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CLINICAL STUDY



# Characteristics of acute ischemic stroke in patients with Nephrotic syndrome

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**ABSTRACT**

The incidence of ischemic stroke (IS) is higher in nephrotic syndrome (NS) patients compared to general population. However, there is limited information on the specific characteristics to stroke patients with NS. In this study, we aimed to examine the clinical manifestations of acute IS in a large group of NS patients, comparing to those without NS. We conducted a retrospective cohort study to compare the clinical presentations of acute IS in patients with and without NS. This study was a multi-institutional study and used data from Chang Gung Research Database of Taiwan from 1 January 2001, to 31 December 2017. A total of 233 IS patients with NS and 1358 IS patients without NS were enrolled. The median age of participants was 68 (range: 59–79) years. The risk of dependent functional status (modified Rankin Scale score≧3) after IS was higher in NS patients compared to those without NS (Odd ratio (OR) 4.02, 95% confidence interval (CI) 2.39 to 6.76, $p<0.001$), particularly in stroke subtypes as small-artery occlusion (OR 8.02, 95% CI 3.94 to 16.32, $p<0.001$), and stroke of undetermined etiology (OR 2.47, CI 1.06 to 5.76, $p=037$). The risks of mortality or stroke recurrence within 30 days were similar between the two groups for all stroke subtypes. In conclusion, NS was associated with a higher risk of functional dependence following IS. Intensive treatment and rehabilitation should be considered for IS patients with NS.

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## 1. Introduction

Nephrotic syndrome (NS) is characterized by the presence of proteinuria, hypoalbuminemia, hyperlipidemia and peripheral edema. These patients have increased risks of both venous and arterial thrombosis due to a hypercoagulable state caused by an imbalance between procoagulant/prothrombotic and anticoagulant/antithrombotic factors [1,2]. Although arterial thromboses are less common than venous thromboses, they do occur in a significant number of adult patients with NS. Previous studies have shown that patients with NS have an increased risk of thrombosis in peripheral arteries, coronary artery disease (CAD), and ischemic stroke (IS) [3–10].

Lines of evidence suggest that the incidence of IS is higher in patients with NS [6,9]. However, research comparing the clinical characteristics and functional outcomes of acute IS patients with and without NS is limited. Different IS subtypes are associated with varying clinical presentations and outcomes [11], making it important to understand the clinical differences between IS in patients with and without NS, stratified by subtype. To address this gap in knowledge, we conducted a retrospective cohort study using real-world data from the Chang Gung (CG) Research Database to compare the clinical presentations of patients with IS who have NS to those who do not have NS in a larger number of patients. This study included a large number of patients and the results provide valuable insights into the pattern and outcomes of IS in patients with NS.

## 2. Materials and methods

### 2.1. Ethical standards

This clinical research was conducted according to a protocol approved by the Medical Ethics Committee of CG Memorial Hospital, Taipei, Taiwan, in accordance with the Helsinki

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Declaration of 1975 (the IRB approval number: 202001012B0). The informed consent of individual subject was waived by Medical Ethics Committee of CG Memorial Hospital, Taipei, Taiwan. All the data from the existing databases were anonymized and the results were presented in aggregate.

### 2.2. Data source and collection

The CG Research Database is a de-identified database comprising multi-institutional standardized electronic medical records, including diagnoses, demographic data, medical records, laboratory data, radiological images, and examination reports dating back to 2000, from the CG Medical Foundation [12]. The CG Medical Foundation, the largest medical system in Taiwan, is made up of branches of CG Memorial Hospital, including two medical centers, two regional, and three district hospitals. The CG Medical Foundation has a capacity over 10,000 beds, with admits more than 280,000 patients per year [13]. The electronic medical records are fully implemented in all branches of CG Memorial Hospital.

### 2.3. Study population

The study subjects were selected from the CG Research Database, and the study period was from January 1, 2001 to December 31, 2017. We recruited subjects admitted for acute IS with a diagnosis of NS from all branches of CG Memorial Hospital. Firstly, we screened the database using international classification of diseases (ICD)-9-clinical modification (CM) [14] and ICD-10-CM [15] codes for patients with both NS (ICD-9: 5810-5819, ICD-10: N04.1-N04.9 and N04.A) and IS (ICD-9: 433, 434, 436 and 437; ICD-10: I63-68, G45-46). Then we reviewed the medical records and laboratory data to confirm if the patients fulfilled the diagnostic criteria of NS, which were defined as proteinuria greater than 3.5 g/day, serum albumin level < 3 g/dL, and peripheral edema [16]. We exclude patients with acute kidney injury on admission. The control group, defined as the subjects admitted for acute IS with normal kidney function and no proteinuria, was recruited from the CG Research Database of CG Memorial Hospital Keelung branch from 1 January 2016 to 31 December 2019. Patients with normal kidney function were defined as: 1. estimated glomerular filtration rate (eGFR)≧60 mL/min/1.73 $m^2$, 2. no previously known chronic kidney disease (CKD) [17], 3. No significant abnormality in urinary analysis. To recruit control subjects, we first screened a database of patients using ICD-9 and ICD-10 codes for IS (IS; ICD-9: 433, 434, 436, and 437; ICD-10: I63–68, G45–46). We then reviewed the medical records and laboratory data of these patients in detail to exclude those with NS and those meeting the criteria for CKD according to the KDIGO guideline [17]. Patients with severe major medical disease, such as severe hepatitis, end-stage malignancy or meningoencephalitis, were also excluded from the study. The diagnoses of acute IS and underlying medical diseases were identified by the ICD-9-CM or ICD-10-CM codes combined with the medical records. Normal kidney function and absence of proteinuria were confirmed using laboratory data.

### 2.4. Classification of IS

The subtypes of IS were classified by the Trial of ORG 10172 in Acute Stroke Treatment classification system [18], and the subtypes of clinical syndromes were grouped using the Oxfordshire Community Stroke Project classification system [19]. Three board-certified neurologists (Chang KH, Chang CW and Huang WY) performed a thorough review of the medical records to evaluate the subtypes of IS, and to identify and record comorbidities, vascular risk factors, clinical course, acute complications during admission, and the laboratory test. The primary end point was 30-day mortality, and all causes of death were recorded. The secondary endpoints included dependent functional outcome, defined as a modified Rankin scale score ≧ 3, and recurrent stroke within 30 days.

### 2.5. Statistical analysis

Categorical variables were expressed as a number (percentage), and continuous variables were expressed as mean ± standard deviation if they were normally distributed, and were expressed as median (interquartile range) if they were not normally distributed [20]. Missing laboratory data were handled by the 'mean substitution' method [21]. Comparisons between NS patients and the control group in all acute IS or individual stroke subtypes were performed using the chi-square (for categorical variables) or Student's *t*-test (for continuous variables that were normally distributed) or Mann-Whitney *U* (for continuous variables that were not normally distributed) [20]. The independent associations between the variables and the endpoints were analyzed using logistic regression. All variables with a $p < 0.1$ in the univariate logistic regression entered a stepwise, backward multivariate logistic regression [22]. All statistical analyses were performed with IBM SPSS statistics 19 for Windows. Statistical significance was defined as $P$ value < 0.05.

## 3. Results

### 3.1. Patient selection and demographic presentations

We identified 6446 hospitalization records for detailed evaluation according to the diagnosis at discharge. Following a thorough chart review, we finally recruited 1591 patients, including 233 patients with NS and 1358 patients with normal kidney function and no proteinuria (Supplementary Figure 1). Of the 233 patients with NS, 34 (14.6%) patients had received a kidney biopsy. Of the 199 patients without kidney biopsy, 118 patients were classified as diabetic nephropathy because they had history of diabetes mellitus (DM) for more than 10 years or triopathy of DM. The results of kidney biopsy and etiology of NS were shown in

Supplementary Table 1. The information of CKD stages in patients with NS was shown in Supplementary Table 2. The age at onset was 68.31 ± 13.67 years, with NS patients being significantly younger than the control group. The mean level of proteinuria in patients with NS was 4930 mg ±1250 mg/24 h. Of the 233 patients with NS, 120 patients had received renin-angiotensin-aldosterone system (RAAS) blockade agents, 98 patients used only angiotensin II receptor blockers (ARB) (losartan, valsartan, irbesartan, telmisartan, or candesartan), 18 patients used only angiotensin converting enzyme inhibitors (ACEi) (enalapril, benazepril, captopril, or fosinopril), 4 patients used more than one type of RAAS blockade agents (ARB plus ACEi: 3 patients, aliskiren plus benazepril: 1 patient). The prevalence of hypertension, DM, hyperlipidemia, CAD, congestive heart failure (CHF), previous transient ischemic attack (TIA), hyperuricemia, and peripheral arterial occlusive disease (PAOD) was significantly higher in NS patients compared to the control group. On the other hand, the prevalence of atrial fibrillation (AF) and smoking was significantly lower in NS patients compared to the control group. Laboratory data showed that NS patients had higher levels of fibrinogen, glycohemoglobin, erythrocyte sedimentation rate (ESR), blood urea nitrogen (BUN), creatinine, total cholesterol, triglyceride, low-density lipoprotein (LDL), and uric acid compared to the control group. By contrast, NS patients had significantly lower levels of hemoglobin, eGFR, calcium, and albumin compared to the control group. The informationondemographic features and laboratory data were summarized in Table 1 and Supplementary Table 3.

### 3.2. Clinical course of NS patients with acute is

The percentage of total anterior circulation syndrome (TACS) was significantly lower in NS patients compared to the control group, while posterior circulation syndrome was higher in NS patients compared to the control group. The percentages of small-artery occlusion and stroke of other determined etiology were significantly higher in NS patients compared to the control group, while cardioembolism and stroke of undetermined etiology were lower in NS patients compared to the control group. Patients with NS had a significantly lower rate of receiving intravenous thrombolysis compared with the control group. The mean length of stay in the acute medicine ward, the rates of mortality, common complications (infection, gastrointestinal bleeding, acute coronary syndrome, or venous thromboembolism) and recurrent stroke within 30 days were similar between the two groups. However, the rate of pulmonary edema was significantly higher in patients with NS compared to the control group. The uses of P2Y12 inhibitor and heparin in the acute stroke stage were higher in NS patients compared to the control group. The uses of non-vitamin K antagonist oral anticoagulants (NOACs) and statins were significantly lower in NS patients compared to the control group. The rate of

**Table 1.** Demographic features of ischemic stroke patients with or without nephrotic syndrome.

| | Nephrotic syndrome ($n=233$) | No nephrotic syndrome ($n=1358$) | $P$ value |
|---|---|---|---|
| Age (year-old) | 60.58 ± 13.35 | 69.64 ± 13.28 | <0.001* |
| Male | 145 (62.2%) | 837 (61.6%) | 0.462 |
| Smoking | 22 (9.4%) | 218 (16.1%) | 0.005† |
| SBP at admission (mmHg) | 169.95 ± 27.15 | 159.06 ± 29.79 | 0.032* |
| Hypertension | 195 (83.7%) | 1014 (74.7%) | 0.001[a] |
| Diabetes mellitus | 152 (65.2%) | 574 (42.3%) | <0.001[a] |
| Hyperlipidemia | 149 (63.9%) | 759 (55.9%) | 0.013[a] |
| Coronary artery disease | 35 (15.0%) | 146 (10.8%) | 0.040[a] |
| Congestive heart failure | 32 (13.7%) | 81 (6.0%) | <0.001[a] |
| Previous TIA | 15 (6.4%) | 45 (3.3%) | 0.022[a] |
| Atrial fibrillation | 23 (9.9%) | 285 (21.0%) | <0.001[a] |
| Hyperuricemia | 40 (17.2%) | 140 (10.3%) | 0.002[a] |
| PAOD | 9 (3.9%) | 17 (1.3%) | 0.009[a] |
| Systemic lupus erythematosis | 6 (2.6%) | 2 (0.1%) | <0.001[a] |
| Lab data | | | |
| Hemoglobin (g/dL) | 12.02 ± 2.22 | 13.62 ± 2.09 | <0.001* |
| Fibrinogen (mg/dL) | 441.54 ± 172.69 | 334.89 ± 123.19 | <0.001* |
| Glycohemoglobin (%) | 8.05 ± 2.44 | 6.77 ± 1.86 | <0.001* |
| ESR (mm/hr) | 44.84 ± 32.87 | 16.68 ± 17.12 | <0.001* |
| BUN (mg/dL) | 31.06 ± 11.80 | 16.19 ± 6.08 | <0.001* |
| Creatinine (mg/dL) | 2.85 ± 1.24 | 0.92 ± 0.61 | <0.001* |
| eGFR (mL/min/1.73 $m^2$) | 46.57 ± 29.81 | 79.84 ± 14.82 | <0.001* |
| Total cholesterol (mg/dL) | 234.38 ± 88.97 | 183.36 ± 42.86 | <0.001* |
| Triglyceride (mg/dL) | 208.24 ± 96.21 | 134.78 ± 41.15 | <0.001* |
| LDL (mg/dL) | 154.57 ± 45.60 | 117.41 ± 38.65 | <0.001* |
| Uric acid (mg/dL) | 6.60 ± 1.94 | 5.48 ± 2.22 | <0.001* |
| Calcium (mg/dL) | 8.38 ± 1.16 | 8.70 ± 0.98 | 0.007* |
| Albumin (g/dL) | 2.82 ± 0.77 | 3.58 ± 0.56 | <0.001* |

SBP: systolic blood pressure; TIA: transient ischemic attack; PAOD: peripheral arterial occlusive disease; ESR: erythrocyte sedimentation rate; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; LDL: low-density lipoprotein.
Data are presented as mean ± standard deviation or $n$ (%).
*$p < 0.05$, Student $t$ test.
[a]$p < 0.05$, Chi-square test.

**Table 2.** Clinical courses of ischemic stroke patients with or without nephrotic syndrome.

| | Nephrotic syndrome ($n=233$) | No nephrotic syndrome($n=1358$) | *P* value |
|---|---|---|---|
| Clinical syndromes | | | |
| TACS | 15 (6.4%) | 205 (15.1%) | <0.001[a] |
| POCS | 60 (25.8%) | 218 (16.1%) | <0.001[a] |
| TOAST classification | | | |
| Large-artery atherosclerosis | 43 (18.45%) | 216 (15.91%) | 0.316 |
| Cardioembolism | 23 (9.87%) | 259 (19.07%) | <0.001[a] |
| Small-artery occlusion | 118 (50.64%) | 419 (30.85%) | <0.001[a] |
| Stroke of other determined etiology | 11 (4.72%) | 27 (1.99%) | 0.012[a] |
| Stroke of undetermined etiology | 38 (16.31%) | 437 (32.18%) | <0.001[a] |
| Intra-venous thrombolysis | 4 (1.7%) | 74 (5.4%) | 0.006 [a] |
| Complication at admission | | | |
| Pulmonary edema | 13 (5.6%) | 25 (1.8%) | 0.002[a] |
| Medication during admission | | | |
| P2Y12 inihbitors | 57 (24.5%) | 264 (19.4%) | 0.049[a] |
| Heparin in acute stage | 10 (4.3%) | 25 (1.8%) | 0.024[a] |
| NOACs | 1 (0.4%) | 146 (10.8%) | <0.001† |
| Statins | 82 (35.2%) | 596 (43.9%) | 0.008[a] |
| Glasgow coma scale score | | | |
| Upon admission | 15 (15-15) | 15 (15–15) | 0.001* |
| Upon discharge | 15 (15-15) | 15 (15–15) | <0.001* |
| Modified Rankin scale score | | | |
| Upon admission | 3 (2-4) | 2 (1–4) | <0.001* |
| Upon discharge | 3 (2-4) | 2 (1–4) | <0.001* |
| Death within 30 days | 8 (3.4%) | 64 (4.7%) | 0.249 |
| Recurrent stroke within 30 days | 0 (0%) | 7 (0.5%) | 0.331 |
| modified Rankin scale score≧3 | 151 (64.8%) | 640 (47.1%) | |
| Odds ratio (95% CI) | 2.07 (1.55–2.76) | 1 | <0.001[a] |
| Adjusted odds ratio (95% CI) | 4.02 (2.39–6.76)[b] | 1 | <0.001[b] |

TACS: total anterior circulation syndrome; POCS: posterior circulation syndrome; TOAST: Trial of ORG 10172 in Acute Stroke Treatment; NOACs: non-vitamin K antagonist oral anticoagulants; CI: confidence interval.
Data are presented as median (interquartile range) or *n* (%).
*$p<0.05$, Mann-Whitney *U* test;
[a]$p<0.05$, Chi-square test;
[b]$p<0.05$,adjusted odds ratio and *P* value using multivariate logistic regression analysis, variates include age, male gender, hyperlipidemia, congestive heart failure, atrial fibrillation, nephrotic syndrome, total anterior circulation syndrome, pneumonia, pulmonary edema, white blood cell count > 10000 1000/$\mu$L, Hemoglobin < 12 g/dL, estimated glomerular filtration rate < 60 mL/min/1.73 m$^2$, Sodium < 135 mmol/L, and high-sensitivity C-reactive protein > 3 mg/L.

dependent outcome status was significantly higher in NS patients compared to the control group (odds ratio (OR) 2.07, 95% confidence interval (CI) 1.55 to 2.76, $p<0.001$). In the multivariate analysis (adjusted for age, gender, lipid level, CHF, AF, NS, TACS, pneumonia, pulmonary edema, white blood cell count, hemoglobin, eGFR, sodium, and high-sensitivity C-reactive protein levels), NS remained a significant risk factor for dependent outcome status (OR 4.02, CI 2.39 to 6.76, adjusted $p<0.001$) (Supplementary Table 4). The information of clinical course and outcomes were summarized in Table 2 and Supplementary Table 5.

We performed a subgroup analysis using the same sampling from the same hospital (Keelung branch) and years (2016 to 2017). The rate of dependent outcome status was significantly higher in NS patients compared to the control group (OR 4.56, 95% CI 1.47 to 14.11, $p=0.004$). In the multivariate analysis (adjusted for age, gender, lipid level, CHF, AF, NS, TACS, pneumonia, pulmonary edema, white blood cell count, hemoglobin, eGFR, sodium, and high-sensitivity C-reactive protein levels), NS remained a significant risk factor for dependent outcome status (OR 3.95, CI 1.10 to 14.11, adjusted $p=0.035$) (Supplementary Table 6).

For investigate whether low eGFR or NS contributes to the higher risk of outcome, we compared NS patients with eGFR > 60 mL/min/1.73 m$^2$ to patients without NS. The results revealed that the rate of dependent outcome status was significantly higher in NS patients compared to the control group (OR 2.20, 95% CI 1.37 to 3.54, $p=0.001$), and this association remained significant after adjusting for confounding factors in the multivariate analysis (OR 4.24, CI 2.51 to 7.14, adjusted $p<0.001$) (Supplementary Table 7).

### 3.3. Clinical features of NS patients with subtypes of IS

The age was younger in all subtypes of IS patients with NS compared with those without NS. In the patients with large-artery atherosclerosis, the prevalence of CHF and hyperuricemia was significantly higher in NS patients compared to the control group ($p<0.001$ and $p=0.008$, respectively). Among patients with cardioembolism, NS was associated with a significant higher prevalence of hypertension and hyperuricemia compared to the control group ($p=0.029$ and $p=0.005$, respectively). In the small-artery occlusion subgroup, NS patients have a significantly higher prevalence of DM, CAD, CHF, previous TIA, and PAOD compared to the control group ($p<0.001$, $p=0.018$, $p<0.001$, $p=0.012$, and $p=0.009$, respectively). The prevalence rates of partial anterior circulation syndrome and posterior circulation syndrome were significantly higher, while lacunar syndrome was significantly lower in NS patients compared to the control group

Table 3. Demographic features and clinical courses of ischemic stroke patients, with and without nephrotic syndrome.

| | Large-artery atherosclerosis | | Cardioembolism | | Small-artery occlusion | | Stroke of other determined etiology | | Stroke of undetermined etiology | |
|---|---|---|---|---|---|---|---|---|---|---|
| | NS ($n=43$) | No NS ($n=216$) | NS ($n=23$) | No NS ($n=259$) | NS ($n=118$) | No NS ($n=419$) | NS ($n=11$) | No NS ($n=27$) | NS ($n=38$) | No NS ($n=437$) |
| Age (years) | 60.16 ± 15.39* | 68.59 ± 12.53 | 68.35 ± 10.42* | 76.47 ± 11.49 | 61.03 ± 10.20* | 67.08 ± 12.47 | 36.91 ± 14.69* | 53.93 ± 14.86 | 61.77 ± 13.71* | 69.48 ± 13.50 |
| Male (%) | 25 (58.1%) | 142 (65.7%) | 16 (69.6%) | 135 (52.1%) | 75 (63.6%) | 266 (63.5%) | 6 (54.5%) | 13 (48.1%) | 24 (63.2%) | 277 (63.4%) |
| Smoking | 4 (9.3%) | 34 (15.7%) | 0 (0%) | 28 (10.8%) | 15 (12.7%) | 67 (16.0%) | 0 (0%) | 3 (11.1%) | 3 (7.9%)† | 86 (19.7%) |
| Hypertension | 38 (88.4%) | 171 (79.2%) | 21 (91.3%)[a] | 185 (71.4%) | 101 (85.6%) | 341 (81.4%) | 7 (63.6%) | 9 (33.3%) | 29 (76.3%) | 302 (69.1%) |
| DM | 30 (69.8%) | 124 (57.4%) | 7 (30.4%) | 81 (31.3%) | 95 (80.5%)[a] | 192 (45.8%) | 1 (9.1%) | 8 (29.6%) | 20 (52.6%) | 167 (38.2%) |
| Hyperlipidemia | 30 (69.8%) | 143 (66.2%) | 7 (30.4%) | 93 (35.9%) | 82 (69.5%) | 265 (63.2%) | 6 (54.5%) | 9 (33.3%) | 25 (65.8%) | 244 (55.8%) |
| CAD | 3 (7.0%) | 23 (10.6%) | 6 (26.1%) | 41 (15.8%) | 19 (16.1%)[a] | 36 (8.6%) | 0 (0%) | 1 (3.7%) | 7 (18.4%) | 36 (8.9%) |
| CHF | 8 (18.6%)[a] | 5 (2.3%) | 6 (26.1%) | 47 (18.1%) | 12 (10.2%)[a] | 9 (2.1%) | 1 (9.1%) | 1 (3.7%) | 5 (13.2%)† | 19 (4.3%) |
| Previous TIA | 2 (4.7%) | 8 (3.7%) | 2 (8.7%) | 9 (3.5%) | 9 (7.6%)[a] | 10 (2.4%) | 1 (9.1%) | 1 (3.7%) | 1 (2.6%) | 17 (3.9%) |
| Hyperuricemia | 10 (23.3%)[a] | 18 (8.3%) | 8 (34.8%)[a] | 29 (11.2%) | 14 (11.9%) | 46 (11.0%) | 3 (27.3%) | 2 (7.4%) | 6 (15.8%) | 45 (10.3%) |
| PAOD | 3 (7.0%) | 4 (1.9%) | 1 (4.3%) | 7 (2.7%) | 4 (3.4%)[a] | 1 (0.2%) | 0 (0%) | 1 (3.7%) | 1 (2.6%) | 4 (0.9%) |
| SLE | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 6 (54.5%)[a] | 2 (7.4%) | 0 (0%) | 0 (0%) |
| Clinical syndromes | | | | | | | | | | |
| TACS | 8 (18.6%) | 50 (23.1%) | 6 (26.1%) | 111 (42.9%) | 0 (0%) | 0 (0%) | 0 (0%) | 4 (14.8%) | 1 (2.6%) | 37 (8.5%) |
| PACS | 13 (30.2%) | 78 (36.1%) | 7 (30.4%) | 96 (37.1%) | 19 (16.1%)[a] | 5 (1.2%) | 8 (72.7%) | 14 (51.9%) | 20 (52.6%) | 224 (51.3%) |
| LACS | 8 (18.6%) | 24 (11.1%) | 4 (17.4%) | 21 (8.1%) | 72 (61.0%)[a] | 372 (88.8%) | 0 (0%) | 3 (11.1%) | 7 (18.4%) | 95 (21.7%) |
| POCS | 14 (32.6%) | 63 (29.2%) | 6 (26.1%) | 30 (11.6%) | 27 (22.9%)[a] | 39 (9.3%) | 3 (27.3%) | 6 (22.2%) | 10 (26.3%) | 79 (18.1%) |

NS: nephrotic syndrome; DM: diabetes mellitus; CAD: coronary artery disease; CHF: congestive heart failure; TIA: transient ischemic attack; PAOD: peripheral arterial occlusive disease; SLE: systemic lupus erythematosus; TACS: total anterior circulation syndrome; PACS: partial anterior circulation syndrome; LACS: lacunar syndrome; POCS: posterior circulation syndrome.
Data are presented as mean ± standard deviation or *n* (%).
*$p < 0.05$, Student *t* test.
[a]$p < 0.05$, Chi-square test.

($p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). In the subgroup of patients with stroke of other determined etiology, the prevalence of systemic lupus erythematosus was significantly higher in NS patients compared to the control group ($p = 0.004$). In the subgroup with stroke of undetermined etiology, NS patients had a significantly higher rate of CHF and a significantly lower rate of smoking compared to the control group ($p = 0.038$ and $p = 0.042$, respectively). The information on clinical features was summarized in Table 3 and Supplementary Table 8.

### 3.4. Laboratory features of NS patients with subtypes of IS

In the subgroup with large-artery atherosclerosis, patients with NS had higher glycohemoglobin, ESR, BUN, creatinine, total cholesterol, and triglyceride levels, but lower hemoglobin, eGFR, and albumin levels compared to the control group ($p = 0.021$, $p = 0.023$, $p < 0.001$, $p < 0.001$, $p = 0.001$, $p = 0.002$, $p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). For patients with cardioembolism, BUN and uric acid levels were higher in NS patients compared to the control group ($p = 0.001$ and $p = 0.003$, respectively). The levels of the eGFR, high-density lipoprotein and albumin were significantly lower in NS patients compared to the control group ($p < 0.001$, $p < 0.001$ and $p < 0.001$, respectively). In the small-artery occlusion subgroup, NS patients had higher levels of glycohemoglobin, ESR, BUN, creatinine, total cholesterol, triglyceride, LDL, uric acid, and fibrinogen ($p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p = 0.001$, $p < 0.001$, and $p = 0.010$, respectively). On the other hand, hemoglobin, eGFR, and albumin levels were significantly lower in NS patients compared to the control group ($p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). In the subgroup with stroke of other determined etiology, NS patients had higher levels of BUN, creatinine, uric acid, and potassium ($p = 0.020$, $p = 0.007$, $p = 0.047$, and $p = 0.002$, respectively). In the subgroup with stroke of undetermined etiology, NS patients had higher levels of fibrinogen, ESR, BUN, creatinine, total cholesterol, LDL, uric acid, and potassium compared to the control group ($p = 0.008$, $p = 0.015$, $p < 0.001$, $p < 0.001$, $p = 0.012$, $p = 0.018$, $p < 0.001$, and $p = 0.011$, respectively). By contrast, the levels of hemoglobin, eGFR, calcium, and albumin were significantly lower in NS patients compared to the control group ($p < 0.001$, $p < 0.001$, $p = 0.004$, and $p < 0.001$, respectively). The information of clinical features was summarized in Table 4 and Supplementary Table 9.

### 3.5. Treatment and clinical outcomes of NS patients with subtypes of IS

In the subgroup with large-artery atherosclerosis, patients with NS had higher rates of pulmonary edema and infection other than pneumonia or urinary tract infection compared with the control group ($p = 0.028$ and $p = 0.017$, respectively). In the subgroup with cardioembolism, NS patients had a significantly higher usage of aspirin, but a significantly lower

**Table 4.** Laboratory findings of ischemic stroke patients, with and without nephrotic syndrome.

| | Large-artery atherosclerosis | | Cardioembolism | | Small-artery occlusion | | Stroke of other determined etiology | | Stroke of undetermined etiology | |
|---|---|---|---|---|---|---|---|---|---|---|
| | NS ($n=43$) | No NS ($n=216$) | NS ($n=23$) | No NS ($n=259$) | NS ($n=118$) | No NS ($n=419$) | NS ($n=11$) | No NS ($n=27$) | NS ($n=38$) | No NS ($n=437$) |
| Hemoglobin (g/dL) | 11.89 ± 2.41* | 13.85 ± 2.23 | 12.64 ± 2.31 | 13.29 ± 2.04 | 11.99 ± 2.06* | 13.94 ± 1.81 | 12.33 ± 3.92 | 12.04 ± 3.16 | 11.77 ± 1.84* | 13.49 ± 2.15 |
| Glycohemoglobin (%) | 8.56 ± 2.79* | 7.23 ± 2.10 | 6.79 ± 1.52 | 6.22 ± 0.98 | 8.31 ± 2.43* | 6.97 ± 2.09 | 6.26 ± 1.59 | 6.74 ± 2.08 | 7.60 ± 2.27 | 6.64 ± 1.76 |
| ESR (mm/hr) | 57.44 ± 42.59* | 17.51 ± 6.54 | 29.20 ± 15.07 | 16.53 ± 10.68 | 43.80 ± 21.32* | 12.90 ± 6.13 | 32.75 ± 24.72 | 33.45 ± 27.08 | 47.67 ± 24.16* | 18.99 ± 15.33 |
| BUN (mg/dL) | 31.79 ± 20.21* | 15.71 ± 5.76 | 26.20 ± 10.42* | 17.91 ± 6.28 | 32.32 ± 15.76* | 15.52 ± 3.05 | 27.68 ± 12.74* | 15.32 ± 4.81 | 30.78 ± 19.76* | 16.11 ± 6.91 |
| Creatinine (mg/dL) | 2.79 ± 1.82* | 0.93 ± 0.28 | 1.82 ± 1.01 | 1.13 ± 0.99 | 3.07 ± 2.02* | 0.94 ± 0.23 | 1.92 ± 0.85* | 0.87 ± 0.25 | 3.17 ± 2.11* | 0.97 ± 0.31 |
| eGFR (mL/min/1.73 $m^2$) | 46.23 ± 30.92* | 81.41 ± 14.13 | 53.96 ± 25.02* | 76.72 ± 14.44 | 45.04 ± 30.02* | 80.95 ± 14.67 | 51.69 ± 29.78* | 83.82 ± 16.04 | 45.70 ± 31.21* | 75.79 ± 15.19 |
| Total cholesterol (mg/dL) | 244.76 ± 93.77* | 187.46 ± 41.82 | 202.10 ± 65.64 | 173.12 ± 44.23 | 240.50 ± 90.30* | 184.10 ± 40.50 | 226.4 ± 72.51 | 208.24 ± 69.12 | 224.09 ± 54.44* | 185.22 ± 41.45 |
| Triglyceride (mg/dL) | 271.62 ± 79.43* | 139.70 ± 52.61 | 122.70 ± 52.76 | 102.86 ± 34.92 | 213.41 ± 104.54* | 152.12 ± 89.28 | 224.40 ± 117.19 | 211.67 ± 123.58 | 169.84 ± 71.17 | 129.77 ± 45.12 |
| LDL (mg/dL) | 150.10 ± 53.24 | 121.59 ± 36.23 | 123.13 ± 38.71 | 107.74 ± 34.67 | 163.64 ± 44.97* | 116.29 ± 35.81 | 130.29 ± 31.12 | 134.48 ± 46.64 | 154.40 ± 46.23* | 121.11 ± 39.81 |
| HDL (mg/dL) | 41.18 ± 15.53 | 39.14 ± 10.29 | 34.69 ± 7.65* | 46.03 ± 10.46 | 38.95 ± 11.23 | 41.11 ± 14.12 | 46.71 ± 10.12 | 34.77 ± 8.65 | 48.43 ± 19.43 | 40.20 ± 13.04 |
| Uric acid (mg/dL) | 6.66 ± 1.85 | 5.58 ± 1.72 | 6.93 ± 2.08* | 5.51 ± 1.53 | 6.46 ± 1.85* | 5.51 ± 1.14 | 7.98 ± 2.37* | 5.82 ± 1.87 | 6.56 ± 2.13* | 5.36 ± 1.51 |
| Fibrinogen (mg/dL) | 473.00 ± 197.40 | 320.27 ± 151.76 | 731.50 ± 395.27 | 428.86 ± 182.15 | 396.79 ± 117.09* | 298.70 ± 43.56 | 341.67 ± 112.48 | 320.10 ± 116.17 | 465.15 ± 157.48* | 336.06 ± 110.23 |
| Potassium (mmol/L) | 4.06 ± 0.78 | 3.91 ± 1.13 | 3.71 ± 0.90 | 4.05 ± 1.10 | 4.01 ± 0.61 | 4.43 ± 0.78 | 4.60 ± 0.70* | 3.87 ± 0.47 | 4.17 ± 0.75* | 3.82 ± 0.45 |
| Calcium (mg/dL) | 8.24 ± 0.90 | 8.85 ± 0.71 | 8.59 ± 1.10 | 8.34 ± 1.23 | 8.38 ± 0.95 | 8.65 ± 1.01 | 8.16 ± 0.67 | 8.33 ± 0.47 | 8.44 ± 0.73* | 8.87 ± 0.58 |
| Albumin (g/dL) | 2.76 ± 0.49* | 3.61 ± 0.55 | 2.69 ± 0.56* | 3.39 ± 0.61 | 2.85 ± 0.78* | 3.81 ± 0.43 | 2.86 ± 1.02 | 2.18 ± 0.38 | 2.88 ± 0.72* | 3.60 ± 0.62 |

NS = nephrotic syndrome; ESR: erythrocyte sedimentation rate; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; LDL: low-density lipoprotein; HDL: high-density lipoprotein.
Data are presented as mean ± standard deviation.
*$p < 0.05$, Student $t$ test.

**Table 5.** Treatment, complication and clinical outcomes of ischemic stroke patients, with and without nephrotic syndrome.

| | Large-artery atherosclerosis | | Cardioembolism | | Small-artery occlusion | | Stroke of other determined etiology | | Stroke of undetermined etiology | |
|---|---|---|---|---|---|---|---|---|---|---|
| | NS ($n=43$) | No NS ($n=216$) | NS ($n=23$) | No NS ($n=259$) | NS ($n=118$) | No NS ($n=419$) | NS ($n=11$) | No NS ($n=27$) | NS ($n=38$) | No NS ($n=437$) |
| Treatment | | | | | | | | | | |
| Aspirin | 25 (58.1%) | 130 (60.2%) | 10 (43.5%)† | 54 (20.8%) | 82 (69.5%)[a] | 357 (85.2%) | 5 (45.5%) | 16 (59.3%) | 23 (60.5%) | 292 (66.8%) |
| NOACs | 0 (0%) | 3 (1.4%) | 1 (4.3%)a | 128 (49.4%) | 0 (0%) | 4 (1.0%) | 0 (0%) | 0 (0%) | 0 (0%) | 11 (2.5%) |
| Statins | 17 (39.5%)[a] | 118 (54.6%) | 4 (17.4%) | 74 (28.6%) | 44 (37.3%)[a] | 209 (49.9%) | 2 (18.2%) | 7 (25.9%) | 15 (39.5%) | 185 (42.3%) |
| Heparin in acute stage | 4 (9.3%) | 12 (5.6%) | 1 (4.3%) | 3 (1.2%) | 4 (3.4%) | 1 (0.2%) | 1 (9.1%) | 0 (0%) | 0 (0%) | 9 (2.1%) |
| Length of stay in acute care unit (days) | 18.81 ± 16.59 | 16.30 ± 11.01 | 22.74 ± 19.34 | 17.72 ± 12.99 | 11.02 ± 8.44* | 8.17 ± 4.25 | 20.00 ± 12.58 | 14.33 ± 9.24 | 15.15 ± 9.12 | 14.41 ± 9.90 |
| Stroke in evolution | 10 (23.3%) | 61 (28.2%) | 5 (21.7%) | 56 (21.6%) | 7 (5.9%)[a] | 7 (1.7%) | 3 (27.3%) | 6 (22.2%) | 4 (10.5%) | 51 (11.7%) |
| Complication at admission | | | | | | | | | | |
| Pneumonia | 12 (27.9%) | 61 (28.2%) | 5 (21.7%) | 96 (37.1%) | 11 (9.3%)[a] | 15 (3.6%) | 1 (9.1%) | 5 (18.5%) | 11 (28.9%) | 71 (16.2%) |
| Other infection | 7 (16.3%)[a] | 11 (5.1%) | 1 (4.3%) | 20 (7.7%) | 5 (4.2%) | 12 (2.9%) | 1 (9.1%) | 3 (11.1%) | 3 (7.9%) | 20 (4.6%) |
| GI bleeding | 5 (11.6%) | 31 (14.4%) | 2 (8.7%) | 52 (20.1%) | 5 (4.2%)[a] | 5 (1.2%) | 1 (9.1%) | 3 (11.1%) | 8 (21.1%)† | 42 (9.6%) |
| Pulmonary edema | 4 (9.3%)[a] | 4 (1.9%) | 3 (13%) | 16 (6.2%) | 4 (3.4%)[a] | 0 (0%) | 0 (0%) | 1 (3.7%) | 2 (5.3%) | 4 (0.9%) |
| Outcomes | | | | | | | | | | |
| Death within 30 days | 4 (9.3%) | 18 (8.3%) | 1 (4.3%) | 27 (10.4%) | 2 (1.7%) | 1 (0.2%) | 0 (0%) | 6 (22.2%) | 1 (2.6%) | 12 (2.7%) |
| Recurrent stroke within 30 days | 0 (0%) | 1 (0.5%) | 0 (0%) | 2 (0.8%) | 0 (0%) | 2 (0.5%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (0.5%) |
| mRS score≧3 | 33 (76.7%)[a] | 133 (61.6%) | 18 (78.3%) | 182 (70.3%) | 68 (57.6%)a[b] | 67 (16.0%) | 3 (27.3%) | 12 (44.4%) | 30 (78.9%)†‡ | 242 (55.4%) |
| OR (95% CI) | 2.04 (0.95–4.35) [a] | | 1.50 (0.54–4.20) | | 6.98 (4.45–10.95)[a] | | 0.47 (0.10–2.16) | | 2.66 (1.23-5.73)† | |
| Adjusted OR (95% CI) | 1.41 (0.50–3.94) | | | | 8.02 (3.94–16.32)[b] | | | | 2.47 (1.06-5.76)‡ | |

NS: nephrotic syndrome; NOACs: non-vitamin K antagonist oral anticoagulants; GI: gastrointestinal; mRS: modified Rankin scale; OR: odds ratio; CI: confidence interval.
Data are presented as mean ± standard deviation or *n* (%).
*$p < 0.05$, Student *t* test;
[a]$p < 0.05$, Chi-square test;
[b]$p < 0.05$, adjusted *P* value using multivariate logistic regression analysis.

usage of NOACs compared with the control group ($p = 0.018$ and $p < 0.001$, respectively). In the subgroup with small-artery occlusion, NS patients had a longer average length of stay in the acute medicine ward and higher rates of stroke in evolution, pneumonia, gastrointestinal bleeding, and pulmonary edema compared to the control group ($p = 0.001$, $p = 0.019$, $p = 0.014$, $p = 0.047$, and $p = 0.002$, respectively). Moreover, NS patients had a lower usage of aspirin and statins during the acute stage of stroke, but a higher usage of heparin ($p < 0.001$, $p = 0.008$, and $p = 0.009$, respectively). The rate of dependent functional status was also significantly higher in NS patients compared to the control group (OR 6.98, CI 4.45 to 10.95, $p < 0.001$), and this association remained significant after adjusting for confounding factors in the multivariate analysis (OR 8.02, CI 3.94 to 16.32, adjusted $p < 0.001$) (Supplementary Table 10). In the subgroup with stroke of undetermined etiology, NS patients had a higher risk of gastrointestinal bleeding compared with control group ($p = 0.041$). The risk of dependent functional status was higher in NS patients compared with control group (OR 2.66, CI 1.23 to 5.73, $p = 0.007$), which remained significant after adjusting for confounding factors in multivariate analysis (OR 2.47, CI 1.06 to 5.76, adjusted $p = 0.037$) (Supplementary Table 11). The information of clinical course and outcomes were summarized in Table 5 and Supplementary Table 12.

## 4. Discussion

The different subtypes of IS can influence the presentations and outcomes of stroke [11]. To investigate the impact of NS on the outcome of acute IS, we compared the clinical features of IS patients with and without NS in a large cohort study, stratified by IS subtypes. We found that NS increased functional dependence risk following IS compared to general population. This risk was higher for small-artery occlusion and stroke of undetermined etiology. These results reveal characteristics and outcomes of IS in patients with NS.

Our results showed that patients with NS had a higher risk of being dependent after acute IS than general population, especially if they had small-artery occlusion and stroke of undetermined etiology. However, NS did not affect the rates of all-cause mortality and recurrent stroke in IS patients. It has shown that IS patients with CKD have more severe stroke and worse functional outcomes compared to the general IS population [23]. In the acute stroke stage, their National Institutes of Health Stroke Scale scores and risk of neurological deterioration are higher than those without CKD [23]. IS patients with more severe CKD are also less likely to be independent at home [24].

Our study found higher prevalence of several common vascular risk factors in IS patients with NS than those without NS. In large-artery atherosclerosis, NS patients had higher prevalence of CHF and hyperuricemia than controls. In cardioembolism subtype, hypertension and hyperuricemia was more prevalent in NS patients compared to controls. In the small-artery occlusion, NS patients had higher prevalence of DM, CAD, CHF, previous TIA, and PAOD than controls. In stroke of undetermined etiology, only CHF was more prevalent in NS patients compared to controls. Cerebrovascular disease and CKD have a complex relationship involving multiple mechanisms. In addition to common vascular risk factors such as hypertension, DM, and hyperlipidemia, factors directly resulting from the sequelae of kidney disease such as oxidative stress, chronic inflammation, and high levels of urea and uric acid may also contribute to the development of cerebrovascular disease in patients with CKD [24]. CKD patients have higher prevalence of hypertension than the general population, and DM is a common secondary cause of NS [25]. CKD impairs uric acid excretion, and uric acid causes CKD and acute kidney injury [26]. The prevalence of CHF in CKD patients is around 25-70%, increasing with kidney function declines [27,28]. CHF is an important cause of CKD progression, and conversely, CKD itself is also a crucial contributor to severe cardiac damage [28].

Patients with large-artery atherosclerosis who also had NS experienced more pulmonary edema and infection other than pneumonia or urinary tract infection during their acute stroke admission period than those without NS. NS also prolonged the acute ward stay and increased the occurrence of stroke evolution, pneumonia, gastrointestinal bleeding and pulmonary edema in patients with small-artery occlusion. Patients with stroke of undetermined etiology had more gastrointestinal bleeding if they had NS. However, NS did not affect the clinical course or common complications of patients with cardioembolism and stroke of other determined etiology during their acute stroke period. NS increases risk of infection due to the loss of proteins that affect immune system, such as immunoglobulin G and factor B [29]. Moreover, long-term immunosuppressive therapy for NS can also increase the risk of infection [30]. CKD can also lead to gastrointestinal bleeding due to hemostasis disturbances, such as platelet dysfunction and variations in plasmatic levels of clotting factors [31].

Our results showed that patients with NS had a significantly younger age of IS onset than those in the general population, for all IS subtypes. Patients with CKD undergo accelerated aging, which precipitates the appearance of premature atherosclerosis and may lead to stroke at a younger age [32,33]. In addition to common atherosclerotic risk factors such as age, hypertension, DM, dyslipidemia, and smoking, other CKD-related atherosclerotic risk factors, including endothelial dysfunction, oxidative stress, inflammation, abnormal lipid modifications, uremic toxins, mineral bone metabolism, and vascular calcification, have also been identified [34]. Therefore, CKD is characterized by an increased atherosclerotic burden from early stages, and CKD patients are more prone to coagulation disorders and cardiovascular problems than the general population [35].

This study has several limitations. The retrospective design may have introduced some confounding factors that affected the analysis, such as selection bias or information bias.

Additionally, only 14.6% of patients with NS received a kidney biopsy, so the detailed etiology of NS remains

uncertain in a large proportion of patients. We were not able to separately report the presentations and outcomes of NS patients according to the underlying etiologies of NS. However, 59.3% of NS patients without kidney biopsy had history of DM for more than 10 years or triopathy of DM, suggesting diabetic nephropathy was the most likely etiology for these patients. The low percentage of patients receiving a kidney biopsy is likely due to two factors: (1) many of these patients had DM (146/199 = 73.4%), which is a common secondary cause of NS, and (2) many of these patients were relatively old and had other comorbidities, therefore they were hesitant to undergo the procedure due to concerns about potential complications. Furthermore, the information about the treatment response of immunosuppressive therapies for NS is limited in a large proportion of patients in the CG Research Databases, which may influence the outcomes of IS. Recruiting control patients from only one regional hospital may raise the possibility of differential outcomes due to location, hospital practices, and year. We may miss some patients who met the criteria of NS if they were not coded by our searching ICD codes. We did not account for possible variation in acute IS outcomes across different hospitals. Future large prospective studies with comprehensive data on NS characteristics and hospital factors that may affect stroke care quality will be warranted to confirm the clinical outcomes in NS patients with IS.

## 5. Conclusion

This study finds the impact of NS on functional outcome after IS. NS is associated with poor functional outcome in IS patients particularly with small-artery occlusion and stroke of undetermined etiology. These findings highlight the importance of aggressive vascular risk factor management and early rehabilitation for patients with NS and IS, especially those with small-artery occlusion and stroke of undetermined etiology.

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