JCN Open Access ORIGINAL ARTICLE

pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2020;16(4):605-611 / https://doi.org/10.3988/jcn.2020.16.4.605

Causes, Risk Factors, and Clinical Outcomes of Stroke in Korean Young Adults: Systemic Lupus Erythematosus is Associated with Unfavorable Outcomes

Hyuk Sung Kwon[a]
Young Seo Kim[a], Jong-Min Lee[a]
Seong-Ho Koh[a], Hyun Young Kim[a]
Chulho Kim[b], Seung-Hoon Lee[c]
Keun-Hwa Jung[c], Young Dae Kim[d]
Hyung-Min Kwon[e]
Beom Joon Kim[f], Jeong-Min Kim[g]
Bum Joon Kim[h], Sung Hyuk Heo[i]
Dae-Il Chang[j], on Behalf of the SKY Investigators

[a]Department of Neurology, Hanyang University College of Medicine, Seoul, Korea
[b]Department of Neurology, Hallym University Sacred Heart Hospital, Chuncheon, Korea
[c]Department of Neurology, Seoul National University Hospital, Seoul, Korea
[d]Department of Neurology, Yonsei University College of Medicine, Seoul, Korea
[e]Department of Neurology, Seoul National University College of Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, Korea
[f]Department of Neurology and Cerebrovascular Center, Seoul National University Bundang Hospital, Seongnam, Korea
[g]Department of Neurology, Chung-Ang University Hospital, Seoul, Korea
[h]Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[i]Department of Neurology, Kyung Hee University College of Medicine, Seoul, Korea

Received February 4, 2020
Revised June 1, 2020
Accepted June 2, 2020

Correspondence
Young Seo Kim, MD, PhD
Department of Neurology, Hanyang University College of Medicine, 222 Wangsimni-ro, Seongdong-gu, Seoul 04763, Korea
Tel +82-2-2290-8375
Fax +82-2-2290-2391
E-mail aescula@hanmail.net

Background and Purpose The incidence of ischemic stroke (IS) in young adults is increasing, and the associated large socioeconomic impact makes understanding IS in young adults important. We investigated the causes of and risk factors for IS in young adults, and their impact on outcomes.

Methods The Stroke in Korean Young Adults (SKY) study is a standardized multicenter prospective study involving eight medical centers of the Republic of Korea. First-ever IS patients aged 18 years to 44 years were prospectively included in this study within 7 days of stroke onset. Their outcomes at 3 months were analyzed.

Results This study enrolled 270 patients from April 2014 to December 2018, most (67.8%) of whom were male. About 41.5% of the patients had one or more vascular risk factors from among hypertension, diabetes mellitus, and dyslipidemia. However, only half of them had received regular treatment. Arterial dissection was more common in males, and systemic lupus erythematosus (SLE) and Moyamoya disease were more common in females. The outcome was favorable (modified Rankin Scale score of 0 or 1) in 81.9% of the patients at 3 months after stroke onset. More severe initial symptoms, higher initial glucose level, and SLE as a comorbidity were associated with unfavorable outcomes.

Conclusions Young adult IS patients in Korea exhibit low awareness and poor management of their risk factors. Although the short-term outcome was relatively favorable in those patients, having SLE was associated with unfavorable outcomes. More attention needs to be paid for improving awareness and controlling risk factors in this population.

Key Words ischemic stroke, young adults, outcome, systemic lupus erythematosus.

INTRODUCTION

The incidence of ischemic stroke (IS) in young adults is increasing substantially worldwide.[1,2] Since young adults have long lifespans ahead of them and are productive members of the labor force, knowledge about IS in young adults deserves more attention.[2] However, investigating the causes of and risk factors for stroke in young adults is often challenging. Current guidelines provide limited information on the clinical management of stroke in young adults.[3] In addition, most studies involving young stroke victims have had retrospective designs and been limited by missing data, nonstandardized evaluations, and high dropout rates during follow-up.

The prevalence of traditional vascular risk factors is increasing in young adult patients with IS, and their origins differ from those of older adults.[1] IS in young adults is associated with arterial dissection, Moyamoya disease (MMD), primary and secondary central ner-

vous system vasculitis, antiphospholipid syndrome (APS), reversible cerebral vasoconstriction syndrome (RCVS), cerebral venous thrombosis (CVT), and genetic diseases such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and Fabry disease. However, the causes of 15−35% of the strokes in young adults are still unidentified.[4] In addition, the connection between these etiological factors and stroke outcomes remains unclear.

The Stroke in Korean Young Adults (SKY) study aimed to evaluate the traditional and emerging risk factors for stroke in young adults. We also investigated the etiologies, treatments, and outcomes of stroke in these patients.

METHODS

Study design and diagnostic workup

The SKY study is a standardized multicenter prospective study performed in eight medical centers in the Republic of Korea. Details of the rationale and design of this study have been reported previously.[5] From April 2014 to December 2018, 270 patients with first-ever IS visited the Department of Neurology, and those aged 18 years to 44 years were consecutively enrolled as case subjects. We intended to include 470 case subjects and 470 age- and sex-matched community control subjects.[5] However, we stopped adding patients after enrolling 270 case subjects because an interim analysis of the association between job strain and IS produced somewhat positive results.

Demographic data were collected, and brain imaging, cardiac evaluations, and laboratory studies were performed as described previously.[5] For the cardiac evaluations, all of the available patients underwent 24-hour Holter monitoring, transthoracic echocardiography, and transesophageal echocardiography. We sought to identify well-supported risk factors and uncommon etiologies among the young patients with IS. In addition, the acute management and 3-month outcomes of acute IS were investigated. The study was approved by the ethics committee at each participating center, and is registered at clinicaltrials.gov under the number NCT02682914.

Stroke classification, definition of other etiologies, and follow-up

The IS subtypes were classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[6] The classification was reviewed independently by two neurologists, and a consensus approach was applied if there were discrepancies. Stroke in a patient with both high- and moderate-risk cardiac sources of embolism and no other cause of stroke was considered a case of cardioembolic stroke.[6]

Arterial dissection was diagnosed by angiography if there was a double lumen, intramural hematoma, nonatherosclerotic tapered, flame-shaped stenosis/occlusion or pearl-and-string sign, or a dissecting aneurysm at a nonbranching site.[7] MMD was diagnosed if there was chronic, occlusive cerebrovascular disease with Moyamoya vessels.[8] Systemic lupus erythematosus (SLE) was diagnosed according to the classification criteria of the Systematic Lupus International Collaborating Clinics group,[9] and was regarded as the culprit etiology when an event was not assigned to a conventional stroke etiology. The updated Sapporo classification criteria were used for APS.[10] RCVS was characterized by thunderclap headaches and diffuse segmental constriction of the cerebral arteries that resolved within 3 months.[11] If a thrombus in a venous sinus was detected by magnetic resonance or computed tomography venography in clinically suspected patients, CVT was diagnosed.[12] Two patients died, and the remaining 268 of the 270 patients were followed up to 3 months in the outpatient clinic of each hospital. Modified Rankin Scale (mRS) scores were obtained at 3 months.

Statistical analysis

Mean±SD values were calculated for continuous variables, and numbers with percentages were calculated for discrete variables. We used Student's *t*-tests, the chi-square test, and the Mann-Whitney U test to evaluate differences between groups. Correlations between clinical characteristics and a favorable outcome (mRS score of 0 or 1) were measured by logistic regression analysis, adjusting covariates for which $p<0.2$ in the univariate analysis. The adjusted variables were the initial National Institutes of Health Stroke Scale (NIHSS) score, a patent foramen ovale (PFO), SLE, RCVS, white-blood-cell count, and blood urea nitrogen, fasting glucose, and fibrinogen levels.

RESULTS

Demographic data and risk factors

The 270 enrolled patients were aged 37.1±6.3 years, of which 183 were males. The median NIHSS score was 2 [interquartile range (IQR)=0−4] at admission and 1 (IQR=0−2) at discharge. At discharge, 30.0% of the patients had hypertension, 12.2% had diabetes mellitus (DM), and 17.4% had dyslipidemia. However, the risk factors had been known and treated regularly for only half of the patients. In addition, 47.8% of them were current smokers and 17.8% were obese [body mass index (BMI) ≥30.0 kg/m^2].

The baseline characteristics including demographic data and risk factors are presented in Table 1. The males were significantly older than the females (mean age=37.9 years vs. 35.4 years, $p=0.002$) and they had significantly higher rates of hy-

pertension (p=0.021) and current smoking (p<0.001), and a higher BMI (p<0.001). There were no other sex-related differences.

Subtypes of ischemic stroke and other determined etiologies

The IS subtypes according to the TOAST classification are

Table 1. Baseline characteristics including classification of ischemic stroke in the study patients

	Total (n=270)	Males (n=183)	Females (n=87)	p
Demographics				
Age, years	37.1±6.3	37.9±5.8	35.4±7.0	0.002
Risk factor				
Hypertension	81 (30.0)	63 (34.4)	18 (20.7)	0.021
Diabetes mellitus	33 (12.2)	27(14.8)	6 (6.9)	0.065
Dyslipidemia	47 (17.4)	35 (19.1)	12 (13.8)	0.280
Current smoking	129 (47.8)	110 (60.1)	19 (21.8)	<0.001
Atrial fibrillation	6 (2.2)	2 (1.1)	4 (4.6)	0.087
Coronary artery disease	4 (1.5)	3 (1.6)	1 (1.1)	1.000
PFO	23 (8.5)	15 (8.2)	8 (9.2)	0.784
Chronic kidney disease	11 (4.1)	5 (2.7)	6 (6.9)	0.183
BMI, kg/m^2	25.5±5.0	26.3±4.4	23.8±5.7	<0.001
Obesity	48 (17.8)	34 (18.6)	14 (16.1)	0.617
Medication history				
Antihypertensives	46 (17.0)	35 (19.1)	11 (12.6)	0.186
Antidiabetes	16 (5.9)	10 (5.5)	6 (6.9)	0.641
Statins	30 (11.1)	22 (12.0)	8 (9.2)	0.490
Stroke subtype				0.065
Large-artery disease	42 (15.6)	35 (19.1)	7 (8.0)	
Small-vessel occlusion	48 (17.8)	37 (20.2)	11 (12.6)	
Cardioembolism*	34 (12.6)	20 (10.9)	14 (16.1)	
Undetermined, two or more	2 (0.7)	2 (1.1)	0 (0.0)	
Undetermined, negative	55 (20.4)	33 (18.0)	22 (25.3)	
Undetermined, incomplete	1 (0.4)	1 (0.5)	0 (0.0)	
Other determined	88 (32.6)	55 (30.1)	31 (35.6)	
Dissection	38 (14.1)	30 (16.4)	8 (9.2)	0.112
SLE†	10 (3.7)	1 (0.5)	9 (10.3)	<0.001
Moyamoya disease	10 (3.7)	2 (1.1)	8 (9.2)	0.002
APS without SLE	8 (3.0)	7 (3.8)	1 (1.1)	0.443
Cerebral venous thrombosis	6 (2.2)	3 (1.6)	3 (3.4)	0.391
RCVS	4 (1.5)	3 (1.6)	1 (1.1)	1.000
CADASIL	2 (0.7)	2 (1.1)	0 (0.0)	1.000
Primary angiitis of CNS	2 (0.7)	2 (1.1)	0 (0.0)	1.000
Thrombosed aneurysm	2 (0.7)	2 (1.1)	0 (0.0)	1.000
Others‡	6 (2.2)	3 (1.6)	3 (1.6)	1.000
Lesion location				0.469
Anterior circulation	147 (54)	95 (52)	52 (60)	
Posterior circulation	115 (43)	82 (45)	33 (38)	
Combined	8 (3)	6 (3)	2 (2)	
Initial NIHSS score	2 (0–4)	2 (1–4)	2 (0–4)	0.908

Data are mean±SD, median (interquartile range), or n (%) values. Obesity was defined as BMI ≥30.0 kg/m^2. Pearson's chi-square test, Student's t-test, Fisher's exact test, and the Mann-Whitney U test were used as appropriate.

*One patient had both SLE and dilated cardiomyopathy, †If both SLE and APS were present, SLE was considered the etiology, ‡Others include radiation-induced angiopathy, hyperhomocysteinemia, Fabry disease, aortic angiosarcoma, hypereosinophilic syndrome, and calcium pyrophosphate deposition.

APS: antiphospholipid syndrome, BMI: body mass index, CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, CNS: central nervous system, NIHSS: National Institutes of Health Stroke Scale, PFO: patent foramen ovale, RCVS: reversible cerebral vasoconstriction syndrome, SLE: systemic lupus erythematosus.

listed in Table 1. Patients were classified as follows: large artery disease in 42 patients (15.6%), small vessel occlusion in 48 (17.8%), cardioembolism in 34 (12.6%), other determined etiologies in 88 (32.6%), and undetermined etiology in 58 (21.5%). Among the 34 patients with cardioembolic stroke, 6 (17.6%) had atrial fibrillation (3 lone and 3 other than lone), 18 (52.9%) had PFO, 2 (5.9%) had recent myocardial infarction, 2 (5.9%) had a mechanical prosthetic valve, 2 (5.9%) had mitral stenosis, 2 (5.9%) had myxoma, 1 (2.9%) had dilated cardiomyopathy, and 1 (2.9%) had infective endocarditis. The 88 patients with other determined etiologies comprised 38 (14.1%) with arterial dissection, 11 (4.4%) with SLE, 10 (3.7%) with MMD, 8 (3.0%) with primary APS without SLE, 6 (2.2%) with CVT, 4 (1.5%) with RCVS, and 2 each (0.7%) with CADASIL, primary angiitis, and thrombosed aneurysm (Table 1). One patient with both SLE and dilated cardiomyopathy was included in SLE, but the cause was classified as cardioembolism. Males had a higher rate of arterial dissection and females a higher rate of SLE and MDD. Factor V Leiden was not identified in any patient.

Clinical outcomes and factors associated with unfavorable outcomes

The characteristics of patients according to favorable and unfavorable outcomes at 3 months are presented in Table 2. Patients with an unfavorable outcome had a higher initial NIHSS score, SLE and higher white-blood-cell count. Intravenous thrombolysis (IVT) and/or intra-arterial thrombectomy (IAT) were applied to 24 patients (8.9%). Early neurological improvement (NIHSS score of 0 to 1 or improvement of ≥8 at discharge) occurred in 56% of those who received IVT alone and in 73% of those who received IAT with or without IVT. However, the proportion of patients receiving IAT or IVT did not differ between the two subgroups (Table 2).

During the 3-month follow-up there were five (1.8%) stroke events (four IS and one hemorrhagic stroke), and two (0.7%) patients died. There were no myocardial infarction events, and post-stroke seizure occurred in four (1.4%) patients. At 3 months after stroke onset, 81.9% of the patients (213 of 260) had a favorable outcome (mRS score of 0 or 1), while more than 90.4% of them had an mRS score of ≤2 (Fig. 1). After adjusting for potential confounding variables, higher initial NIHSS score, higher initial glucose level, and having SLE were associated with an unfavorable outcome (Table 3).

DISCUSSION

This study found relatively favorable outcomes in young-adult IS patients. More than 80% and 90% of the included patients had mRS scores of ≤1 and ≤2, respectively, at 3 months after stroke onset. This proportion was much higher than in patients of all ages, 50% of whom reportedly had an mRS score of 0 or 1 at 3 months.[13] An unfavorable outcome was associated with higher initial NIHSS score, higher initial glucose level, and SLE as comorbidity. IS was more common in males than females (67.8% vs 32.2%). About 41.5% of the patients had one or more of the vascular risk factors among hypertension, DM, and dyslipidemia, but only half of them had been aware of their risk factors and received regular treatment. We consider that neglect of these risk factors could be an important cause of IS in young patients.

Poststroke mortality occurred in only two (0.7%) patients during the 3-month follow-up, and five (1.8%) patients suffered recurrent stroke. These outcomes are more favorable than in previous reports. In a Swiss prospective study involving 624 IS patients, 61% and 85% had mRS scores of ≤1 and ≤2, respectively.[14] In a French study, mRS scores of ≤2 were present in 87% of 287 young adults with IS after 3 years of follow-up.[15] The higher rate of favorable outcomes in our study may have been due to improved stroke treatments including the use of mechanical thrombectomy. Fourteen of the 15 patients who received IAT showed recanalization more than Thrombolysis in Cerebral Infarction (TICI) grade 2b, and 11 patients showed early neurological improvement. The patients who benefited from IAT may have shifted from poor outcome patients to favorable-outcome patients. Thus, investigating the IAT outcomes of young IS patients would be useful.

Our detailed and standardized evaluation of the etiologies of stroke in young adults classified 31.9% of the patients as other determined etiologies. Arterial dissection was more common in males, and SLE and MMD were more common in females. Having SLE was associated with poor outcome.

According to our results, the initial NIHSS scores did not differ between patients with and without SLE (median=2 vs. 2, IQR=1−6 vs. 0−4; p=0.393). However, SLE was associated with poor functional outcome at 3 months after stroke onset. We can therefore speculate that cerebrovascular inflammation due to autoantibodies leads to poor recovery after IS. In addition, inflammation may damage diverse other organs such as the kidneys, lungs, and heart, and lead to poor stroke outcome.[16] In contrast to our results, there are previous reports of outcomes being similar in patients with and without SLE after stroke onset.[17] However, those studies had retrospective designs, included all age groups, and had low proportions of patients with SLE (0.2−0.3%). Our study included only young adult patients, and had a much higher proportion of SLE patients (4.1%). Although SLE itself could not be an independent risk factor for IS, we believe that having SLE may be a poor prognostic factor for IS in young patients,

and so more careful management may be called for.

We found that a higher initial glucose level was independently associated with poor outcome. This is consistent with previous studies showing an association between hyperglycemia on admission and a worse clinical outcome of IS.[18,19] The release of catecholamine and inflammatory cytokines

Table 2. Baseline characteristics of patients with favorable and unfavorable outcomes at 3 months

	mRS score=0 or 1 at 3 months		*p*
	Yes (*n*=213)	No (*n*=57)	
Demographics			
Age, years	37.2±6.3	36.8±6.3	0.636
Sex, male	146 (69)	37 (65)	0.602*
Risk factor			
Hypertension	60 (28)	21 (37)	0.204*
Diabetes mellitus	24 (11)	9 (16)	0.355*
Dyslipidemia	37 (17)	10 (18)	0.976*
Current smoking	99 (47)	30 (53)	0.409*
Atrial fibrillation	4 (2)	2 (4)	0.610†
Coronary heart disease	4 (2)	0 (0)	0.582†
PFO	22 (10)	1 (2)	0.059†
Chronic kidney disease	7 (3)	4 (7)	0.252†
Body mass index, kg/m^2	25.5±4.8	25.4±5.7	0.899
Clinical findings			
Initial NIHSS score	1 (0–3)	4 (2–8)	<0.001†
Initial SBP, mm Hg	147.2±32.7	150.5±27.3	0.484
Initial DBP, mm Hg	88.2±19.9	91.0±19.3	0.339
Other etiologies			
Dissection	31 (15)	7 (13)	0.661*
SLE	6 (3)	5 (9)	0.043*
APS without SLE	7 (3)	1 (2)	1.000†
Cerebral venous thrombosis	6 (3)	0 (0)	0.348†
RCVS	2 (1)	2 (4)	0.197†
Laboratory findings			
White-blood-cell count, 10^3/mm^3	8.5±2.8	9.5±3.1	0.030
Hemoglobin, g/dL	14.7±2.0	14.3±2.0	0.191
Blood urea nitrogen, mg/dL	13.4±5.8	15.4±10.8	0.196
Creatinine, mg/dL	0.9±1.0	0.9±0.8	0.881
Total cholesterol, mg/dL	188.3±45.4	185.7±63.9	0.727
Low-density lipoprotein, mg/dL	115.8±38.8	110.6±40.6	0.373
Glucose, mg/dL	118.7±44.3	133.0±73.1	0.187
Hemoglobin A1c, %	5.9±1.5	6.1±1.6	0.335
C-reactive protein, mg/dL	1.1±2.5	2.0±5.3	0.208
Erythrocyte sedimentation rate, mm/hour	14.5±18.1	16.8±19.4	0.387
Homocysteine, mmol/L	10.3±5.7	10.7±6.7	0.709
Fibrinogen, mg/dL	323.0±101.1	355.2±153.7	0.069
Thyroid-stimulating hormone, mIU/mL	2.2±5.7	2.5±8.2	0.814
Acute management			
IVT only	6 (2.8)	3 (5.3)	0.290†
IAT with/without IVT	11 (5.2)	4 (7.0)	0.393†

Data are mean±SD, median (interquartile range), or *n* (%) values. Student's *t*-test was used except where indicated otherwise.
*Pearson's chi-square test, †Mann-Whitney U test, ‡Fisher's exact test.
APS: antiphospholipid syndrome, DBP: diastolic blood pressure, IAT: intra-arterial thrombectomy, IVT: intravenous thrombolysis, mRS: modified Rankin scale, NIHSS: National Institutes of Health Stroke Scale, PFO: patent foramen ovale, RCVS: reversible cerebral vasoconstriction syndrome, SBP: systolic blood pressure, SLE: systemic lupus erythematosus.

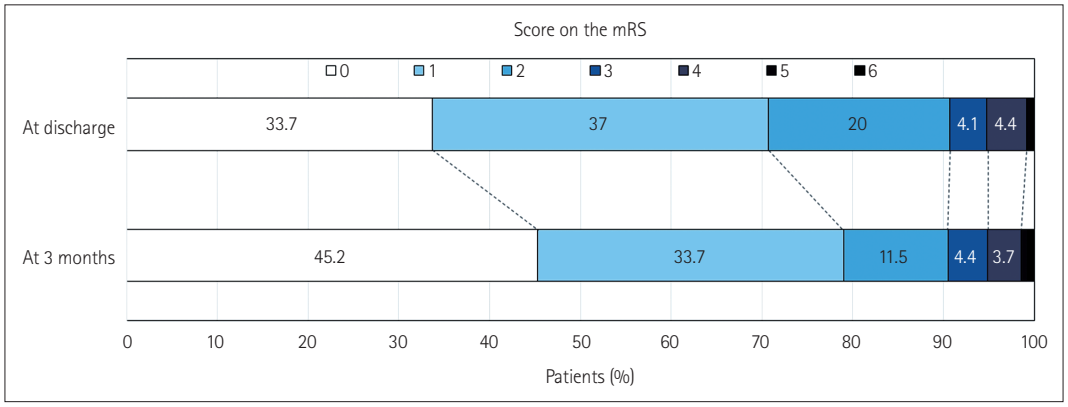

Fig. 1. mRS scores at discharge and after 3 months. The mRS scores range from 0 to 6: 0, no symptoms; 1, no clinically significant disability; 2, slight disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability; and 6, death. About 90% of patients had a good outcome (mRS score ≤2) at 3 months after stroke onset. mRS: modified Rankin Scale.

Table 3. Results of multivariable logistic regression analysis of potential factors for an unfavorable outcome

	Unadjusted OR	Adjusted OR	*p*
Initial NIHSS score	1.225 (1.135–1.321)	1.209 (1.115–1.311)	<0.001
PFO	0.155 (0.020–1.176)	0.180 (0.017–1.924)	0.156
SLE	3.317 (0.974–11.294)	4.633 (1.068–20.101)	0.041
RCVS	3.836 (0.528–27.850)	4.545 (0.483–42.798)	0.186
White-blood-cell count, per $10^3/mm^3$ increase	1.109 (1.009–1.220)	1.082 (0.959–1.221)	0.205
Blood urea nitrogen, per 1 mg/dL increase	1.032 (0.996–1.070)	1.032 (0.990–1.075)	0.141
Glucose, per 1 mg/dL increase	1.005 (0.999–1.010)	1.006 (1.000–1.012)	0.049
Fibrinogen, per 1 mg/dL increase	1.002 (1.000–1.005)	1.000 (0.997–1.003)	0.941

p values are for the multivariate model. Data are OR (95% confidence interval) values. Adjusted for covariates for which $p<0.2$ in the univariate analysis (NIHSS score, PFO, SLE, RCVS, white-blood-cell count, blood urea nitrogen, fasting glucose, and fibrinogen).
NIHSS: National Institute of Health Stroke Scale, OR: odds ratio, PFO: patent foramen ovale, RCVS: reversible cerebral vasoconstriction syndrome SLE: systemic lupus erythematosus.

after IS might increase the glucose level,[18] and an elevated glucose level can exacerbate ischemic brain injury by enhancing edema, diminishing vascular reactivity, promoting disruption of the blood–brain barrier, and provoking lactic acidosis and the production of free radicals.[18,19]

Previous Korean studies had a male preponderance, as in our study.[20,21] Higher prevalence rates of hypertension and smoking and a higher BMI in males seem to be the reasons for this difference. A previous multicenter study of IS in young Korean adults (aged between 15 and 45 years) from 2007 to 2010 found hypertension in 18.0%, DM in 7.8%, and dyslipidemia in 2.6% of the enrolled patients. Since the diagnostic criteria for risk factors were not described in detail in that report, direct comparisons might not be justified. However, most of the risk factors including HTN, DM, dyslipidemia, and BMI (mean: 24.1 kg/m^2→25.5 kg/m^2) appear to have increased in frequency.[20] In our study, the rates of traditional risk factors were increasing but the awareness and treatment rates were relatively low, which might increase the incidence of stroke. Sustained efforts are required to improve the awareness and treatment of traditional vascular risk factors.

This study was subject to some limitations. First, we enrolled patients from a single ethnic group (Korean) and observed them for only 3 months. However, the study data might be applicable at least to all Asians, and ongoing follow-up may provide further significant results. Second, we only included IS patients. However, information about this single group is also meaningful. Third, mostly metropolitan centers were included in this study, and lifestyle and risk factors may differ between rural and urban areas. However, young adults tend to live in cities and we believe that the data for the total population of young patients would not differ greatly.[22] Fourth, since SLE was diagnosed in only 4.1% of the participants and this condition is accompanied by many systemic problems, caution is needed when interpreting the results. Finally, excluding patients with recurrent stroke and those admitted to departments other than neurology due to a need for surgery or the presence of severe trauma may have been responsible for the relatively good prognoses in our study.

In conclusion, the findings of this study emphasize the importance of improving the awareness and prevention of traditional vascular risk factors for IS in young adults, including

hypertension, DM, dyslipidemia, smoking, and obesity. Although the outcomes tended to be favorable with a good response to thrombolysis, SLE was associated with poor functional outcome.

Author Contributions

Conceptualization: Hyuk Sung Kwon, Young Seo Kim, Seung-Hoon Lee. Data curation: Seong-Ho Koh, Hyun Young Kim, Chulho Kim, Seung-Hoon Lee, Keun-Hwa Jung, Young Dae Kim, Hyung-Min Kwon, Beom Joon Kim, Jeong-Min Kim, Bum Joon Kim, Sung Hyuk Heo, Dae-Il Chang. Formal analysis: Hyuk Sung Kwon, Jong-Min Lee, Young Seo Kim. Funding acquisition: Young Seo Kim. Methodology: Hyuk Sung Kwon, Young Seo Kim, Seong-Ho Koh, Hyun Young Kim, Chulho Kim, Seung-Hoon Lee, Keun-Hwa Jung, Young Dae Kim, Hyung-Min Kwon, Beom Joon Kim, Jeong-Min Kim, Bum Joon Kim, Sung Hyuk Heo, Dae-Il Chang. Supervision: Seong-Ho Koh, Hyun Young Kim, Chulho Kim, Seung-Hoon Lee, Keun-Hwa Jung, Young Dae Kim, Hyung-Min Kwon, Beom Joon Kim, Jeong-Min Kim, Bum Joon Kim, Sung Hyuk Heo, Dae-Il Chang. Visualization: Hyuk Sung Kwon. Writing—original draft: Hyuk Sung Kwon. Writing—review & editing: Young Seo Kim.

ORCID iDs

Hyuk Sung Kwon	https://orcid.org/0000-0002-2005-0983
Young Seo Kim	https://orcid.org/0000-0002-7050-3426
Jong-Min Lee	https://orcid.org/0000-0002-0892-6217
Seong-Ho Koh	https://orcid.org/0000-0001-5419-5761
Hyun Young Kim	https://orcid.org/0000-0003-2105-1547
Chulho Kim	https://orcid.org/0000-0001-8762-8340
Seung-Hoon Lee	https://orcid.org/0000-0001-8614-8345
Keun-Hwa Jung	https://orcid.org/0000-0003-1433-8005
Young Dae Kim	https://orcid.org/0000-0001-5750-2616
Hyung-Min Kwon	https://orcid.org/0000-0002-6101-7127
Beom Joon Kim	https://orcid.org/0000-0002-2719-3012
Jeong-Min Kim	https://orcid.org/0000-0001-7213-5527
Bum Joon Kim	https://orcid.org/0000-0002-3278-3252
Sung Hyuk Heo	https://orcid.org/0000-0002-9215-5119
Dae-Il Chang	https://orcid.org/0000-0001-7638-5830

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Acknowledgements

This work was supported by the research fund of the Korean Cerebrovascular Research Institute.

REFERENCES

1. George MG, Tong X, Bowman BA. Prevalence of cardiovascular risk factors and strokes in younger adults. *JAMA Neurol* 2017;74:695-703.
2. Ekker MS, Boot EM, Singhal AB, Tan KS, Debette S, Tuladhar AM, et al. Epidemiology, aetiology, and management of ischaemic stroke in young adults. *Lancet Neurol* 2018;17:790-801.
3. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2018;49:e46-e110.
4. Kefi A, Larbi T, Abdallah M, Ouni AE, Bougacha N, Bouslama K, et al. Young ischemic stroke in Tunisia: a multicentric study. *Int J Neurosci* 2017;127:314-319.
5. Kwon HS, Kim C, Lee SH, Jung KH, Kim YD, Kwon HM, et al. Protocol of the stroke in Korean young adults study: a multicenter case-control study and prospective cohort study. *J Stroke Cerebrovasc Dis* 2016;25:1503-1508.
6. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of org 10172 in acute stroke treatment. *Stroke* 1993;24:35-41.
7. Kim JS, Lee HB, Kwon HS. RNF213 polymorphism in intracranial artery dissection. *J Stroke* 2018;20:404-406.
8. Kim JS. Moyamoya disease: epidemiology, clinical features, and diagnosis. *J Stroke* 2016;18:2-11.
9. Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012;64:2677-2686.
10. 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.
11. Ducros A. Reversible cerebral vasoconstriction syndrome. *Lancet Neurol* 2012;11:906-917.
12. Saposnik G, Barinagarrementeria F, Brown RD Jr, Bushnell CD, Cucchiara B, Cushman M, et al. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011;42:1158-1192.
13. Kim BJ, Park JM, Kang K, Lee SJ, Ko Y, Kim JG, et al. Case characteristics, hyperacute treatment, and outcome information from the clinical research center for stroke-fifth division registry in South Korea. *J Stroke* 2015;17:38-53.
14. Goeggel Simonetti B, Mono ML, Huynh-Do U, Michel P, Odier C, Sztajzel R, et al. Risk factors, aetiology and outcome of ischaemic stroke in young adults: the Swiss Young Stroke Study (SYSS). *J Neurol* 2015;262:2025-2032.
15. Leys D, Bandu L, Hénon H, Lucas C, Mounier-Vehier F, Rondepierre P, et al. Clinical outcome in 287 consecutive young adults (15 to 45 years) with ischemic stroke. *Neurology* 2002;59:26-33.
16. Tsokos GC. Systemic lupus erythematosus. *N Engl J Med* 2011;365:2110-2121.
17. Nguyen-Oghalai TU, Wu H, McNearney TA, Granger CV, Ottenbacher KJ. Functional outcome after stroke in patients with rheumatoid arthritis and systemic lupus erythematosus. *Arthritis Rheum* 2008;59:984-988.
18. Hu GC, Hsieh SF, Chen YM, Hu YN, Kang CL, Chien KL. The prognostic roles of initial glucose level and functional outcomes in patients with ischemic stroke: difference between diabetic and nondiabetic patients. *Disabil Rehabil* 2012;34:34-39.
19. Lindsberg PJ, Roine RO. Hyperglycemia in acute stroke. *Stroke* 2004;35:363-364.
20. Park WB, Cho JS, Shin SD, Kong SY, Kim JJ, Lim YS, et al. Comparison of epidemiology, emergency care, and outcomes of acute ischemic stroke between young adults and elderly in Korean population: a multicenter observational study. *J Korean Med Sci* 2014;29:985-991.
21. Kwon SU, Kim JS, Lee JH, Lee MC. Ischemic stroke in Korean young adults. *Acta Neurol Scand* 2000;101:19-24.
22. Cortright J. Young and Restless and the Nation's Cities [Internet]. Portland, OR: City Observatory;2014 [cited 2020 Feb 3]. Available from: http://cityobservatory.org/ynr/.