Nephrotic Syndrome is Associated with Increased Risk of Ischemic Stroke

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Background: To determine if the nephrotic syndrome (NS) is an independent risk factor of ischemic stroke. *Methods*: This is a retrospective nationwide cohort study through an analysis of the National Health Insurance Research Database in Taiwan. To evaluate the risk of stroke, the corresponding controls were selected at a 4:1 ratio in the number of subjects, and they were matched with the study group in age, gender, Charlson comorbidity index (CCI), and index date. *Results*: From a total of 16,245 surveyed subjects, ischemic stroke occurred in 1235 (7.6%) and hemorrhagic stroke in 129 (.74%) of them. The incidence of ischemic stroke was significantly higher in patients with NS (n = 3496) compared to control patients without NS (n = 13,984) (9.92 versus 7.10, per 1000 person-year, $P < .001$). In the multivariate analysis, the overall adjusted hazard ratio (aHR) of stroke in NS patients was 1.37 (95% CI, 1.21-1.54, $P < .001$). The risk factors of ischemic stroke were NS (aHR, 1.38 [95% confidence interval {CI}, 1.21-1.57]; $P < .001$), age greater than 45 years (aHR, 7.98 [95% CI, 6.47-9.48]; $P < .001$), male gender (aHR, 1.23 [95% CI, 1.10-1.38]; $P < .001$), CCI greater than or equal to 1 (aHR $\geq$ 1.25 in different CCI score groups, all at $P \leq .003$), ischemic heart disease (aHR, 1.95 [95% CI, 1.67-2.29]; $P < .001$), heart failure (HR, 1.77 [95% CI, 1.30-2.42]; $P < .001$). Risk factors of hemorrhagic stroke were those aged greater than 45 years, or with systemic lupus erythematosus, but not NS. *Conclusions*: We provided the first evidence that patients with NS had an increased risk of ischemic stroke.

Key Words: Nephrotic syndrome—stroke—ischemic stroke—hemorrhagic stroke

Introduction

Both venous and arterial thromboses are major complications of nephrotic syndrome (NS). The association between renal vein thrombosis and NS has been widely reported in the past few decades.[1,2] Arterial thrombosis occurs less frequently than venous thrombosis, with renal vein being the commonest thrombotic site in NS patients.[2] An imbalance between procoagulant/prothrombotic and anticoagulant/antithrombotic factors promotes in situ thrombosis in the deep veins or arteries, which attributed to the "Hypercoagulable" state in NS patients.[3-5] Changes in platelet activation and aggregation as well as urinary loss of low molecular weight proteins (such as plasminogen and antithrombin III) could lead to impaired fibrinolysis and poor coagulation in NS patients.[6]

The association between arterial thrombosis and NS was suggested in patients treated with steroid and

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diuretics.[7] Although arterial thrombosis occurs mainly in children, it is not uncommon to observe strokes, especially ischemic stroke, in adult patients with NS.[8-11] Awareness of the risk of ischemic stroke is important to develop an appropriate prophylactic management in these adult patients. But the risk of stroke in adult patients with NS has never been determined in large cohort studies.[8,9] Here, we performed a retrospective nationwide cohort study to analyze the risk of stroke in adult NS patients. The registry data of the National Health Insurance Research Database in Taiwan was used.

Materials and Methods

We enrolled patients who were diagnosed of NS, aged between 18 and 110 years old. To evaluate the risk of stroke, we selected 4 controls with 1 NS patient with them matched in age, sex, Charlson comorbidity index (CCI), and index date.

Data Source

The registry data of the National Health Insurance Research Database (NHIRD) of Taiwan is a nationwide database comprising demographic data, clinical diagnosis, medical resource utilization data of outpatient and inpatient visits, treatment patterns, and costs of services. The traceable personal identifiers were removed from the database for confidentiality purposes. All diagnoses in NHIRD are based on the International Classification of Diseases, Ninth Revision, Clinical Modification diagnostic criteria (ICD-9-CM). Launched in 1995, NHIRD covers greater than 99% of the national population (23 million), and has been in continuous operation since 1997. The database has been used to conduct many population-level studies.[12,13] A subset of NHIRD, called the Longitudinal Health Insurance Database, LHID2010, contains claim information of a million beneficiaries randomly selected in 2010. By using DBMS-RANDOM package of Oracle, which provides a built-in random number generator, all the registration and claim data of these 1,000,000 individuals collected by the National Health Insurance Program constitute the LHID 2010. There is no significant difference in the gender distribution, age distribution, or average insured payroll-related amount between the patients in the LHID 2010 and the original NHIRD.

Ethical Statement

Identification numbers for all of the subjects in the NHRID were encrypted to protect the privacy of the individuals. The Institutional Review Board of the Taichung Veterans General Hospital approved this study project (CE13152B-4) and the patient informed consent was waived because of the encryption.

Study Population

We identified patients first listed in LHID 2010 with the diagnosis of NS (ICD-9-CM codes: 581) during clinical visit or admission. The diagnosis of NS was confirmed in at least 3 clinical visits or 1 admission during the period from 2000 to 2008. The date when a patient was first diagnosed of NS was defined as the index date. We excluded those patients diagnosed with stroke (ICD-9-CM codes 430 and 437) before the index date, and those aged less than 18 or greater than 110 years old, or with incomplete demographic data. A matched group without NS was selected from LHID 2010 to act as the controls. The NS group and the controls (4 times in number) were matched in age, sex, CCI, and index date to minimize selection bias. All patients were followed until the episode of stroke, death, withdrawal from the NHI program, or till December 31, 2011 (which ever had occurred first).

The codes of ICD-9-CM used in this study are as follows: 581 for NS, 433-437 for ischemic stroke, 430-432 for hemorrhagic stroke, 410-414 for ischemic heart disease, 428 for heart failure, 393-398 for chronic rheumatic heart disease, 346 for migraine, 710.0 for systemic lupus erythematosus, and 441 for aortic aneurysm and dissection.

Statistical Analyses

Demographic characteristics and the prevalence of comorbidities were compared between the 2 groups using chi-square test for categorical variables. The cumulative incidence of 2 types of stroke was calculated using the Kaplan-Meier method, and the log-rank test was used to evaluate intergroup differences. We calculated in each group the incidence density of mortality in terms of person-years. We used univariable and multivariable Cox proportional-hazard regression models to determine the effect of NS on the risk of strokes (ischemic and hemorrhagic) using hazard ratio (HR) and its 95% confidence interval (CI). The multivariable models were adjusted for age, sex, CCI, urbanization, and existence of ischemic heart disease, heart failure, chronic heart disease of rheumatic origin, migraine, systemic lupus erythematosus, aortic aneurysm, and dissection. Patients were stratified according to age, sex, CCI, urbanization, and comorbidities in the NS group and the controls and analyzed with Cox regression models. All analyses were conducted using SAS software Version 9.4 (SAS Institute; Cary, NC), and the significant level of 2-tailed statistics was set at P less than .05.

Results

Figure 1 shows the flow chart of patient selection. A total of 3496 patients were in the NS group. Another 13,984 subjects without NS (matched in age, gender, CCI, and index date) were in the control group. The NS demographic data are as follows: male (n = 2007) 57.4%, age

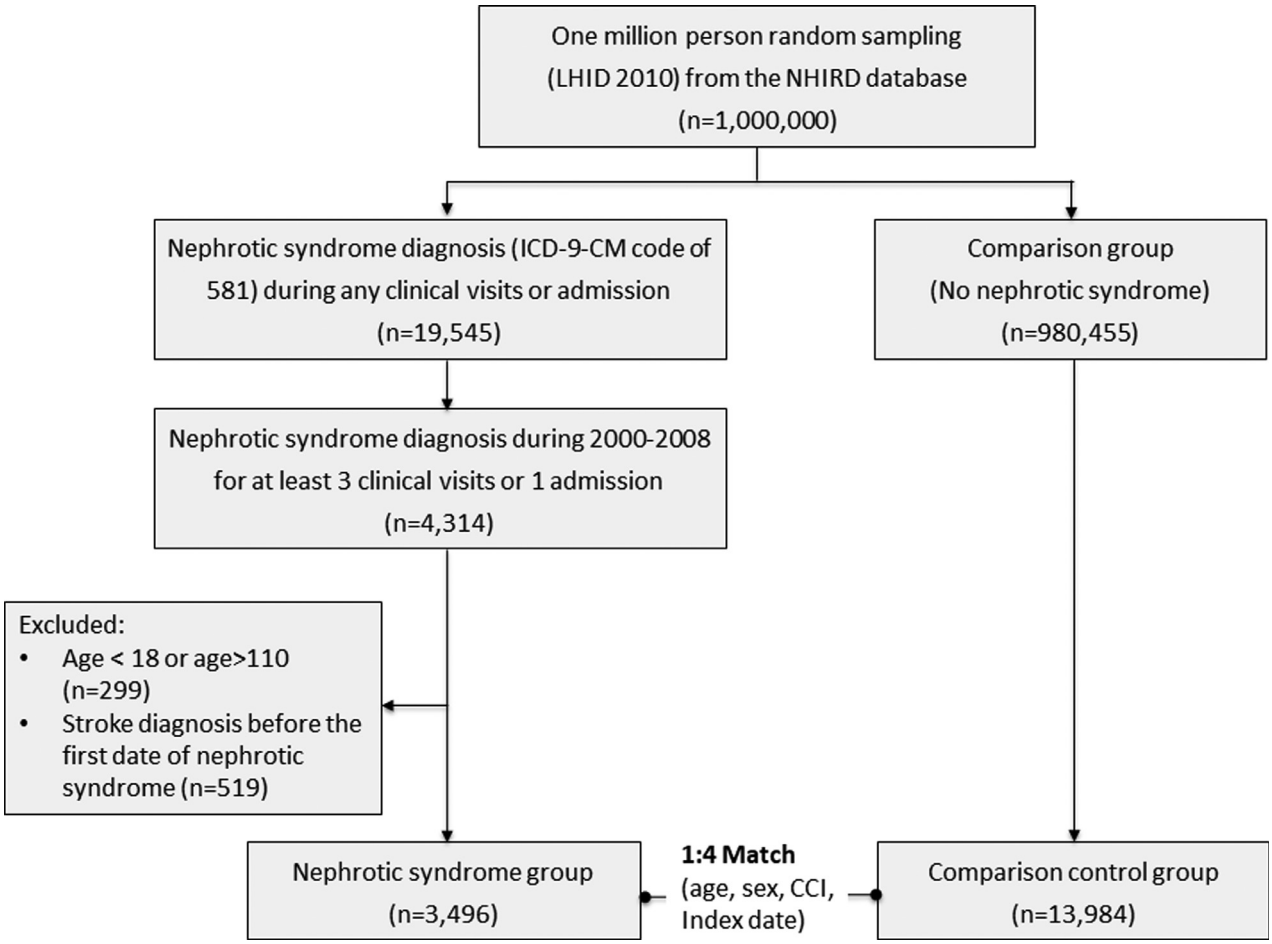

Figure 1. *Flow chart of patient selection.*

(mean ± standard deviation) 48.6 ± 15.2 years, CCI = (0 [n = 2027, 58%], 1 [n = 755, 21.6%], 2 [n = 373, 10.7%], ≥3 [n = 341, 9.8%]), ischemic heart disease (n = 240) 6.9%, heart failure (n = 37) 1.1%, chronic rheumatic heart disease (n = 8) .2%, migraine (n = 34) 1.0%, systemic lupus erythematosus (n = 44) 1.3%, and aortic aneurysm and dissection (n = 1) 0%. Table 1 shows the baseline characteristics of study subjects with or without NS. We noted higher percentages of ischemic heart disease and systemic lupus erythematosus in the NS group. Cox regression analysis models were then used for the following risk analyses.

In the total of all 17,480 study subjects, ischemic stroke occurred in 1,235 subjects (7.1%) and hemorrhagic stroke in and 129 subjects (.74%). Table 2 shows univariate analysis of factors associated with stroke. After the multivariate analysis which took into account of the following: ie, NS, age, gender, CCI, urbanization, ischemic heart disease, heart failure, chronic rheumatic heart disease, migraine, systemic lupus erythematosus, aortic aneurysm, and dissection, we found factors associated with increased risk of ischemic stroke being NS (HR, 1.38 [95% CI, 1.21-1.57]; $P < .001$), age greater than 45 years (HR, 7.98 [95% CI, 6.47-9.48]; $P < .001$), male sex (HR, 1.23 [95% CI, 1.10-1.38]; $P < .001$), CCI = 1 (HR, 1.25 [95% CI, 1.08-1.44]; $P = .003$), CCI = 2 (HR, 1.46 [95% CI, 1.24-1.73]; $P < .001$), CCI greater than or equal to 3 (HR, 1.85 [95% CI, 1.57-2.18]; $P < .001$), ischemic heart disease (HR, 1.95 [95% CI, 1.67-2.29]; $P < .001$), heart failure (HR, 1.77 [95% CI, 1.30-2.42]; $P < .001$). For hemorrhagic stroke, the risk factors were age greater than 45 years (HR, 2.56 [95% CI, 1.69-3.87]; $P < .001$), and systemic lupus erythematosus (HR, 11.22 [95% CI, 3.91-32.19]; $P < .001$). The overall adjusted HR of stroke was 1.37 (95% CI, 1.21-1.54, $P < .001$) in patients with NS (Table 3). Compared to controls, the incidence rate of ischemic stroke during the follow-up period (9.1 ± 2.9 years) was significantly higher in the NS group (9.92 versus 7.10, per 1000 person-year, $P < .001$).However, the incidence rate of hemorrhagic stroke appeared lower in the NS group, but the difference with the controls was not statistically significant (.72 versus .96, per 100 person-year, $P = .165$).

Since age contributed strongly to the development of stroke, we performed a subgroups multivariate Cox regression analysis for age (Table 4). In patients with age greater than 45 years, regardless of gender, we found increased risks of ischemic stroke. The adjusted HR was 1.27 (95% CI, 1.03-1.57, $P = .024$) in females and 1.27 (95% CI, 1.06-1.52, $P = .010$) in males. Specifically, in male subjects aged

Table 1. *Characteristics of study subjects with and without nephrotic syndrome, 2000-2008*

Characteristic	Comparison group (n = 13,984) n (%)	Nephrotic syndrome group (n = 3496) n (%)	Total n	*P* value
Age, mean ± SD	48.2 ± 15.3	48.6 ± 15.2		1.000
18-45	5944 (42.5)	1486 (42.5)	7430	
>45	8040 (57.5)	2010 (57.5)	10,050	
Gender				1.000
Female	5956 (42.6)	1489 (42.6)	7445	
Male	8028 (57.4)	2007 (57.4)	10,035	
CCI				1.000
0	8108 (58)	2027 (58)	10,135	
1	3020 (21.6)	755 (21.6)	3775	
2	1492 (10.7)	373 (10.7)	1865	
≥3	1364 (9.8)	341 (9.8)	1705	
Urbanization				.255
Urban	8680 (62.3)	2120 (61.1)	10,800	
Suburban	1770 (12.7)	436 (12.6)	2206	
Rural	3484 (25)	915 (26.4)	4399	
Ischemic heart disease				**<.001**
No	13,232 (94.6)	3256 (93.1)	16,488	
Yes	752 (5.4)	240 (6.9)	992	
Heart failure				.851
No	13,841 (99)	3459 (98.9)	17,300	
Yes	143 (1)	37 (1.1)	180	
Chronic rheumatic heart diseases				.763
No	13,948 (99.7)	3488 (99.8)	17,436	
Yes	36 (.3)	8 (.2)	44	
Migraine				.107
No	13,885 (99.3)	3462 (99)	17,347	
Yes	99 (.7)	34 (1)	133	
Systemic lupus erythematosus				**<.001**
No	13,962 (99.8)	3452 (98.7)	17,414	
Yes	22 (.2)	44 (1.3)	66	
Aortic aneurysm and dissection				.596
No	13,977 (99.9)	3495 (100)	17,472	
Yes	7 (.1)	1 (0)	8	

Bold values are important findings of the results.

between 18 and 45, the risk of ischemic stroke increased to 3.33 (adjusted HR, 3.33 [95% CI, 2.09-5.32]; $P < .001$).

The association between CCI and ischemic stroke occurred in patients across different age groups, regardless of gender. In older patients, aged 45 years or older, with the CCI scored 3 or higher, the adjusted HR was 1.72 (95% CI, 1.34-2.22, $P < .001$) in females, and 1.77 (95% CI, 1.41-2.23, $P < .001$) in males. Moreover, in those younger patients, aged less than 45 years, with CCI scored 3 or higher, the adjusted HR was elevated to 4.81 (95% CI, 1.38-16.75, $P = .014$) in females, and 3.63 (95% CI, 1.66-7.93, $P = .001$) in males. The association between ischemic stroke and ischemic heart disease, or heart failure occurred only in those patients older than 45 years. Figure 2 shows the results of Kaplan-Meier survival analysis and log-rank test on the development of ischemic stroke in patients with or without NS ($P < .001$). In the subgroup analysis of factors associated stroke, we found that NS had the highest adjusted HR to predict stroke in male patients aged between 18 and 45 years old (adjusted HR, 3.33, [95% CI, 2.09-5.32], $P < .001$, Table 4).

Discussion

Hypercoagulability usually represents a group of hereditary or acquired conditions, which tends to have thrombi developed in veins and/or arteries.[14] Hypercoagulability exists in NS patients.[3,4,5] Current evidence is not yet strong enough to support a routine preventive strategy on ischemic stroke for NS patients. In fact, most studies on the association between ischemic stroke and NS are limited to case reports or case series studies.

In the present study, it is important to point out that the incidence of ischemic stroke, ie, 9.92 per 1000 person-year,

Table 2. *Univariate analysis of factors associated with stroke*

Variables	Ischemic stroke		Hemorrhage stroke		Stroke	
	Crude HR (95% CI)	*P* value	Crude HR (95% CI)	*P* value	Crude HR (95% CI)	*P* value
Nephrotic syndrome	**1.40 (1.23-1.59)**	**<.001**	1.33 (.89-1.98)	.165	1.39 (1.23-1.56)	<.001
Age						
18-45	1.00 (ref)		1.00 (ref)		1.00 (ref)	
>45	**9.48 (7.71-11.65)**	**<.001**	2.38 (1.60-3.55)	<.001	8.11 (6.79-9.70)	<.001
Gender						
Female	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Male	1.09 (.97-1.22)	.138	1.18 (.83-1.68)	.362	1.08 (.97-1.20)	.155
CCI						
0	1.00 (ref)		1.00 (ref)		1.00 (ref)	
1	**1.68 (1.46-1.94)**	**<.001**	1.22 (.80-1.87)	.357	1.65 (1.45-1.88)	<.001
2	**2.30 (1.95-2.71)**	**<.001**	1.05 (.58-1.90)	.875	2.19 (1.88-2.55)	<.001
≥3	**3.26 (2.79-3.81)**	**<.001**	1.63 (.96-2.78)	.070	3.13 (2.71-3.61)	<.001
Urbanization						
Urban	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Suburban	1.16 (.98-1.37)	.087	1.18 (.69-2.00)	.544	1.18 (1.01-1.38)	.036
Rural	1.13 (.99-1.28)	.071	1.40 (.95-2.06)	.087	1.16 (1.03-1.31)	.015
Ischemic heart disease	**3.84 (3.31-4.46)**	**<.001**	1.31 (.67-2.59)	.431	3.52 (3.05-4.06)	<.001
Heart failure	**4.89 (3.66-6.52)**	**<.001**	NA		4.30 (3.23-5.72)	<.001
Chronic rheumatic heart diseases	3.00 (1.50-6.01)	.002	NA		3.01 (1.56-5.80)	.001
Migraine	1.53 (.90-2.59)	.114	NA		1.41 (.85-2.34)	.189
Systemic lupus erythematosus	.64 (.21-1.99)	.443	**8.50 (3.14-23.00)**	**<.001**	1.30 (.62-2.73)	.487
Aortic aneurysm and dissection	2.24 (.32-15.89)	.419	NA		1.92 (.27-13.61)	.515

Abbreviation: HR, hazard ratio.

Bold values are important findings of the results.

Table 3. *Multivariate analysis of factors associated with stroke*

Variables	Ischemic stroke		Hemorrhage stroke		Stroke	
	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Nephrotic syndrome	1.38 (1.21-1.57)	<.001	1.26 (.84-1.88)	.266	1.37 (1.21-1.54)	<.001
Age						
18-45	1.00 (ref)		1.00 (ref)		1.00 (ref)	
>45	7.98 (6.47-9.84)	<.001	**2.56 (1.69-3.87)**	**<.001**	6.99 (5.83-8.38)	<.001
Gender						
Female	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Male	**1.23 (1.10-1.38)**	**<.001**	1.30 (.91-1.86)	.150	1.22 (1.10-1.35)	<.001
CCI						
0	1.00 (ref)		1.00 (ref)		1.00 (ref)	
1	**1.25 (1.08-1.44)**	**.003**	1.03 (.67-1.58)	.903	1.24 (1.08-1.41)	.002
2	**1.46 (1.24-1.73)**	**<.001**	.85 (.46-1.56)	.599	1.43 (1.22-1.70)	<.001
≥3	**1.85 (1.57-2.18)**	**<.001**	1.29 (.74-2.24)	.372	1.83 (1.58-2.14)	<.001
Urbanization						
Urban			1.00 (ref)		1.00 (ref)	
Suburban			1.19 (.70-2.01)	.526	1.18 (1.01-1.38)	.037
Rural			1.41 (.96-2.07)	.084	1.16 (1.04-1.32)	.010
Ischemic heart disease	**1.95 (1.67-2.29)**	**<.001**	1.04 (.52-2.08)	.914	1.83 (1.58-2.13)	<.001
Heart failure	**1.77 (1.30-2.42)**	**<.001**	NA		1.60 (1.18-2.18)	.003
Chronic rheumatic heart diseases	1.08 (.53-2.21)	.837	NA		1.23 (.63-2.41)	.549
Migraine			NA		1.03 (.62-1.72)	.899
Systemic lupus erythematosus			**11.22 (3.91-32.19)**	**<.001**	1.87 (.88-3.94)	.102
Aortic aneurysm and dissection			NA		1.07 (.15-7.58)	.950

Abbreviation: HR, hazard ratio.

Bold values are important findings of the results.

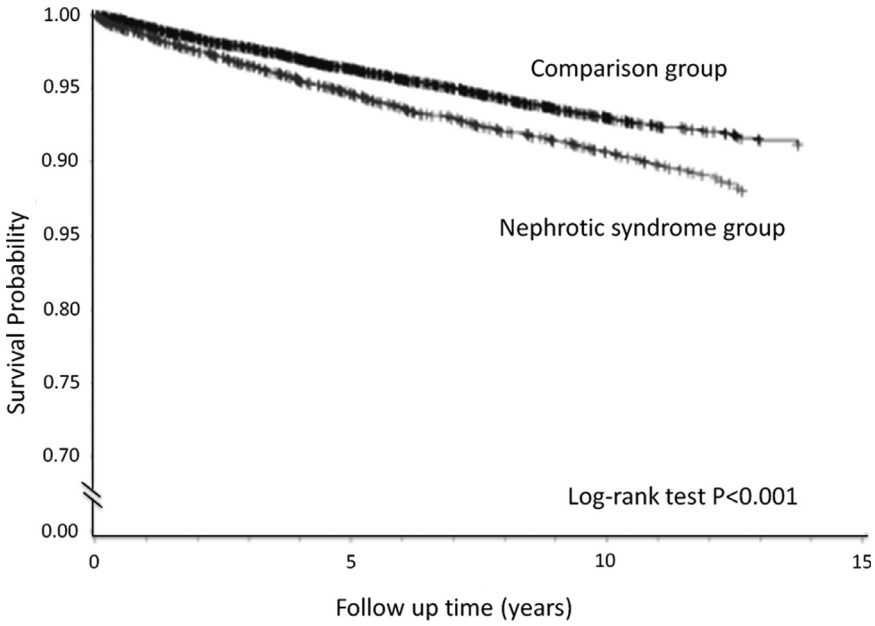

Figure 2. *Analysis for the development of ischemic stroke in patients with or without nephrotic syndrome.*

was not very rare. In additional to the traditional risk factors of ischemic stroke, (such as age > 45 years, male, higher CCI, ischemic heart disease, and heart failure), NS is a strong independent risk factor for ischemic stroke. Whereas migraine, chronic rheumatic heart disease, and aortic aneurysm with dissection did not increase risks of ischemic stroke in our patients.

Old age is known to be a strong risk factor for ischemic stroke.[15] Interestingly, patients with ages greater than 45 years, we found that male NS patients and those aged less than 45 years both presented significantly increased risks for ischemic stroke. Strokes in young adults had been thought to be associated with rare risk factors, including arterial dissection, reversible cerebral vasoconstriction syndrome, inflammatory arteritis, cardiomyopathy, and several hypercoagulable factors.[16] Thus, hypercoagulable status of young patients with NS could contribute to this association. Consistent with our findings are results from Roy et al, who found that stroke occurs in young NS patients and stroke could appear as an initial event.[3]

On the other hand, the association between CCI score and ischemic stroke has seldom been reported before. CCI is the most extensively studied comorbidity index for predicting mortality.[17,18] Predictive validity of CCI has been confirmed by reports based on various outcome criteria, such as mortality, disability, readmissions, and length of stay.[18-22] High CCI score has been used to predict poor outcome and death in patients with spontaneous intracerebral hemorrhage and ischemic stroke.[23] Our study is the first report that CCI could be useful as a predictive tool for ischemic stroke.

The association between systemic lupus erythematosus and hemorrhagic stroke is another interesting finding of this study. Only some case reports presented the uncommon subarachnoid hemorrhage in patients with systemic lupus erythematosus.[24] Further researches to clarify the mechanisms behind them are needed to understand hemorrhagic stroke in patients with systemic lupus erythematosus. There are some limitations with regard to the retrospective design of this study. It is unclear what impact anticoagulants might have on the incidence of ischemic stroke, although anticoagulants are not routinely used in most Taiwanese NS patients. The information remained insufficient on those nonmodifiable, modifiable, or potentially modifiable risk factors, such as birth weight, race/ethnicity, genetic factors, exposure to cigarette smoke, postmenopausal hormone therapy, poor diet, physical inactivity, obesity and body fat distribution, alcohol abuse, oral contraceptive use, and sleep-disordered breathing.[25,26] Despite of these shortcomings, given the substantial mortality and long-term disability associated with stroke, it is important to note that NS patients have higher risk of ischemic stroke. A large-scale prospective randomized control trial is a potential solution to confirm our results.

In summary, we have demonstrated the strong association between NS and ischemic stroke. Although other undiscovered factors might contribute to the risk of thromboembolism in NS patients, the prevention of ischemic stroke remains a challenge for nephrologists. Our results have provided strong evidence to support the need to develop an appropriate prophylactic management of ischemic stroke in adult NS patients.

Table 4. *Subgroup analysis of factors associated with stroke*

Variables	Age 18-45 y				Age > 45 y			
	Female		Male		Female		Male	
	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Nephrotic syndrome	2.1 (.92-4.79)	.077	**3.33 (2.09-5.32)**	**<.001**	**1.27 (1.03-1.57)**	**.024**	**1.27 (1.06-1.52)**	**.010**
CCI								
0	1.00 (ref)		1.00 (ref)		1.00 (ref)			
1	2.76 (.99-7.67)	.051	1.41 (.76-2.63)	.279	1.14 (.91-1.45)	.260	1.26 (1.03-1.53)	.022
2	7.77 (2.88-21.02)	<.001	2.15 (1.00-4.61)	.051	1.18 (.89-1.55)	.253	**1.52 (1.21-1.90)**	**<.001**
≥3	4.81 (1.38-16.75)	.014	**3.63 (1.66-7.93)**	**.001**	**1.72 (1.34-2.22)**	**<.001**	**1.77 (1.41-2.23)**	**<.001**
Urbanization								
Urban	1.00 (ref)		1.00 (ref)		1.00 (ref)			
Suburban	1.62 (.59-4.39)	.348	.98 (.46-2.09)	.956	1.19 (.91-1.56)	.204	1.13 (.90-1.42)	.294
Rural	.78 (.29-2.12)	.624	1.27 (.76-2.14)	.362	1.25 (1.02-1.54)	.034	1.06 (.89-1.27)	.533
Ischemic heart disease	3.4 (.43-26.64)	.244	2.00 (.60-6.66)	.261	2.38 (1.87-3.02)	<.001	**1.71 (1.38-2.12)**	**<.001**
Heart failure	-	-	-	-	1.50 (.95-2.37)	.085	**2.15 (1.41-3.30)**	**<.001**
Chronic rheumatic heart diseases	-	-	-	-	1.56 (.57-4.23)	.388	.81 (.29-2.27)	.692
Migraine	4.25 (.98-18.47)	.054	-	-	.75 (.31-1.80)	.514	1.40 (.66-2.96)	.385
Systemic lupus erythematosus	.97 (.12-7.8)	.980	-	-	1.33 (.33-5.36)	.691	-	-
Aortic aneurysm and dissection	-	-	-	-	-	-	2.10 (.30-14.99)	.459

Abbreviation: HR, hazard ratio.

Bold values are important findings of the results.

Declaration of Competing Interest

The authors declare that they have no conflict of interests.

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