/probable APS in terms of the rate of poststroke seizure (18.8% vs 20.8%,  $P = 0.87$ ) and stroke recurrence (43.8% vs 20.8%,  $P = 0.12$ ).

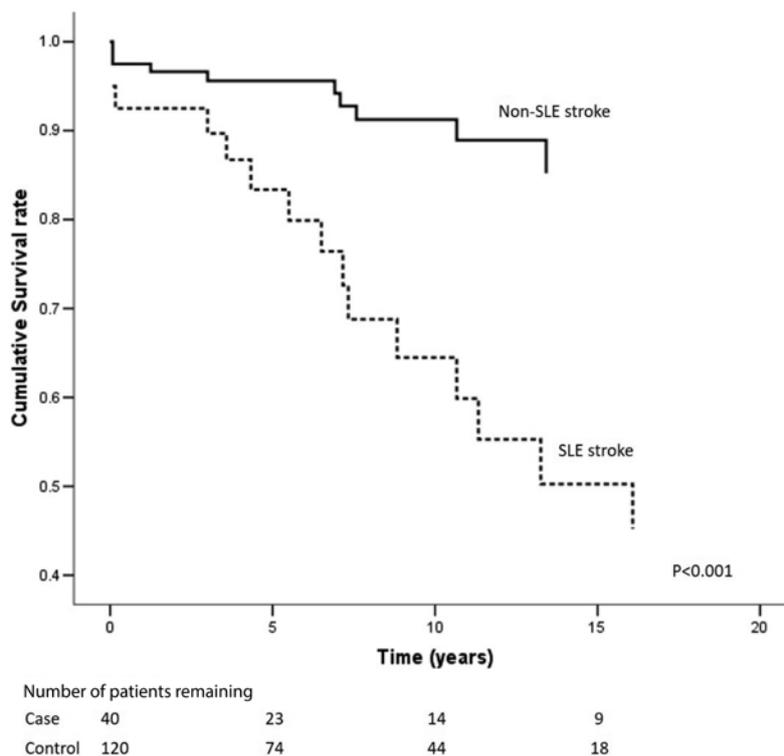


Figure 1. Kaplan-Meier plot of the cumulative survival rates of SLE stroke and non-SLE stroke patients. SLE: systemic lupus erythematosus.

Table 5. Cox regression analysis for predictors of long-term all-cause mortality.

Risk Factors	HR (95% CI)	P
SLE	39.4 (5.2–297)	< 0.001
Age of stroke/every year	1.0 (1.0–1.1)	0.21
Male sex	11.1 (1.5–84.1)	0.02
Previous stroke	11.3 (0.9–142)	0.061
Hypertension	0.3 (0.1–1.50)	0.14
Diabetes mellitus	4.5 (0.3–56.8)	0.27
Active smoker	1.1 (0.2–5.5)	0.89
High AIP > 0.21 <sup>a</sup>	1.9 (0.5–7.6)	0.36
Atrial fibrillations	0.2 (0.004–5.2)	0.30
NIHSS $\geq$ 6	7.3 (1.4–38.9)	0.02
Ischemic stroke	0.8 (0.2–4.3)	0.82
Moderate to severe CKD <sup>b</sup>	4.2 (0.3–56.8)	0.27
Previous use of antithrombotic agents	0.1 (0.01–0.8)	0.03
Use of corticosteroids	0.3 (0.1–2.2)	0.26
Use of HCQ	0.2 (0.02–1.9)	0.15

<sup>a</sup> AIP defined by logarithm of serum (triglyceride/HDL cholesterol) level. AIP > 0.21 suggestive of high atherosclerosis risk. <sup>b</sup> Defined as CKD stage 3a or below. AIP: atherogenic index of plasma; CKD: chronic kidney disease; HCQ: hydroxychloroquine; HDL: high-density lipoprotein; NIHSS: National Institute of Health Stroke Scale; SLE: systemic lupus erythematosus.

## DISCUSSION

Hemorrhagic stroke is more common in the Chinese population. The proportion of hemorrhage among stroke was up to 30% according to studies in our locality (Hong Kong) and mainland China<sup>26,27</sup>. This is similar to the ischemic-to-hemorrhagic stroke ratio observed in our non-SLE controls. Despite this, ischemic stroke was significantly more common in our patients with SLE, indicating atherosclerosis and vascular thrombosis are more important mechanisms of stroke in SLE. In addition, we observed that patients with SLE had more severe stroke at onset when compared to controls. This could be related to the higher prevalence of past stroke in our SLE patients, and hence a higher level of preexisting functional dependence. Moreover, the greater extent of infarction in patients with SLE might also contribute to greater stroke severity. In fact, regression analysis showed that SLE, previous stroke, and stroke severity were 3 independent risk factors for a poorer functional outcome at 90 days poststroke.

There is little information regarding the neuroradiological patterns of stroke in SLE. Various patterns such as large vessel occlusion, basal ganglia infarction, border zone infarction, discrete cortical/subcortical infarction, bilateral white matter lesion, and single infarcted lesion have been described in SLE patients with ischemic stroke<sup>28</sup>. A study of Japanese SLE stroke patients with or without APS<sup>29</sup> showed that large territorial infarction, localized cortical infarction, and lacunar infarction were the most common radiological patterns. In our SLE stroke patients, border zone infarct and multiple infarcts were the most common imaging patterns observed. Asian patients tend to have more intracranial stenosis<sup>30</sup> with concurrent extracranial stenosis<sup>20,31</sup>, and this might contribute to the higher incidence of border zone infarct and infarcts from multiple territories<sup>20,32</sup>.

As these infarct patterns are well-known poor prognostic factors for stroke<sup>33,34</sup>, their higher incidence in SLE patients might also account for the poorer functional outcome as compared to controls.

In our study, more active disease at stroke onset was not shown to be associated with short-term functional outcome or NIHSS score in patients with SLE. This contradicts a previous study, which showed that more active SLE disease at baseline correlated with stroke severity at presentation<sup>11</sup>. Further imaging study is needed to delineate the role of vascular wall inflammation and stroke severity in patients with SLE.

Our observation of a poorer short-term functional outcome of stroke in SLE than non-SLE patients is in concordance with a national study from Sweden<sup>35</sup>, in which the risk of having a worse functional outcome at 3 months was nearly 2-fold in SLE compared to non-SLE patients. The higher incidence of poor functional outcome (4.4-fold increased risk) in our study could be related to more severe stroke at presentation as compared to the Swedish study. The exclusion of patients who died within 90 days for analysis in the Swedish study<sup>35</sup> might also contribute to an apparently better functional outcome among patients evaluated, as compared to ours, in which death was included in the category of poor functional outcome according to the mRS.

In our study, SLE was an independent risk factor for a poor 90-day functional outcome after stroke. While this observation is intriguing, there are several postulated reasons for this. First, stroke recurrence within 90 days was nonsignificantly higher in patients with SLE. This could contribute to a further functional deterioration during hospital stay. Second, we observed a generally longer length of hospitalization in the SLE stroke patients because of the more complicated clinical course (data not included in the regression models). These complications included severe infections, deep venous thrombosis, and SLE flare in other organ systems, which could delay poststroke recovery. Third, our SLE stroke patients had a higher degree of functional dependence at stroke onset related to previous stroke or other comorbidities. This could have led to a higher level of functional dependence after the current stroke. Finally, patients with SLE are more prone to other NP complications such as depression, cognitive impairment, or psychosis. These conditions, which were not assessed, might also contribute to slower recovery in our SLE stroke patients.

Higher incidence of poststroke seizure was observed in our SLE than non-SLE patients, which is consistent with studies from Taiwan<sup>36</sup> and United States<sup>37</sup>. Approximately half of our epilepsy patients developed seizure events soon after or during onset of stroke symptoms. Recurrent seizures after stroke in SLE could either be the result of SLE disease activity or reduced seizure threshold due to stroke itself (brain injury). This may account for a higher seizure rate observed in SLE stroke patients.

The strength of our study is a long follow-up period after stroke and the availability of matched non-SLE controls for comparison. Data on NIHSS score, the imaging pattern, and functional outcome of stroke were available for evaluation. However, our study was limited by its retrospective nature.

Some important confounding variables were missing, such as the aPL antibody status in the control group. Standard investigations in younger patients with stroke, such as angiography and echocardiogram, were not performed in all the SLE and non-SLE patients. Second, the infarct volume on imaging was not quantified to correlate with functional outcome. Third, the sample size of our study was inadequate for a complete evaluation of the contribution of SLE and other confounding factors to the stroke outcomes. In particular, logistic regression analysis for a poor 90-day functional outcome, which was  $\geq 10\%$  of the incidence, tended to overestimate the true relative risk. The small sample size did not allow for other analyses such as the modified Poisson and binomial regression models. Finally, other clinical factors such as C-reactive protein levels, BMI, neurocognitive state, carotid intima-media thickness, and mood assessment after stroke were not available in all the patients.

In conclusion, this is the first case-control study to evaluate the clinical outcomes and imaging patterns of stroke in Asian patients with SLE, to our knowledge. SLE stroke patients had a poorer short-term functional outcome, and higher mortality and recurrence rate of stroke, than matched non-SLE patients. SLE was a risk factor for these outcomes independent of conventional prognostic factors for stroke. Further prospective population-based studies are needed to investigate the mechanism of poorer functional outcomes of SLE stroke, which include semiquantitative analysis of neuroradiological patterns as well as SLE-specific risk factors and biomarkers of vascular injury.

## REFERENCES

- Popescu A, Kao AH. Neuropsychiatric systemic lupus erythematosus. *Curr Neuroparmacol* 2011;9:449-57.
- Unterman A, Nolte JE, Boaz M, Abady M, Shoenfeld Y, Zandman-Goddard G. Neuropsychiatric syndromes in systemic lupus erythematosus: a meta-analysis. *Semin Arthritis Rheum* 2001;41:1-11.
- Liang MH, Corzillius M, Bae SC, Lew RA, Fortin PR, Gordon C, et al. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum* 1999;42:599-608.
- Mok CC, To CH, Mak A. Neuropsychiatric damage in Southern Chinese patients with systemic lupus erythematosus. *Medicine* 2006;85:221-8.
- Aarnio K, Haapaniemi E, Melkas S, Kaste M, Tatlisumak T, Putaala J. Long-term mortality after first-ever and recurrent stroke in young adults. *Stroke* 2014;45:2670-6.
- Krishnan E. Stroke subtypes among young patients with systemic lupus erythematosus. *Am J Med* 2005;118:1415.
- Holmqvist M, Simard JF, Asplund K, Arkema EV. Stroke in systemic lupus erythematosus: a meta-analysis of population-based cohort studies. *RMD Open* 2015;1:e000168.
- Wang IK, Muo CH, Chang YC, Liang CC, Lin SY, Chang CT, et al. Risks, subtypes, and hospitalization costs of stroke among patients with systemic lupus erythematosus: a retrospective cohort study in Taiwan. *J Rheumatol* 2012;39:1611-8.
- Roman MJ, Shanker BA, Davis A, Lockshin MD, Sammaritano L, Simantov R, et al. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003;349:2399-406.
- Bessant R, Duncan R, Ambler G, Swanton J, Isenberg DA, Gordon C, et al. Prevalence of conventional and lupus-specific risk factors for cardiovascular disease in patients with systemic lupus erythematosus: a case-control study. *Arthritis Rheum* 2006;55:892-99.
- Mikdashi J, Handwerker B, Langenberg P, Miller M, Kittner S. Baseline disease activity, hyperlipidemia, and hypertension are predictive factors for ischemic stroke and stroke severity in systemic lupus erythematosus. *Stroke* 2007;38:281-5.
- Petri M, Roubenoff R, Dallal GE, Nadeau MR, Selhub J, Rosenberg IH. Plasma homocysteine as a risk factor for atherothrombotic events in systemic lupus erythematosus. *Lancet* 1996;348:1120-4.
- Hanly JG, Urowitz MB, Su L, Bae SC, Gordon C, Clarke A, et al. Autoantibodies as biomarkers for the prediction of neuropsychiatric events in systemic lupus erythematosus. *Ann Rheum Dis* 2011;70:1726-32.
- Tolosa SM, Uribe AG, McGwin G Jr, Alarcón GS, Fessler BJ, Bastian HM, et al. Systemic lupus erythematosus in a multiethnic US cohort (LUMINA). XXIII. Baseline predictors of vascular events. *Arthritis Rheum* 2004;50:3947-57.
- Lyden P, Brott T, Tilley B, Welch KM, Mascha EJ, Levine S, et al. Improved reliability of the NIH Stroke Scale using video training. NINDS TPA Stroke Study Group. *Stroke* 1994;25:2220-6.
- Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271.
- Shen S, Lu Y, Qi H, Li F, Shen Z, Wu L, et al. Association between ideal cardiovascular health and the atherogenic index of plasma. *Medicine* 2016;95:e3866.
- Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003;139:137-47.
- Suh DC, Lee SH, Kim KR, Park ST, Lim SM, Kim SJ, et al. Pattern of atherosclerotic carotid stenosis in Korean patients with stroke: different involvement of intracranial vs extracranial vessels. *AJNR Am J Neuroradiol* 2003;24:239-44.
- Man BL, Fu YP, Chan YY, Lam W, Hui ACF, Leung WH, et al. Lesion patterns and stroke mechanisms in concurrent atherosclerosis of intracranial and extracranial vessels. *Stroke* 2009;40:3211-5.
- Caplan LR, Wityk RJ, Glass TA, Tapia J, Pazdera L, Vemmos K. New England Medical Center posterior circulation registry. *Ann Neurol* 2004;56:389-98.
- Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002;29:288-91.
- Dooley MA, Aranow C, Ginzler EM. Review of ACR renal criteria in systemic lupus erythematosus. *Lupus* 2004;13:857-860.
- Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006;4:295-306.
- Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJA, Van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;19:604-7.
- Chau PH, Woo J, Goggins WB, Tse YK, Chan KC, Lo SV, et al. Trends in stroke incidence in Hong Kong differ by stroke subtype. *Cerebrovasc Dis* 2011;31:138-46.
- Zhao D, Liu J, Wang M, Zhang X, Zhou M. Epidemiology of cardiovascular disease in China: current features and implications. *Nat Rev Cardiol* 2019;16:203-12.
- Lalani TA, Kanne JP, Hatfield GA, Chen P. Imaging findings in systemic lupus erythematosus. *Radiographics* 2004;24:1069-86.
- Hojnik M, George J, Ziporen L, Shoenfeld Y. Heart valve involvement (Libman-Sacks endocarditis) in the antiphospholipid syndrome. *Circulation* 1996;93:1579-87.

30. Feldmann E, Daneault N, Kwan E, Ho KJ, Pessin MS, Langenberg P, et al. Chinese-white differences in the distribution of occlusive cerebrovascular disease. *Neurology* 1990;40:154-5.
31. Lee SJ, Cho SJ, Moon HS, Shon YM, Lee KH, Kim DI, et al. Combined extracranial and intracranial atherosclerosis in Korean patients. *Arch Neurol* 2003;60:1561-4.
32. Mok VCT, Fan YH, Lam WWM, Hui ACF, Wong KS. Small subcortical infarct and intracranial large artery disease in Chinese. *J Neurol Sci* 2003;216:55-9.
33. Bang OY, Lee PH, Heo KG, Joo US, Yoon SR, Kim SY. Specific DWI lesion patterns predict prognosis after acute ischaemic stroke within the MCA territory. *J Neurol Neurosurg Psychiatry* 2005;76:1222-8.
34. Arauz A, Murillo L, Cantú C, Barinagarrementeria F, Higuera J. Prospective study of single and multiple lacunar infarcts using magnetic resonance imaging: risk factors, recurrence, and outcome in 175 consecutive cases. *Stroke* 2003;34:2453-8.
35. Rossides M, Simard JF, Svenungsson E, von Euler M, Arkema EV. Mortality and functionality after stroke in patients with systemic lupus erythematosus. *J Rheumatol* 2017;44:1590-6.
36. Tsai JD, Lin CL, Lin CC, Sung FC, Lue KH. Risk of epilepsy in patients with systemic lupus erythematosus—a retrospective cohort study. *Neuropsychiatr Dis Treat* 2014;10:1635.
37. Mikdashi J, Krumholz A, Handwerker B. Factors at diagnosis predict subsequent occurrence of seizures in systemic lupus erythematosus. *Neurology* 2005;64:2102-7.