

## Imaging pattern and outcome of stroke in patients with systemic lupus erythematosus: a case-control study

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## Abstract

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

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

**Results:** 40 SLE patients and 120 non-SLE patients with stroke (age at stroke  $44.6 \pm 13.8$  years; 88% women) were studied. Ischemic type of stroke (90% versus 63%;  $p=0.001$ ) and extensive infarction (69% versus 28%;  $p<0.001$ ) was 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 post-stroke. 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[1.1-26.0];  $p=0.035$ ). Stroke mortality at 30 days was non-significantly 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 post-stroke 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 SLE patients is associated with a poorer outcome than matched controls in terms of functional recovery, recurrence and mortality.

**Key words:** cerebrovascular, complication, atherosclerosis, morbidity, lupus

**Short running title:** Outcome of stroke in SLE

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## Introduction

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

Cerebrovascular accident (stroke) is uncommon in the younger population but carries substantial functional impairment to patients and economic burden to the society (5). SLE patients are at 2-3-fold increased risk of developing all types of stroke (6,7) compared to the general population and may require prolonged hospitalization, leading to higher cost of illness (8). 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 SLE patients (9,10). Younger age, male sex, hyperlipidemia, smoking, hypertension, homocysteine level and the use of steroid were reported to be risk factors for stroke in SLE patients, while the use of hydroxychloroquine (HCQ) is protective (9-12). Cohort studies have identified the antiphospholipid (aPL)

antibodies as an additional risk factor for vascular events, including stroke, in SLE (13,14).

Although the incidence and risk factors of stroke in SLE patients have been well reported (6-8), little is known about the imaging pattern of stroke, its functional recovery, and complications. This prompts the current study to evaluate the functional outcome of stroke and its long-term complications in a group of Chinese SLE patients.

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### Patients 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 in 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  $\geq 18$  years) who were admitted to our acute medical wards for stroke between years 1997 and 2017 were identified from our hospital database using the ICD-9 codes for stroke (430-435). Exclusion criteria were: (1) absence of imaging findings; (2) a diagnosis of retinal artery occlusion; (3) a diagnosis of cerebral venous thrombosis; and (4) a 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 gender 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 selected by random 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 hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, previous stroke, use of anti-thrombotic 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) (15). A 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 HDL-cholesterol level (16). An elevated AIP value of  $>0.21$  was regarded as high risk for vascular events (17). Chronic kidney disease (CKD) was defined according to the National Kidney foundation (NKF) criteria (18) when the calculated eGFR was  $<60$  ml/min/1.73m<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 [TIA]) or hemorrhagic. Ischemic stroke was classified into that involved the anterior or posterior circulation with reference to brain imaging (MRI or CT 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 2-15mm); (3) border zone infarct from any of the major cerebral vessel (anterior cerebral [ACA], middle cerebral [MCA] or posterior cerebral [PCA] artery); (4) multiple ( $\geq 2$ ) infarcts involving

multiple ( $\geq 2$ ) major cerebral vessel territory or multiple ( $\geq 2$ ) sub-branch artery within the same major cerebral vessel; (5) Large territorial infarct (one single major cerebral vessel  $>2/3$  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 (19,20) for anterior circulation stroke and the New England Medical Center Posterior Circulation Registry (NEMC-PCR) by Caplan et al. (21) 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 (ie. 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 (22), use of immunosuppressants (glucocorticoids [GCs] and HCQ), renal involvement according to the ACR criteria (23) and the presence of antiphospholipid syndrome (APS), which was defined according to the updated classification criteria in 2006 (24).

### **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 lupus disease activity in the preceding 10 days (22). High SLE



disease activity was arbitrarily defined when 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 (25). It consists of an ordinal scale ranging from zero to six. 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 score 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 (standard deviation). Continuous variables of two groups were compared by the Students' 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

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data in around 10% of patients) were replaced by the group mean. Factors associated with a poor functional outcome at 90 days post-stroke were studied by logistic regression. Survival analysis for all-cause mortality and stroke recurrence was performed by the Kaplan-Meier curve with time zero referred to the time of stroke. The log-rank test was used to compare the survival between the two 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 diabetes mellitus, hypertension, 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), use of antithrombotic treatment. Statistical significance was defined as a p value of  $<0.05$ , 2-tailed. All data was 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 gender matched non-SLE patients were studied (Table 1). All were ethnic Chinese. Baseline demographic data were similar between the two groups, except for a higher proportion of SLE patients using anti-thrombotic therapy before the stroke episode. The median NIHSS score was significantly higher in SLE patients than controls (4.0 versus 2.0;  $p=0.01$ ) and more SLE patients had moderate/severe stroke (NIHSS score  $\geq 6$ ) (27.5% versus 10.8%;  $p=0.01$ ).

### Traditional atherosclerotic risk factors

SLE patients 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 SLE patients 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 GCs before the current stroke. Sixteen (40%) patients had positive aPL antibodies: lupus anticoagulant (LAC) ( $n=3$ ; 19%), moderate/high titers of IgG anticardiolipin antibodies ( $n=8$ ; 50%) and both ( $n=5$ ; 31%). Ten of these patients were

anti-coagulated before the stroke episodes studied because of previous stroke or other indications. Five patients with positive LAC were anti-coagulated 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% versus 62.5%;  $p=0.001$ ). A significantly higher proportion of SLE patients had border zone infarct (27.8% versus 12%;  $p<0.001$ ) and multiple infarcts (33.3% versus 4%;  $p<0.001$ ). In patients with ischemic stroke, more SLE patients had extensive disease on imaging than non-SLE patients (69.4% versus 18.7%;  $p<0.001$ ). Patients with more extensive infarct had a significantly higher NIHSS score than those without (median score  $4.0\pm 6.6$  versus  $2.0\pm 1.6$ ;  $p=0.001$ ). In SLE patients with more extensive infarct, the SLEDAI-2K score was non-significantly higher than those with less extensive lesions ( $20.8\pm 10.4$  versus  $13.6\pm 3.7$ ;  $p=0.054$ ).

### **Functional outcome at 90 days post-stroke**

Table 3 shows the clinical outcomes of stroke in our patients. At 90 days post-stroke, 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% versus 8.3%;  $p<0.001$ ). A non-significantly higher 30-day post-stroke mortality was also observed in the SLE group (7.5% versus 2.5%;  $p=0.15$ ).

Logistic regression showed that SLE (OR 5.4[1.1-26.0];  $p=0.035$ ), history of previous stroke (OR 12.1[1.9-76.0];  $p=0.008$ ) and higher stroke severity (NIHSS  $\geq 6$ ) (OR 15.1 [3.8-60.3];  $p<0.001$ ) were independently associated with a poorer functional outcome (mRS 3-6) at 90 days post-stroke (Table 4).

In patients with SLE, a separate logistic regression did not demonstrate 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 anti-phospholipid 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% versus 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% versus 8.3%;  $p<0.001$ ). More SLE patients died of stroke or its recurrence than non-SLE patients (15% versus 3.3%;  $p=0.008$ ). No significant difference in other causes of death was found between the two groups.

The cumulative survival rate 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 (Hazard ratio [HR] 39.4 [5.2-297];  $p<0.001$ ). Among SLE patients, there was no difference in mortality between those with and without the definite/probable APS (25.0% versus 45.8%;  $p=0.18$ ).

### **Stroke complications and recurrence**

A significantly higher proportion of SLE patients had post-stroke epilepsy than non-SLE patients (22.5% versus 3.3%;  $p<0.001$ ) (Table 3). In SLE patients, seven developed generalized tonic-clonic seizure (GTCS) and one developed partial seizure with secondary generalization. In non-SLE patients, three developed GTCS and one patient developed partial seizure with secondary generalization. Non-SLE were more likely than SLE patients to receive neurosurgical intervention after stroke (27.5% versus 7.5%;  $p=0.009$ ). Other complications had similar frequencies in the two groups.

The 90-day stroke recurrence was not significantly different between SLE and non-SLE

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patients (10% versus 4.2%;  $p=0.18$ ). However, significantly more SLE patients had recurrence of stroke (ischemic or hemorrhagic) at long-term follow-up (30% versus 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 two groups ( $2.3\pm 3.4$  years in SLE versus  $1.2\pm 4.4$  years 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 [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 post-stroke seizure (18.8% versus 20.8%;  $p=0.87$ ) and stroke recurrence (43.8% versus 20.8%;  $p=0.12$ ).

## 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 and mainland China (26, 27). 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 SLE patients, indicating atherosclerosis and vascular thrombosis are more important mechanisms of stroke in SLE. In addition, we observed that SLE patients 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 pre-existing functional dependence. Moreover, the greater extent of infarction in the SLE patients might also contribute to greater stroke severity. In fact, regression analysis showed that SLE, previous stroke and stroke severity were three independent risk factors for a poorer functional outcome at 90 days post-stroke.

There is little information regarding the neuro-radiological 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 (28). A study of Japanese SLE stroke patients with or without the APS (29) 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 commonest imaging patterns observed. Asian patients tend to have more intra-cranial stenosis (30) with concurrent extra-cranial stenosis (20,31) and this might contribute to the higher incidence of border zone infarct and infarcts from multiple territories (20,32). As these infarct patterns are well-known poor prognostic factors for stroke (33,34), 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 SLE patients. This contradicts a previous study which showed that more active SLE disease at baseline correlated with stroke severity at presentation (11). 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 (35), 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 deceased within 90 days for analysis in the Swedish study (35) might also contribute to an apparently better functional outcome of

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, postulated reasons include the following. First, stroke recurrence within 90 days was non-significantly higher in SLE patients. 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-up in other organ system, which could delay post-stroke 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, SLE patients are more prone to other neuropsychiatric 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 post-stroke seizure was observed in our SLE than non-SLE patients, which is consistent with studies from Taiwan (36) and United States (37). About 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 (CRP) levels, body mass index, neuro-cognitive state, carotid intima thickness, 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 SLE patients. SLE stroke patients had a poorer

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short-term functional outcome, 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 semi-quantitative analysis of neuro-radiological patterns, as well as SLE-specific risk factors and biomarkers of vascular injury.

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**Disclosures**

Nil from all authors

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## Figure legend

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

Accepted Article

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

Characteristics	SLE stroke (N=40)	Controls (N=120)	Total (N=160)	p
Age at stroke, years	44.7±13.7	44.7±13.7	44.7±13.7	1.00
Women	35 (87.5)	105 (87.5)	140 (87.5)	1.00
NIHSS				
Range	0-32	0-32	0-32	
Median, IQR	4 (0-4)	2 (2-7.75)	3 (1-4.25)	0.01
NIHSS <6	25 (62.5)	105 (87.5)	130 (81.3)	0.01
NIHSS ≥6	11 (27.5)	13 (10.8)	24 (15)	
NIHSS 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)	
Non-smokers	32 (80.0)	100 (83.3)	132 (82.5)	
Chronic rheumatic heart disease	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 Chronic kidney disease CKD‡	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
Atherogenic index	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*	9 (22.5)	9 (7.5)	18 (11.3)	0.009

Data are expressed in mean±standard deviation or number (%)

SLE = systemic lupus erythematosus; IQR = interquartile range; NIHSS = National Institute of Health Stroke Scale; SD = standard deviation; IHD = ischemic heart disease; PVD = peripheral vascular disease; HDL = high density lipoprotein; LDL = low density lipoprotein; CKD = chronic kidney disease

‡defined as CKD stage 3a or above (GFR < 60 ml/min/1.73 m<sup>2</sup>)

\*included anti-platelet agents and anticoagulants

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

Features	SLE stroke (N=40)	Non-SLE stroke (N=120)	Total (N=160)	p
Stroke subtypes				
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)	
Stroke Location				
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)	
Infarct lesion pattern				
No infarct	7/36 (19.4)	33/75 (44.0)	40/111 (36.0)	<0.001
Small Single Cortical or Subcortical lacunar infarct (2-15mm)	4/36 (11.1)	28/75 (37.3)	32/111 (28.8)	
Border zone infarct	10/36 (27.8)	9/75 (12.0)	19/111 (17.1)	
Multiple infarcts	12/36 (33.3)	3/75 (4.0)	15/111 (13.5)	
Large territorial infarct	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
Hemorrhage Type / location				
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)	
Hemorrhage etiology				
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 number (%)

SAH = Subarachnoid hemorrhage; IVH = Intraventricular hemorrhage; BG = Basal ganglia; AVM = atrioventricular malformation; SD = standard deviation

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

	<b>SLE (N=40)</b>	<b>Non SLE (N=120)</b>	<b>Total (N=160)</b>	<b>p</b>
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 the end of follow up	15 (37.5)	10 (8.3)	25 (15.6)	<0.001
Mortality due to index or recurrent stroke at the end of follow up	6 (15.0)	4 (3.3)	10 (6.3)	0.008
Cause of death				
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)	
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-year)	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
Complications (within 30 days)				
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±standard deviation or number (%)

mRS: Modified Rankin scale; SD = standard deviation

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

Covariates	All patients (N=160)	
	OR (95% CI)	p
SLE	5.4 (1.1-26.0)	0.035
Age at stroke, per year	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
Atherogenic index (>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 chronic kidney disease (CKD) <sup>‡</sup>	0.9 (0.1-10.8)	0.92

SLE = systemic lupus erythematosus; mRS = modified Rankin scale; OR = odds ratio; CI = confidence interval

NIHSS = National Institute of Health Stroke Scale

<sup>‡</sup> defined as CKD stage 3a or below (eGFR <60 ml/min/1.73 m<sup>2</sup>)

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

<b>Risk factors</b>	<b>HR (95% CI)</b>	<b>p values</b>
SLE	39.4 (5.2-297)	<0.001
Age of stroke / every year	1.0 (1.0-1.1)	0.212
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 Atherogenic index >0.21*	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 Chronic kidney disease CKD‡	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 Hydroxychloroquine	0.2 (0.02-1.9)	0.15

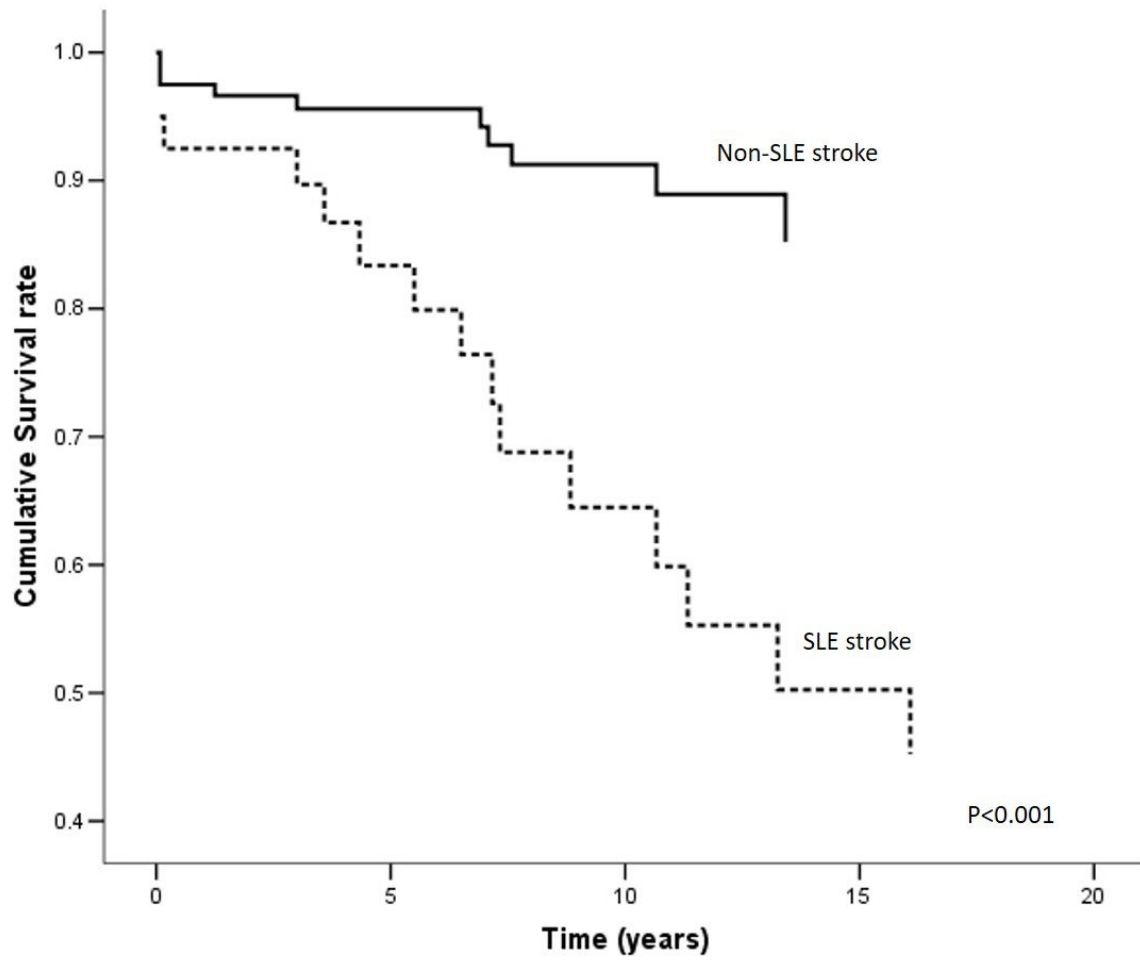
HR = hazard ratio; CI = confidence interval; NIHSS = National Institute of Health Stroke Scale;

CKD = chronic kidney disease

\* Atherogenic index AIP is defined by logarithm of serum [triglyceride/HDL-cholesterol] level. AIP > 0.21 suggestive of high atherosclerosis risk

‡defined as CKD stage 3a or below

Figure 1



Number of Patient remaining

Case	40	23	14	9
Control	120	74	44	18