Mortality and Functionality after Stroke in Patients with Systemic Lupus Erythematosus

Marios Rossides, Julia F. Simard, Elisabet Svenungsson, Mia von Euler, and Elizabeth V. Arkema

ABSTRACT. ***Objective.*** To investigate mortality and functional impairment after stroke in systemic lupus erythematosus (SLE).

Methods. Using Swedish nationwide registers, we identified 423 individuals with SLE and 1652 people without SLE who developed a first-ever ischemic or hemorrhagic stroke (1998–2013) and followed them until all-cause death or for 1 year. HR for death after ischemic or hemorrhagic stroke and the risk ratio of functional impairment (dependence in either transferring, toileting, or dressing) 3 months after ischemic stroke were estimated.

Results. One year after stroke, 22% of patients with SLE versus 16% of those without SLE died. After ischemic stroke, patients with SLE had an increased risk of death (HR 1.85, 95% CI 1.39–2.45), which was attenuated after controlling for SLE-related comorbidities (HR 1.41, 95% CI 1.04–1.91). Functional impairment at 3 months was increased in SLE by almost 2-fold (risk ratio 1.73, 95% CI 1.16–2.57). After hemorrhagic stroke, patients with SLE had an HR of 2.30 (95% CI 1.38-3.82) for death, which was increased even during the first month.

Conclusion. Compared to subjects without SLE, mortality after ischemic stroke increases after the first month in individuals with SLE, and functionality is worse at 3 months. SLE is associated with all-cause death after hemorrhagic stroke even during the first month. A shift of focus to patient functionality and prevention of hemorrhagic strokes is required. (First Release September 15 2017; J Rheumatol 2017;44:1590–6; doi:10.3899/jrheum.170241)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS CEREBROVASCULAR DISORDERS
SURVIVAL ANALYSIS ACTIVITIES OF DAILY LIVING STROKE REHABILITATION

Stroke is a severe complication of systemic lupus erythematosus (SLE), an autoimmune rheumatic disease that most often presents among women in early adulthood. Patients with SLE have a 2-fold greater risk of stroke compared to the general population and stroke occurs at a younger age[1,2,3,4], resulting in an enormous loss of productive years[5]. Except for the traditional modifiable risk factors for stroke that present earlier in SLE, SLE-related factors (e.g., antiphospholipid antibodies) further increase their risk for stroke[6,7,8]. To lessen the risk for stroke and mortality after stroke in patients with SLE, a more rigorous process of risk factor identification and early initiation of prevention strategies is performed in everyday clinical practice[7].

Despite the importance of stroke in SLE, few studies have delved into mortality and functionality of patients after stroke. A Canadian cohort study indicated that SLE is likely associated with an increased risk for stroke-attributable death[9]. Two cross-sectional studies on stroke fatality during hospitalization from the United States observed no association with SLE[10,11]. In addition, a study that included only patients discharged to rehabilitation facilities after stroke in the United States reported no differences in disability between individuals with and without SLE or rheumatoid arthritis measured before or after rehabilitation[12].

To investigate the mortality and functionality of patients with SLE after stroke, we conducted a cohort study using Swedish nationwide registers. Longitudinal followup is critical for investigating post-stroke mortality, particularly beyond the initial hospitalization. Our study aimed to address the methodological problems of previous studies, namely the

From the Clinical Epidemiology Unit, Department of Medicine Solna, and the Unit of Rheumatology, Solna, and Stroke Research Network, Södersjukhuset, and Department of Clinical Science and Education, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden; Division of Epidemiology, Department of Health Research and Policy, and Division of Immunology and Rheumatology, Department of Medicine, Stanford School of Medicine, Stanford University, Stanford, California, USA.

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M. Rossides, MD, MSc, Clinical Epidemiology Unit, Department of Medicine Solna, Karolinska Institutet; J.F. Simard, ScD, Division of Epidemiology, Department of Health Research and Policy, and Division of Immunology and Rheumatology, Department of Medicine, Stanford School of Medicine, Stanford University, and Clinical Epidemiology Unit, Department of Medicine Solna, Karolinska Institutet; E. Svenungsson, MD, PhD, Unit of Rheumatology, Department of Medicine Solna, Karolinska Institutet, Karolinska University Hospital; M. von Euler MD, PhD, Stroke Research Network, and Department of Clinical Science and Education, Karolinska Institutet; E.V. Arkema, ScD, Clinical Epidemiology Unit, Department of Medicine Solna, Karolinska Institutet.

Address correspondence to Dr. M. Rossides, Karolinska Institutet, Department of Medicine Solna, Clinical Epidemiology Unit, T2, 171 76 Stockholm, Sweden. E-mail: marios.rossides@ki.se

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uninformative sample sizes and choice of comparators, the lack of distinction between stroke and other cardiovascular outcomes, and distinguishing ischemic from hemorrhagic stroke.

MATERIALS AND METHODS

Study setting and sources. In Sweden, SLE and stroke care is universally accessible and provided mostly by public hospitals. Residents have a unique personal identification number allowing for the linkage of their records in national registers. The National Patient Register (NPR) holds information on inpatient care since 1964 (nationwide since 1987), and nonprimary/outpatient visits to public and private providers are recorded since 2001. Validation of the inpatient component of the NPR has demonstrated good coverage for SLE and stroke[13,14]. The Swedish Stroke Register (Riksstroke) was established in 1994 and became nationwide in 1998, but coverage is almost complete since 2005[15]. The Cause of Death Register contains information on the date and causes of death for all residents since 1961.

Study population. The study population was derived from the Swedish Lupus Linkage (SLINK), a large register-based cohort described in detail elsewhere[16]. Briefly, population-based registers were used to create a large cohort of individuals with SLE identified from the NPR and a matched 5:1 random sample of general population comparators on age, sex, and county from the Total Population Register. In our current study, we included individuals from the SLINK cohort who developed a first-ever stroke from January 1, 1998, to December 31, 2013, aged 18 to 85 years at stroke onset (Figure 1). We searched for a first-ever ischemic, hemorrhagic, or unspecified stroke in the NPR using corresponding International Classification of Diseases (ICD) codes (ICD-10 I63, ICD-9 433/434, ICD-8 432-434 for ischemic; ICD-10 I61, ICD-9/8 431 for hemorrhagic; and ICD-10 I64, ICD-9/8 436 for unspecified). The date of admission for stroke in the NPR served as the index date.

To link patients to their Riksstroke record, we looked for strokes that were registered ± 10 days from the NPR admission date. Assuming better data quality, Riksstroke was used to correct for stroke type if stroke was coded as unspecified in the NPR. We then excluded unspecified strokes from further analyses because of the heterogeneity of this stroke type. Ethical approval for the study was provided by the Regional Ethics Review Board in Stockholm (DNR 2011/920-31/1).

Mortality and functionality assessment. The primary outcome was all-cause mortality. The date of death was identified from the Cause of Death Register. Patients were followed for 1 year until death, emigration, or the end of the study (December 31, 2013), whichever occurred first. The 1-year limit was chosen to detect stroke-attributable mortality and deal with the depletion of susceptible individuals in the hemorrhagic group due to high fatality directly after onset.

The secondary outcome was functional impairment at 3 months after ischemic stroke in individuals who were functional before stroke onset. Data on functional impairment before stroke and at 3 months was collected from Riksstroke[17]. The followup questionnaire is sent by post; or can be answered over the telephone; or on a return visit to the hospital by the patient, a relative, or the nursing staff. Functional impairment was defined as the need for help from a person or device for either walking inside or outside the house, toileting, or dressing 3 months after stroke onset. Fourteen percent of individuals did not have followup data because of non-response, but it was not associated with SLE ($p = 0.43$ from a chi-square test). Functional impairment after hemorrhagic stroke was not examined owing to the low survival at 3 months.

SLE status and other variables. Patients with prevalent SLE at the time of stroke were compared to non-SLE general population comparators. SLE was defined as at least 2 visits in the NPR with at least 1 in a specialized clinic listing an ICD code for SLE (ICD-10 M32, ICD-9 710A, ICD-8 734.10), excluding drug-induced lupus (ICD-10 M32.0). This SLE definition was evaluated in previous classification work[14].

We collected information on the date of birth, sex, region of residence (grouped into Southern, Middle, and Northern Sweden), country of birth (Nordic, non-Nordic), and education (≤ 9 yrs, 10–12 yrs, > 12 yrs) from the Total Population and Education registers, respectively. We also calculated the time from SLE diagnosis to stroke onset using the date of first hospitalization or outpatient visit for SLE as a proxy for SLE diagnosis. Riksstroke was used to identify individuals with a severe stroke, which was defined as a score ≥ 2 on the Reaction Level Scale[18], admitted to an intensive care unit, or treated with thrombolytic therapy. Individuals were considered as having received rehabilitation if they had either home or daycare rehabilitation in Riksstroke. An indicator variable for calendar

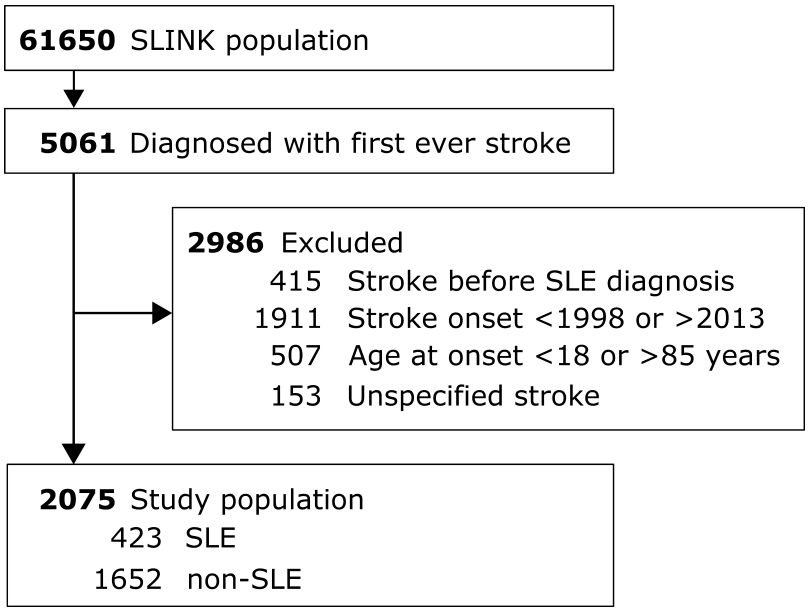

Figure 1. Flow diagram detailing how the study population was created. SLINK: Swedish Lupus Linkage; SLE: systemic lupus erythematosus.

period of stroke occurrence was used to control for period effects (1998–2005 vs 2006–2013).

Comorbidities that are likely associated with death in patients with SLE were defined from the NPR. Individuals were identified who had at least 1 visit for congestive heart disease, hypertension, diabetes, atrial fibrillation, antiphospholipid syndrome (APS), and chronic kidney disease at least 2 weeks prior to stroke onset. Infection frailty was defined as ≥ 3 visits for serious infections with > 90 days between each of them (ICD codes used to identify comorbidities in the NPR are provided in Appendix 1).

Using the Prescribed Drug Register and Anatomical Therapeutic Chemical classification system codes, we assessed use of anticoagulant (B01AA), antiplatelet (B01AC), lipid-lowering (C10), systemic corticosteroids (H02AB), and disease-modifying antirheumatic drugs (L04AX/P01BA02/L04AA06) defined as ≥ 1 dispensation up to 6 months before stroke onset. These data were available only in a subset of patients with stroke onset after January 1, 2006, because the Prescribed Drug Register was established in July 2005.

Statistical analysis. All analyses were done separately for ischemic and hemorrhagic stroke. For all-cause mortality, we compared SLE to non-SLE by estimating HR and corresponding 95% CI for all-cause death over 1 year using Cox proportional hazard models. To analyze the change in risk over time, we also estimated the HR at 1, 3, and 6 months after stroke. Model 1 was adjusted for demographic variables: age at stroke onset, sex, region of residence, country of birth, education, and calendar period. Model 2 was further adjusted for SLE-related comorbidities: congestive heart failure, hypertension, diabetes, atrial fibrillation, chronic kidney disease, and infection frailty. In a sensitivity analysis, we excluded individuals with an ICD-10 code for APS. To better account for age, a significant confounder, we stratified by age at stroke onset (< 65 and ≥ 65 yrs old), and to examine the role of anticoagulant use on all-cause mortality after hemorrhagic stroke, we stratified by history of anticoagulant use.

We plotted fully adjusted survival curves (Model 2) using inverse probability weights[19]. Last, to investigate whether deaths were considered to be attributable to stroke, we identified individuals for whom an ischemic, hemorrhagic, or unspecified stroke was stated as a main or contributory cause of death in the Cause of Death Register. The proportional hazards assumption for the Cox models was tested using Schoenfeld residuals and was found violated for the year-long followup model for ischemic stroke. However, we obtained similar HR estimates when we used parametric models, allowing flexibility in baseline hazard functions[20].

We examined functional impairment at 3 months in a subset of individuals who reported being functional before ischemic stroke onset in Riksstroke. We estimated the risk of functional impairment at 3 months using a modified Poisson model[21] comparing SLE to non-SLE while controlling for age, sex, region of residence, country of birth, education, calendar period, and receipt of rehabilitation. To address any bias due to missing data for the secondary outcome at the 3-month Riksstroke followup, we repeated the model assuming that individuals with missing outcomes had or not had functional impairment. We performed data management and analyses with SAS version 9.4 (SAS Institute Inc.) and Stata version 14.2 (StataCorp LP). All reported P values correspond to 2-sided tests. Missing values were included as an additional category in all analyses.

RESULTS

Characteristics at stroke onset. We included a total of 423 individuals with SLE and 1652 individuals without SLE at stroke onset. Table 1 depicts their baseline characteristics. Ischemic stroke was the most common type (87%). Patients with SLE were younger than non-SLE at stroke onset and less likely to be male. The prevalence of comorbidities was higher in the SLE group than in the general population, except atrial fibrillation in the eschemic stroke group. The use of medications for stroke prevention (anticoagulant, antiplatelet, and lipid-lowering) was higher in the SLE group. Ten percent of patients with SLE presented with a severe ischemic stroke and 8% received intensive care or thrombolysis (Table 2). In the hemorrhagic stroke group, about 1 in 3 patients with or without SLE had a severe stroke. Patients with SLE and hemorrhagic stroke were more likely to be admitted to an intensive care unit compared to those without SLE.

Mortality and functionality after ischemic stroke. During the year-long followup after ischemic stroke, 68 deaths (19%) occurred in the SLE group and 215 (15%) in the non-SLE group (Table 3), with about half occurring during the first month. Over 1 year, the demographics-adjusted HR for all-cause death was 1.85 (95% CI 1.39–2.45). Mortality was not increased in SLE compared to non-SLE during the first month after ischemic stroke (HR 1.10, 95% CI 0.71–1.72), but increased gradually thereafter (Figure 2A). The HR for mortality associated with SLE was higher for individuals aged < 65 years compared to those ≥ 65 years old (HR 2.29, 95% CI 0.99–5.30 vs HR 1.77, 95% CI 1.31–2.40, respectively). However, after adjusting for SLE-related comorbidities, the effect of SLE on all-cause death was attenuated at all timepoints. Results did not change in a sensitivity analysis in which we excluded individuals with APS. When we examined main and contributory causes of death in the Cause of Death Register, we observed that the more time since ischemic stroke, the less likely that stroke would be reported as a cause of death (49% for SLE and 61% for non-SLE at 12 mos).

SLE was associated with a 73% higher risk of functional impairment in those who were alive at 3 months (RR 1.73, 95% CI 1.16–2.57) after adjusting for demographic variables, period effects, and receipt of rehabilitation (Table 4). This finding persisted in sensitivity analyses addressing missing information for the outcome.

Mortality after hemorrhagic stroke. The majority of deaths following hemorrhagic stroke occurred during the first month [18 (30%) in SLE vs 41 (19%) in non-SLE; Table 3]. During the year-long period after stroke, SLE was associated with a more than 2-fold greater hazard of all-cause death (HR 2.30, 95% CI 1.38–3.82; Figure 2B). This was consistent at all 4 timepoints and was not attenuated after controlling for comorbidities. The increased mortality hazard in SLE was also observed in those younger and older than 65 years at onset, and those without a history of anticoagulant use at stroke onset (HR 2.86, 95% CI 1.68–4.88). The HR was not estimable for anticoagulant users because of the rarity of deaths. Stroke was almost always reported as a cause of death (72% at 12 mos for SLE and non-SLE).

DISCUSSION

To the best of our knowledge, this is the first study to use population-based data to investigate the survival of SLE patients after stroke, separately for ischemic and hemorrhagic

Table 1. Characteristics of individuals at ischemic or hemorrhagic stroke onset. Data are n (%) unless otherwise stated.

Characteristics	Ischemic Stroke		Hemorrhagic Stroke	
	SLE, n = 363	Non-SLE, n = 1436	SLE, n = 60	Non-SLE, n = 216
Median age at stroke onset (IQR), yrs	68 (57–76)	74 (66–80)	65 (50–75)	73 (66–79)
Male	65 (18)	339 (24)	7 (12)	48 (22)
Region of residence				
Middle Sweden	132 (36)	559 (39)	24 (40)	86 (40)
Southern Sweden	194 (53)	647 (45)	28 (47)	101 (47)
Northern Sweden	37 (10)	230 (16)	8 (13)	29 (13)
Country of birth				
Nordic	351 (97)	1358 (95)	54 (90)	208 (96)
Non-Nordic	12 (3)	78 (5)	6 (10)	8 (4)
Education, yrs				
≤ 9	150 (41)	747 (52)	25 (41)	110 (51)
10–12	145 (40)	482 (34)	25 (42)	66 (31)
> 12	67 (18)	195 (134)	8 (13)	38 (18)
Missing	1 (< 1)	12 (< 1)	2 (3)	2 (< 1)
Mean time since SLE diagnosis (SD), yrs	2.5 (15.5)	n/a	3.3 (17.6)	n/a
Stroke onset during or after 2006	219 (60)	716 (50)	33 (55)	118 (55)
Comorbidities				
Congestive heart disease	62 (17)	157 (11)	14 (23)	17 (8)
Hypertension	141 (39)	388 (27)	28 (47)	58 (27)
Diabetes	54 (15)	192 (13)	8 (13)	23 (11)
Atrial fibrillation	53 (15)	224 (16)	10 (17)	26 (12)
Chronic kidney disease	41 (11)	28 (2)	12 (20)	4 (2)
Infection frailty	96 (26)	69 (5)	24 (40)	8 (4)
Medications*	n = 219	n = 716	n = 33	n = 118
Anticoagulant	27 (12)	45 (6)	9 (27)	12 (10)
Antiplatelet	83 (38)	257 (36)	11 (33)	37 (31)
Lipid-lowering	60 (27)	176 (24)	10 (30)	28 (24)
Systemic corticosteroid	127 (58)	66 (9)	20 (61)	11 (9)
DMARD	83 (38)	12 (2)	14 (42)	0 (0)

* For strokes with onset after January 1, 2006, allowing for 6-month data accumulation in the Prescribed Drug Register. SLE: systemic lupus erythematosus; IQR: interquartile range; n/a: not applicable; DMARD: disease-modifying antirheumatic drug.

Table 2. Stroke management and functionality before stroke onset in individuals whose stroke was registered in Riksstroke. Data are n/total excluding missing (% of total excluding missing).

Variables	Ischemic Stroke		Hemorrhagic Stroke	
	SLE, n = 238	Non-SLE, n = 1101	SLE, n = 34	Non-SLE, n = 148
Severe stroke*	23/233 (10)	120/1071 (11)	10/32 (31)	32/137 (26)
ICU admission	118/222 (8)	47/946 (5)	6/30 (20)	14/131 (10)
Thrombolysis	118/220 (8)	54/934 (6)	n/a	n/a
Functional impairment before stroke onset	20/234 (9)	54/1094 (5)	3/32 (9)	13/145 (9)

* Score ≥ 2 on the Reaction Level Scale. SLE: systemic lupus erythematosus; ICU: intensive care unit; n/a: not applicable.

stroke. During the first month after ischemic stroke, patients with SLE have comparable mortality to patients without SLE. Our findings are similar to those reported by 2 cross-sectional studies from the United States[10,11] in which the proportions of stroke hospitalizations resulting in death were similar between SLE and non-SLE. However, in the year after ischemic stroke, a higher rate of all-cause death became apparent. This is possibly a reflection of the increased underlying mortality in individuals with SLE[22,23], as the higher hazard was attenuated after adjusting for SLE-related comorbidities. When examining mortality after hemorrhagic stroke, we found that patients with SLE have a more than 2-fold greater hazard of death compared to individuals without SLE.

Despite similar degrees of stroke severity and stroke care, individuals with SLE who survived at least 3 months after ischemic stroke were more likely to be functionally impaired compared to those without SLE. Our results are in contrast with a study that suggested similar disability outcomes

Table 3. Number of all-cause deaths and HR for all-cause death comparing patients with SLE to those without at 4 timepoints of the year-long followup.

Time Since Stroke Onset	All-cause Death*		HR (95% CI)	
	SLE	Non-SLE	Model 1†	Model 2‡
Ischemic stroke	n = 363	n = 1436		
1 mo	25 (7)	115 (8)	1.10 (0.71–1.72)	0.85 (0.53–1.37)
3 mos	40 (11)	152 (11)	1.43 (1.00–2.05)	1.11 (0.75–1.63)
6 mos	50 (14)	178 (12)	1.60 (1.16–2.22)	1.21 (0.85–1.71)
12 mos	68 (19)	215 (15)	1.85 (1.39–2.45)	1.41 (1.04–1.91)
Age < 65 yrs	12/149 (8)	12/304 (4)	2.29 (0.99–5.30)	1.92 (0.78–4.74)
Age ≥ 65 yrs	56/202 (26)	203/1132 (18)	1.77 (1.31–2.40)	1.35 (0.97–1.87)
Hemorrhagic stroke	n = 60	n = 216		
1 mo	18 (30)	41 (19)	2.37 (1.32–4.24)	1.73 (0.87–3.42)
3 mos	24 (40)	45 (21)	2.67 (1.57–4.54)	2.01 (1.08–3.75)
6 mos	25 (42)	49 (23)	2.53 (1.50–4.26)	1.94 (1.05–3.57)
12 mos	25 (42)	56 (26)	2.30 (1.38–3.82)	1.74 (0.95–3.17)
Age < 65 yrs	11/29 (38)	6/47 (13)	5.79 (1.60–20.86)	6.00 (1.23–29.10)
Age ≥ 65 yrs	14/31 (45)	50/169 (30)	1.84 (0.98–3.43)	1.67 (0.81–3.45)

* Data are n (%), or n/total in category (%) for age stratifications. † Adjusted for age at stroke onset, sex, region of residence, country of birth, education, and calendar period (stroke onset during or after 2006). ‡ Further adjusted for history of congestive heart disease, hypertension, diabetes, atrial fibrillation, chronic kidney disease, and infection frailty at stroke onset. SLE: systemic lupus erythematosus.

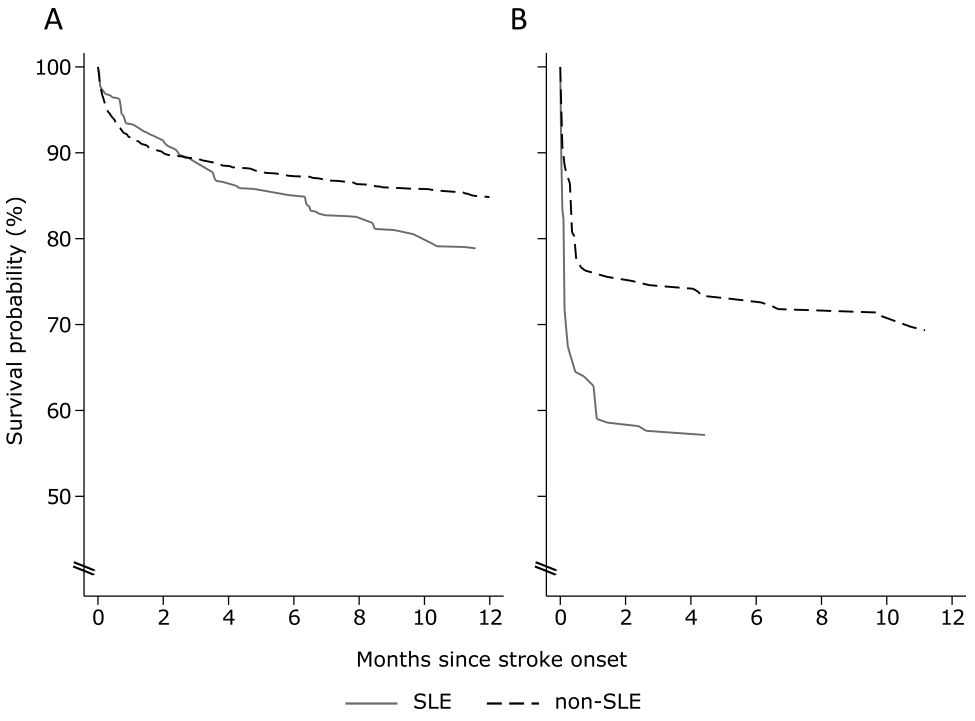

Figure 2. Survival probabilities of patients with and without SLE for up to 12 months after (A) ischemic stroke, and (B) hemorrhagic stroke. SLE: systemic lupus erythematosus.

between stroke patients with and without SLE who were discharged to rehabilitation facilities in the United States[12]. The differences in accessibility to rehabilitation between the United States and Sweden and the different outcome measures used may limit comparability.

Our study has considerable implications for clinical practice. The similar post-ischemic stroke mortality experience between patients with and without SLE that is observed during the first month suggests that the current practice of early initiation of primary prevention measures

Table 4. Functional impairment 3 months after ischemic stroke and receipt of rehabilitation in individuals functional at baseline and who responded to the Riksstroke 3-month followup questionnaire. Data are n (%).

Variables	SLE, n = 170	Non-SLE, n = 826
Functional impairment at 3 mos		
Yes	26 (16)	98 (12)
No	140 (82)	690 (84)
Missing*	4 (2)	38 (5)
Received rehabilitation		
Yes	32 (19)	146 (18)
No	125 (74)	555 (67)
Missing	13 (8)	125 (15)

* Data for at least 1 of the 3 questions on functionality (mobility, toileting, or dressing) were missing. SLE: systemic lupus erythematosus.

against stroke and SLE complications (e.g., anticoagulant, antihypertensive, and lipid-lowering treatments)[7] may have some benefit even for post-stroke survival. It would be interesting to investigate disease activity and disease duration in future studies to determine whether there are subgroups of individuals with SLE and stroke who carry the highest risk of mortality after stroke.

The increased risk of mortality after hemorrhagic stroke could be due to some carryover effect of the use of anticoagulants in treating SLE complications. However, our findings cannot be completely explained by anticoagulant use because nonusers had a similarly high hazard of death. Therefore, considering that our capacity to intervene is greatly limited by the fact that the increased hazard of death is evident even from the first month, potential measures should focus on reducing the risk of hemorrhagic stroke to lessen the risk of death. It should be noted, however, that the absolute risk of death from such an event is low because of its rarity.

The reasons for the observed differences in functional recovery after an ischemic stroke are not easy to disentangle. Possible explanations include functional impairment caused by other aspects of SLE (e.g., musculoskeletal damage, corticosteroid treatment side effects), a different pace or process of recovery in patients with SLE, or differences in reporting functional impairment[12]. In our study, the proportion of patients with SLE who reported functional impairment before ischemic stroke onset was only slightly higher than in the non-SLE group (Table 2). Because patients included in the analysis had no functional impairment at baseline, it is unclear whether 3 months after stroke is enough time for SLE-related features to explain the observed association. Further, we assume that differences in reporting impairment between SLE and non-SLE are less likely because we used a basic and robust measure of disability. We thus advocate for further studies focusing on how to decrease functional impairment in stroke patients with SLE.

There are some limitations to our study. We may have missed a small number of strokes that were either cared for outside hospitals (e.g., nursing homes), or strokes that led to immediate death, but this was unlikely to differ between SLE and non-SLE. We did not include individuals who received their SLE diagnosis after experiencing a stroke. Moreover, the ICD-10 code for APS has not been validated in our data and we have likely missed a number of individuals with the syndrome. Our study covers a long time span during which the SLE definition was changed as a result of the addition of outpatient data to the NPR in 2001, stroke management in Sweden changed markedly with the expansion of stroke units[24], and SLE survival likely improved. Nonetheless, all models were adjusted for calendar period to account for those differences. Last, we required that individuals survive for at least 3 months in our functional outcome assessment, a practice that may have introduced selection bias. However, given that there was no significant association between SLE and 3-month mortality in those with ischemic stroke, we suspect that this bias was negligible.

The main strength of our study is the use of nationwide and population-based registers, which minimized selection bias and achieved the necessary statistical power to consider ischemic and hemorrhagic stroke separately. The linkage to Riksstroke provided relevant clinical variables and the possibility to study functionality in a subset of these patients. In addition, the use of the NPR with its excellent coverage allowed for an accurate identification of SLE and stroke[13,14].

Stroke severity and management for patients with SLE are similar to those of the general population. The observed increased mortality 1 year after ischemic stroke is likely a result of the higher underlying mortality in SLE, evident even in the pre-stroke period. However, mortality is more than twice as high after a hemorrhagic stroke, with the factors accountable for these differences remaining unknown. Better identification of patients who are at risk of a hemorrhagic stroke, which is a complication with severe consequences, is needed. The increase in functional disability after stroke in SLE, despite similar stroke severity and care, further underscores the importance of stroke prevention among patients with SLE by early identification of risk factors for stroke and immediate initiation of evidence-based measures to prevent disability.

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APPENDIX 1. International Classification of Diseases (ICD) codes from the Swedish version of the classification system used to retrieve information on comorbidities.

(a) **Congestive heart disease** (ICD-10 I42, I50; ICD-9 425, 428; ICD-8 425, 427.00, 427.10, 428.90), (b) **hypertension** (ICD-10 I10-I15; ICD-9 401-405; ICD-8 400-404), (c) **diabetes** (ICD-10 E10-E14; ICD-9 250; ICD-8 250), (d) **atrial fibrillation** (ICD-10 I48; ICD-9 427D; ICD-8 427.92), (e) **chronic kidney disease** (ICD-10 N18, N19; ICD-9/8 585, 586), (d) **antiphospholipid syndrome** (ICD-10 D86.6), and (f) **infection frailty** (ICD-10 A00-B99, G00-G02, G04.2, G05-G07, H66, H67, H70, J00-J22, J32, J34.0, J36, J38.3, J39.0, J39.1, K10.2, L00-L08, M00, M01, M46.2-M46.5, M86, N10, N30.0; ICD-9 001-139, 320-322, 382, 383, 460-466, 475, 480-487, 562E, 562F, 590, 680-686, 711A, 711E, 730, 790H, 695; ICD-8 000-136, 320, 322, 381-383, 460-466, 470-474, 480-486, 501, 426.40, 590, 680-686, 710, 720, 782.90).