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Increased risk for central serous chorioretinopathy in nephrotic syndrome patients: A population-based cohort study

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Abstract

Background: Nephrotic syndrome (NS) is characterized by various etiologies that damage the glomerulus. Central serous chorioretinopathy (CSCR) is a retinal disease characterized by neurosensory detachment of the retina. Several case reports have described the relationship between both. Therefore, we try to analyze the epidemiological associations between NS and CSCR using the National Health Insurance Research Database in Taiwan.

Methods: Data spanning 14 years were extracted from the National Health Insurance Research Database and sub-grouped. The variables were analyzed using Pearson's chi-squared test and Fisher's exact test. The risk factors for disease development with or without comorbidities were examined using an adjusted hazard ratio (aHR). Kaplan-Meier analysis was performed to evaluate the cumulative incidence of CSCR with or without NS.

Results: A total of 14 794 patients with NS and 14 794 matched controls without NS were enrolled in this cohort study. The incidence rate of CSCR was higher in the study cohort than in the control cohort (aHR = 3.349, $p < 0.001$). The overall incidence of CSCR was 44.51 per 100 000 person-years in the study cohort and 33.39 per 100 000 person-years in the control cohort. In both groups, CSCR occurred more frequently in males than in females. Patients aged 40–49, 50–59, and ≥60 years in the study cohort had a significantly higher risk of developing CSCR than those in the control cohort (aHR = 3.445, 5.421, and 4.957, all $p < 0.001$). NS patient with a 4-week history of steroid usage has a higher risk of developing CSCR (aHR = 2.010, $p < 0.001$).

Conclusion: Our data showed that patients with NS have an increased risk of developing subsequent CSCR. Physician should routinely refer their NS patients to ophthalmologist for ophthalmic evaluation. This is the first nationwide epidemiological study reporting the association between these two diseases. Further studies are needed to clarify this relationship.

Keywords: Central serous chorioretinopathy; Nation health insurance research database; Nephrotic syndrome

1. INTRODUCTION

Nephrotic syndrome (NS) is a group of clinical symptoms and signs classically defined by the presence of proteinuria, hypoalbuminemia, edema, hyperlipidemia, and lipiduria.[1,2] It might be caused by primary or secondary (systemic) glomerular disease.[3,4] In children, minimal change disease and focal segmental glomerulosclerosis are the most commonly known primary idiopathic NSs,[5] whereas minimal change disease, focal segmental glomerulosclerosis, and membranous nephropathy are the top-listed primary glomerular diseases in adults.[3] Systemic diseases, including diabetes mellitus (DM), systemic lupus erythematosus, Sjögren syndrome, and amyloidosis, can also result in secondary NS.[3] Among all, diabetic nephropathy is one of the most common secondary causes of NS globally,[4] which in many cases eventually develop into chronic kidney disease (CKD) and end-stage renal disease (ESRD) in the United States[6] and in Taiwan.[7] As the underlining cause of diabetic nephropathy, DM can also cause various visual threatening eye diseases, such as diabetic cataract, diabetic retinopathy, and diabetic macular edema, which further leads to severe visual impairment and blindness.[8]

Central serous chorioretinopathy (CSCR) is a very common nonsurgical retinopathy that can cause a significant visual

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disturbance.[9] Patients typically present with blurred vision, metamorphopsia, micropsia, increased hyperopia, dyschromatopsia, and reduced contrast sensitivity.[9] The characteristic finding of CSCR was localized neurosensory retinal detachments caused by an accumulation of subretinal fluid with or without retinal pigment epithelium (RPE) detachments in the macula region.[10] The main mechanisms underlying the accumulation of subretinal fluid in CSCR were hypothesized to be caused by the disruption of the RPE,[11] dysfunctions of choroidal circulation,[12] and the activation of the mineralocorticoid receptor in the choroidal vasculature.[10,13] However, the exact pathophysiology or the molecular pathway of CSCR remains unclear. Despite the enigmatic origin of CSCR, several well-known risk factors, including exposure to glucocorticoids, pregnancy, cardiovascular diseases, hypertension (HTN), obstructive sleep apnea, gastroesophageal reflux with *Helicobacter pylori*, type A personality, and genetic predispositions, have been associated with it.[10,14]

However, in the literature review, several cases with NS have been reported to cause exudative retinal detachment, mimicking CSCR.[15–19] Besides, membranoproliferative glomerulonephritis type II, one of the common NS,[20] has been repeatedly described in the literature to be characterized by serous retinal detachment and subretinal deposits, resembling classical CSCR.[20–22] Moreover, the use of corticosteroids, which have been commonly used to treat NSs,[23,24] is also a well-known risk factor for CSCR.[25,26] Despite these numerous reported associations between NS and CSCR in the literature, there is no epidemiologic evidence linking them together. Our study is the first study to utilize a population database in an attempt to clarify the risk of developing CSCR for patients with NS.

2. METHODS

2.1. Research database

Since 1995, Taiwan has implemented the National Health Insurance (NHI) program, a government-sponsored single-payer health care system. Till June 2017, the NHI program covered 99.6% of the Taiwan's population; approximately 24 million people were enrolled in this program.[27] The original registration files and claims data of the NHI program were collected and scrambled to construct a computerized database, the National Health Insurance Research Database (NHIRD), which is maintained and regulated by the National Health Research Institutes. The Longitudinal Health Insurance Database 2000 (LHID 2000) is a representative subset database of NHIRD, which contains 1 000 000 beneficiaries randomly sampled from the beneficiaries registered in year 2000.[28] The obtained parameters of the LHID 2000 for this current research purpose included gender, age, insurance premium, diagnosis, season, location, urbanization level, and level of care.

2.2. Study design and population

This retrospective population study utilized a matched cohort dataset extracted from the database LHID 2000 to explore the epidemiological relationship between NS and CSCR. All study participants newly diagnosed with NS were included in this study. Participants with newly diagnosed NS with ≥3 outpatient visits or inpatient hospitalization were identified from the LHID 2000 using the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) code (ICD-9-CM code for NS: 581). The date of NS diagnosis was defined as the index date. The diagnosis of NS was clinically made when a patient has persistent proteinuria ≥3.5 g/24 h (adult) or 40 mg/h/m^2 (children), hypoalbuminemia (below 3.5 g/dL), edema (peripheral limb edema, ascites, or pleural effusions), and hyperlipidemia (hypercholesterolemia and hypertriglyceridemia).[1,2] The participants should also have had received laboratory testing of urine protein-to-creatinine ratio 1 month within the index date, examined using the NHI code (urine protein [09040C] and urine creatinine [09016C]). Participants were excluded from the study if they were diagnosed with NS before the index date, diagnosed CSCR before tracking, other-related eye disorders diagnosed 1 year before and after CSCR (including degenerative myopia [ICD-9-CM 360.21], hemorrhagic RPE detachment [ICD-9-CM 362.43], exudative age-related macular degeneration [AMD] [ICD-9-CM 362.52], macular hole [ICD-9-CM 362.54], hereditary retinal dystrophies [ICD-9-CM 362.7], focal chorioretinitis [ICD-9-CM 363.0], disseminated chorioretinitis [ICD-9-CM 363.1], Harada's disease [ICD-9-CM 363.22], angioid streak [ICD-9-CM 363.43],or malignant neoplasm of the choroid [ICD-9-CM 190.6]), age of <20, and unknown gender.

As shown in Fig. 1, the data of 989 753 individuals spanning 14 years of follow-up from 2000 to 2013 were obtained from the LHID 2000 dataset and analyzed. A total of 17 772 individuals met the inclusion criteria and 2978 individuals were further excluded by the exclusion criteria. Eventually, 14 794 individuals were included in the study cohort (patients with NS). For comparison, the data of the control cohort (patients without NS during the whole study period) were collected from the LHID using the same exclusion criteria as the study cohort with a 1-fold propensity score matching by gender, age, and index year. In other words, the control cohort also included 14 794 individuals with the same basic characteristics.

Participants were then followed from the index date until the onset date of CSCR, at the end of year 2013, or withdrawal from the NHI program, whichever occurred first. The diagnosis of CSCR (ICD-9-CM 362.41) was typically made, provided that other differential diagnoses had been excluded, when patients have persistent subretinal fluid seen on fundus examination and on optical coherence tomography (OCT), with RPE changes seen as pigment epithelial detachments on OCT, leakage from RPE seen on fluorescein angiography, or widespread RPE atrophy seen on fundus autofluorescence.[10,14,29,30] The overall incidence of subsequent development of CSCR in both the study and cohort group were then analyzed.

The clinical diagnoses of other comorbidities (DM [ICD-9-CM 250], hyperlipidemia [ICD-9-CM 272], HTN [ICD-9-CM 401–405], CKD [ICD-9-CM 582–586, 588], peptic ulcers [ICD-9-CM 531–534], psychiatric diseases [ICD-9-CM 292–302, 304–309, 311], allergic respiratory diseases [ICD-9-CM 477, 493], coronary artery disease [CAD] [ICD-9-CM 410–414], and ESRD [ICD-9-CM 585]) were also identified using the ICD-9-CM for sub-analysis. The Charlson Comorbidity Index (CCI) was replaced with CCI_R (CCI removed NS, DM, HTN, CKD, CAD, and ESRD) to exclude the variables used in this study.

Based on the well-documented influence of corticosteroid usage in developing CSCR,[25] prescription medications of corticosteroids (all forms of administration) used 1 month before the onset date of CSCR were also identified using the National Drug Codes and further analyzed as a risk factor in this study. This specific interval was examined due to the commonly reported duration of developing CSCR after steroid usage.[25]

2.3. Statistical analysis

Pearson's chi-squared test and Fisher's exact test were used to evaluate the differences in gender, age group, risk factors, and comorbidities in both cohort groups. Statistical significance was defined as $p < 0.05$. After the adjustment of the categorical variables, univariate and multivariate Cox regression analyses were used to evaluate the adjusted hazard ratio (aHR) for the effect of NS on developing CSCR. Kaplan-Meier analysis was used to

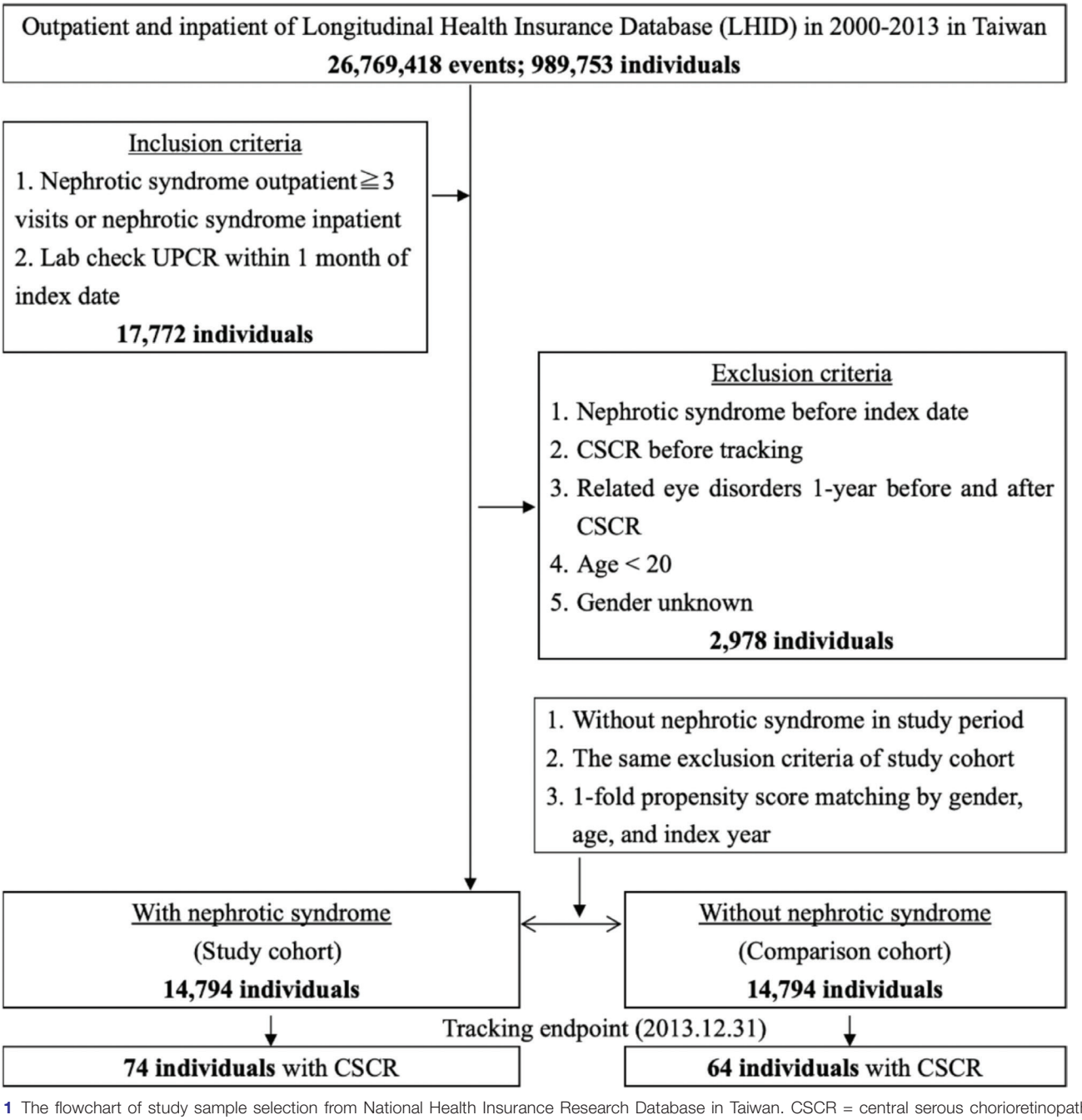


Fig. 1 The flowchart of study sample selection from National Health Insurance Research Database in Taiwan. CSCR = central serous chorioretinopathy; UPCR = urine protein-to-creatinine ratio.

evaluate the cumulative incidence of CSCR in the study and control cohorts. All statistical analyses were performed using SPSS software (Version 22.0, SPSS Inc., Chicago, IL).

2.4. Ethical considerations

All personal information obtained from the NHIRD was encoded to maintain patient privacy and was theoretically prevented from information exploitation. The NHIRD can be used by all qualified researchers who are citizens of the Republic of China; hence, patient consent is not required. The Institutional Review Board of the Tri-Service General Hospital has approved this study and waived the consent requirement (TSGHIRB No.: B-109-43).

3. RESULTS

3.1. Basic characteristics

Each of the study and control cohorts eventually included 14794 individuals for further analysis. The mean age at baseline for the entire study was 51.24 ± 15.79 years (51.29 ± 16.18 years for patients with NS and 51.18 ± 15.40 years for patients without NS). The characteristics of both groups were similar at baseline and the endpoint. Table 1 shows the basic characteristics of both cohorts at the endpoint. Due to the study design of our age- and gender-matched controls, there were no statistical gender differences ($p = 0.999$) in both groups; overall, there were slightly more males (51.42%) than females (48.58%) in

Table 1

Characteristics of study in the endpoint

Nephrotic syndrome	Total		With		Without		
Variables	**N**	**%**	**n**	**%**	**n**	**%**	***p***
Total	29588		14794	50.00	14794	50.00	
CSCR							0.044
Without	29450	99.53	14720	99.50	14730	99.57	
With	138	0.47	74	0.50	64	0.43	
Gender							0.999
Male	15214	51.42	7607	51.42	7607	51.42	
Female	14374	48.58	7187	48.58	7187	48.58	
Age (years)	63.3 ± 15.7		62.5 ± 16.0		64.1 ± 15.3		<0.001
Age group							<0.001
20–29	641	2.17	533	3.60	108	0.73	0.081
30–39	3402	11.50	1857	12.55	1545	10.44	0.056
40–49	5149	17.40	2753	18.61	2396	16.20	0.023
50–59	6653	22.49	3463	23.41	3190	21.56	0.071
≧60	13743	46.45	6188	41.83	7555	51.07	<0.001
DM							<0.001
Without	28123	95.05	13732	92.82	14391	97.28	
With	1465	4.95	1062	7.18	403	2.72	
Hyperlipidemia							<0.001
Without	28617	96.72	14137	95.56	14480	97.88	
With	971	3.28	657	4.44	314	2.12	
HTN							<0.001
Without	26948	91.08	13226	89.40	13722	92.75	
With	2640	8.92	1568	10.60	1072	7.25	
CKD							<0.001
Without	28674	96.91	13926	94.13	14748	99.69	
With	914	3.09	868	5.87	46	0.31	
Peptic ulcer							0.036
Without	28982	97.95	14465	97.78	14517	98.13	
With	606	2.05	329	2.22	277	1.87	
Psychiatric diseases							0.118
Without	28568	96.55	14259	96.38	14309	96.72	
With	1020	3.45	535	3.62	485	3.28	
Allergic respiratory diseases							0.783
Without	28930	97.78	14469	97.80	14461	97.75	
With	658	2.22	325	2.20	333	2.25	
CAD							<0.001
Without	29092	98.32	14438	97.59	14654	99.05	
With	496	1.68	356	2.41	140	0.95	
ESRD							<0.001
Without	29366	99.25	14588	98.61	14778	99.89	
With	222	0.75	206	1.39	16	0.11	
Steroid							0.238
Without	23910	80.81	11915	80.54	11.995	81.08	
With	5678	19.19	2879	19.46	2799	18.92	
CCI_R	0.18 ± 0.75		0.18 ± 0.74		0.18 ± 0.76		0.920

p: Chi-square/Fisher exact test on category variables and t-test on continue variables, and proportion test for the % comparison.

CAD = coronary artery disease; CCI_R = Charlson comorbidity index; CI = confidence interval; CKD = chronic kidney disease; CSCR = central serous chorioretinopathy; DM = diabetes mellitus; ESRD = end-stage renal disease; HTN = hypertension.

our study. There was also no statistical mean age difference (51.29 ± 16.18 years for the study cohort vs 51.18 ± 15.40 years for the control cohort, $p = 0.549$) at baseline. However, the mean age at the endpoint was 62.53 ± 16.03 years for the study cohort and 64.14 ± 15.28 years for the control cohort with statistical significance ($p < 0.001$). There was also a statistical difference ($p < 0.05$) at the endpoint between the study cohort and the control cohort for 40–49 and ≥60 years age groups. In the age groups younger than 60 years, there were more patients with NS than those without NS. In the age group older than 60 years, there were statistically fewer patients with NS than those without NS. In the comorbidity comparison, patients with NS had statistically higher rates of DM ($p < 0.001$), hyperlipidemia ($p < 0.001$), HTN ($p < 0.001$), CKD ($p < 0.001$), peptic ulcers ($p = 0.036$), CAD ($p < 0.001$), and ESRD ($p < 0.001$). There was no statistical difference in steroid usage in both groups at the baseline and endpoint. The CCI_R value was 0.18 ± 0.74 for the study cohort and 0.18 ± 0.76 for the control cohort without statistical significance ($p = 0.920$). As hyperlipidemia, CKD, and ESRD were inherently related to NS, the statistical significance in our study group demonstrated an indirect evidence for confirming the accuracy of the diagnosis of NS.

The mean follow-up duration for the study and control cohorts were 11.24 ± 5.85 years and 12.96 ± 1.94 years, respectively. Throughout the 14 years of the study, 74 patients in the study cohort and 64 patients in the control cohort were diagnosed with CSCR (Fig. 1). The mean number of years for developing CSCR in the study and control cohort were 5.11 ± 3.83 years and 7.19 ± 3.98 years, respectively. The cumulative risk of developing CSCR was calculated using the Kaplan-Meier method, and the results showed that patients with NS had a significantly higher rate of developing CSCR compared with the control cohort (Log-rank test $p < 0.001$) (Fig. 2A). The cumulative risk of CSCR gradually increased to 0.50% (74/14 794 individuals) at the endpoint in the study cohort and to 0.43% (64/14 794 individuals) in the control cohort. Furthermore, there was a significant difference in the number of CSCR in both groups during each year of follow-up ($p < 0.001$ during each year) (Fig. 2B).

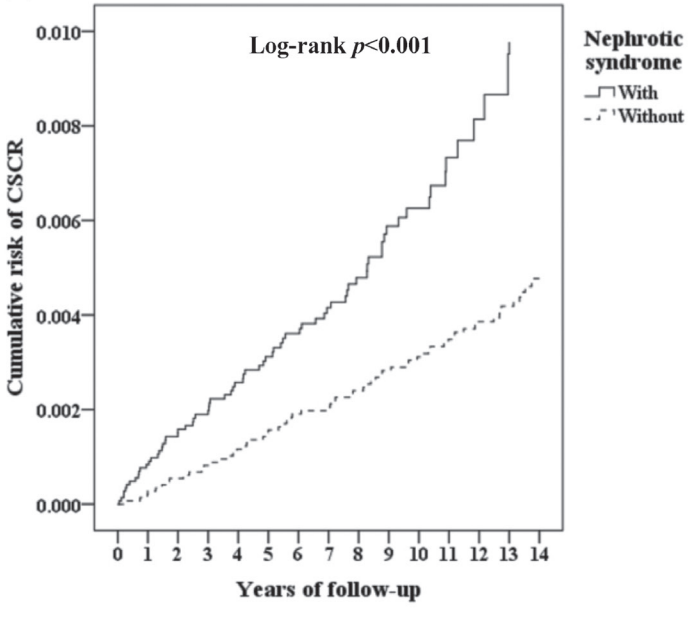
3.2. Cox regression risk factor analysis

Table 2 shows the Cox regression analysis of the risk factors for developing CSCR. The univariate analysis and multivariate analyses showed that the patients in the study cohort had a significantly higher risk of developing CSCR (crude HR = 2.210, 95% confidence interval [CI] = 1.553–3.144, $p < 0.001$; aHR = 3.349, 95% CI = 2.324–4.827, $p < 0.001$). Furthermore, the multivariate analysis showed that older patients (age groups: 50–59 and ≥60 years; aHR = 0.422 and 0.349, $p = 0.007$ and < 0.001) had a lower risk of developing CSCR than younger patients (age groups: 18–29 years). There were no statistical differences in the risk of developing CSCR between both males and females. According to the hazard ratio, there were no significant differences among the risk of developing CSCR associated with comorbidities, such as DM, hyperlipidemia, HTN, CKD, peptic ulcers, psychiatric disease, allergic respiratory diseases, CAD, ESRD, and steroid (all $p > 0.05$).

The stratified subgroup analysis of patients with and without NS (Table 3) showed that the overall incidence of CSCR was 44.51 per 100 000 person-years for the study cohort and 33.39 per 100 000 person-years for the control cohort. In both cohort groups, more male patients than female patients developed CSCR. Both males and females with NS had a higher risk of developing CSCR than patients without NS (aHR = 2.934 in males and 3.995 in females, $p < 0.001$). The age analysis showed that patients with NS in the 40–49, 50–59, and ≥60 years age groups had a significantly higher risk of developing CSCR than those without NS (aHR = 3.445, 5.421, and 4.957, all $p < 0.001$). The subgroup analysis showed that patients without NS in our cohort had no comorbidities, such as DM, hyperlipidemia, HTN, CKD, peptic ulcers, psychiatric disease, allergic respiratory diseases, CAD, and ESRD; most of the patients who developed CSCR in the study cohort did not have comorbidities listed above (only one had DM, one had HTN, and two had psychiatric diseases). Hence, the risk of developing CSCR in patients without these comorbidities was higher in the study cohort than in the control cohort (all aHR = 3.349, all $p < 0.001$).

The usage of corticosteroids was also analyzed for its risk of subsequent CSCR in both cohort groups. Within our series, all reported cases with prior steroid usage have been reported to be prescribed oral forms of corticosteroids (data not shown). Overall, there were no statistical differences in the number of patients with a history of steroid usage 1-month prior CSCR developed between patients with or without NS (27.03% [20/74] vs 25% [16/64], $p = 0.890$) (data not shown). The stratified Cox regression analysis showed that patients with NS have a higher statistical risk of developing CSCR than patients without NS, with or without the influence of steroid (aHR = 3.279 and 3.521, both $p < 0.001$) (Table 3). When considering the effect of steroid usage separately in patients developed CSCR of both cohort groups, the sensitivity test of the frequency of steroid usage and the risk of CSCR showed that no overall statistical difference in patients with and without a history of steroid usage (aHR = 1.425 and 1.149, $p = 0.057$ and 0.204) (Table 4). However, there was a gradually increased risk of developing CSCR in patients with increased duration of steroid usage in

(a)



(b)

Nephrotic syndrome	With (N=14,794)	Without (N=14,794)	*p*
In the tracking of x year(s)	Numbers of CSCR		
1	12	4	<0.001
2	22	8	<0.001
3	26	12	<0.001
4	34	17	<0.001
5	40	22	<0.001
6	45	28	<0.001
7	50	29	<0.001
8	55	35	<0.001
9	62	41	<0.001
10	64	45	<0.001
11	68	50	<0.001
12	70	55	<0.001
13	72	59	<0.001
14	74	64	<0.001

Fig. 2 (A) Kaplan-Meier for cumulative risk of CSCR among aged 20 and (B) over stratified by nephrotic syndrome with log-rank test. CSCR = central serous chorioretinopathy.

Table 2

Factors of CSCR by using Cox regression

Variables	Crude HR	95% CI	95% CI	*p*	Adjusted HR	95% CI	95% CI	*p*
Nephrotic syndrome								
Without	Reference				Reference			
With	2.210	1.553	3.144	<0.001	3.349	2.324	4.827	<0.001
Gender								
Male	1.401	0.998	1.967	0.051	1.176	0.833	1.656	0.337
Female	Reference				Reference			
Age group (years)								
18–29	Reference				Reference			
30–39	0.325	0.137	0.770	0.011	0.433	0.183	1.033	0.070
40–49	0.412	0.184	0.974	0.031	0.612	0.271	1.385	0.214
50–59	0.231	0.101	0.530	0.001	0.422	0.182	0.969	0.007
≧60	0.163	0.073	0.363	<0.001	0.349	0.153	0.795	<0.001
DM								
Without	Reference				Reference			
With	0.163	0.023	1.163	0.070	0.309	0.042	2.251	0.233
Hyperlipidemia								
Without	Reference				Reference			
With	0.000	–	–	0.162	0.000	–	–	0.912
HTN								
Without	Reference				Reference			
With	0.177	0.025	1.268	0.085	0.290	0.040	2.161	0.228
CKD						**Multicollinearity with ESRD**		
Without	Reference					**Multicollinearity with ESRD**		
With	0.000	–	–	0.238		**Multicollinearity with ESRD**		
Peptic ulcer								
Without	Reference				Reference			
With	0.000	–	–	0.263	0.000	–	–	0.955
Psychiatric diseases								
Without	Reference				Reference			
With	0.402	0.100	1.624	0.201	0.478	0.137	1.862	0.277
Allergic respiratory diseases								
Without	Reference				Reference			
With	0.000	–	–	0.232	0.000	–	–	0.930
CAD								
Without	Reference				Reference			
With	0.000	–	–	0.339	0.000	–	–	0.933
ESRD								
Without	Reference				Reference			
With	0.000	–	–	0.375	0.000	–	–	0.489
Steroid								
Without	Reference				Reference			
With	1.986	1.027	2.897	0.014	1.762	0.884	2.595	0.117
CCI_R	0.659	0.408	1.065	0.089	0.601	0.380	0.962	0.031

Adjusted for the variables listed in Table 2.

Adjusted HR = Adjusted Hazard ratio; CAD = coronary artery disease; CCI_R = Charlson comorbidity index; CI = confidence interval; CKD = chronic kidney disease; DM = diabetes mellitus; ESRD = end-stage renal disease; HTN = hypertension.

both cohort groups, which reached a statistical significance in patients with 4 weeks usage in the study group (aHR = 2.010, $p < 0.001$) and in patients over 2 weeks usage in the control group (aHR = 1.444 and 1.428, both $p < 0.05$).

4. DISCUSSION

This population cohort study is the largest study known to evaluate the relationship between NS and the subsequent risk of developing CSCR. In our study, we included 14 794 patients with NS and 14 794 control subjects without NS. After a 14-year follow-up period, the overall incidence of CSCR was 44.51 per 100 000 person-years and 33.39 per 100 000 person-years in the study and control cohorts, respectively. We also found that the adjusted relative risk for developing CSCR in patients with NS was 3.349 higher than that in patients without NS. The cumulative risk of developing CSCR in patients with NS was also significantly higher (Fig. 2A). Therefore, our results demonstrated that the relationship between NS and the subsequent risk of developing CSCR was highly correlated.

Patients who developed CSCR in our study had characteristics similar to those previously described in other epidemiological studies. Even though, both univariate and multivariate analyses of the risk factors for developing CSCR showed no statistically significant gender difference (male to female crude HR = 1.401, $p = 0.051$; aHR = 1.176, $p = 0.337$). We found that more male than female patients developed CSCR during the follow-up period in both cohorts (43 males vs 31 females in patients with NS and 38 males vs 26 females in patients without NS) (Table 3). This male predominance in developing CSCR

Table 3

Factors of central serous chorioretinopathy stratified by variables listed in the table by using Cox regression

Nephrotic syndrome	With			Without			With vs without (reference)				
Stratified	Event	PYs	Rate (per 10^5 PYs)	Event	PYs	Rate (per 10^5 PYs)	Ratio	Adjusted HR	95% CI	95% CI	*p*
Total	74	166 250.72	44.51	64	191 682.79	33.39	1.333	3.349	2.324	4.827	<0.001
Gender											
Male	43	83 919.91	51.24	38	96 890.52	39.22	1.306	2.934	1.835	4.689	<0.001
Female	31	82 330.81	37.65	26	94 792.27	27.43	1.373	3.995	2.231	7.151	<0.001
Age group (years)											
20–29	4	4121.56	97.05	3	1192.54	251.56	0.386	1.156	0.177	7.552	0.842
30–39	8	20 679.69	38.69	12	20 057.19	59.83	0.647	1.504	0.578	3.921	0.384
40–49	24	31 422.05	76.38	15	31 094.69	48.24	1.583	3.445	1.741	6.808	<0.001
50–59	16	40 061.44	39.94	13	42 011.04	30.94	1.291	5.421	2.390	12.012	<0.001
≧60	22	69 965.98	31.44	21	97 327.33	21.58	1.457	4.957	2.568	9.557	<0.001
DM											
Without	73	154 617.23	47.21	64	186 393.61	34.34	1.375	3.349	2.324	4.827	<0.001
With	1	11 633.49	8.60	0	5289.18	0.00	–	–	–	–	–
Hyperlipidemia											
Without	74	158 456.67	46.70	64	187 414.87	34.15	1.368	3.349	2.324	4.827	<0.001
With	0	7794.05	0.00	0	4267.92	0.00	–	–	–	–	–
HTN											
Without	73	148 005.81	49.32	64	174 232.67	36.73	1.343	3.349	2.324	4.827	<0.001
With	1	18 244.91	5.48	0	17 450.12	0.00	–	–	–	–	–
CKD											
Without	74	156 751.55	47.21	64	191 164.96	33.48	1.410	3.349	2.324	4.827	<0.001
With	0	9499.17	0.00	0	517.83	0.00	–	–	–	–	–
Peptic ulcer											
Without	74	162 554.31	45.52	64	188 081.72	34.03	1.338	3.349	2.324	4.827	<0.001
With	0	3696.41	0.00	0	3601.07	0.00	–	–	–	–	–
Psychiatric diseases											
Without	72	159 949.34	45.01	64	185 238.39	34.55	1.303	3.349	2.324	4.827	<0.001
With	2	6301.38	31.74	0	6444.40	0.00	–	–	–	–	–
Allergic respiratory diseases											
Without	74	162 464.53	45.55	64	187 303.11	34.17	1.333	3.349	2.324	4.827	<0.001
With	0	3786.19	0.00	0	4379.68	0.00	–	–	–	–	–
CAD											
Without	74	162 170.79	45.63	64	189 917.34	33.70	1.354	3.349	2.324	4.827	<0.001
With	0	4079.93	0.00	0	1765.45	0.00	–	–	–	–	–
ESRD											
Without	74	163 082.48	45.38	64	191 505.76	33.42	1.358	3.349	2.324	4.827	<0.001
With	0	3168.24	0.00	0	177.03	0.00	–	–	–	–	–
Steroid											
Without	54	125 642.94	42.98	48	155 416.20	30.88	1.392	3.279	2.271	4.729	<0.001
With	20	40 607.78	49.25	16	36 266.59	44.12	1.116	3.521	2.444	5.074	<0.001

Adjusted for the variables listed in Table 2.

Adjusted HR = adjusted hazard ratio; CAD = coronary artery disease; CI = confidence interval; CKD = chronic kidney disease; DM = diabetes mellitus; ESRD = end-stage renal disease; HTN = hypertension; PYs = Person-years.

was a repeated finding in different ethnic groups; it is also well-known in the literature. A regional population study in southeastern Michigan conducted between 1988 and 1994 showed that the male to female ratio was 6.5 in Caucasian patients with CSCR and 3.5 in African American patients with CSCR, respectively.[31] In another epidemiological study conducted in Olmsted County in Minnesota from 1980 to 2002 with a 85% Caucasian in its population, 85% of the patients with CSCR were male.[32] In an Egyptian single-center retrospective study conducted from 2006 to 2009, 91% of the patients with CSCR were male.[33] In a nationwide study with Taiwanese population, the prevalence reported in men was 1.7 times higher than that in women.[34] This phenomenon is speculated to be attributed to the higher levels of androgens in middle-aged men and postmenopausal women.[10,14] Both male and female patients with NS in our study showed a higher risk of developing CSCR (aHR = 2.934 for men and 3.995 for women) than patients without NS (Table 3). Interestingly, even after considering the effect of NS on the risk of developing CSCR, the male predominance still persisted; however, there may be a higher risk for developing CSCR in women than in men for patients with NS than those without NS.

In several previous epidemiological studies, the age for developing CSCR usually fell within 30–50 years. In the southeastern Michigan study, the mean age was 40 years for African Americans and 39 years for Caucasians.[31] In the Olmsted County study, the highest incidence of CSCR was recorded for the 35–44 age range.[32] In the previously mentioned population-based study in Taiwan conducted from 2001 to 2006, the reported higher mean annual incidence was recorded for the 35–39 years age group (0.30%), followed by the 40–44 years age group (0.26%).[34] In the aforementioned Egyptian single-center study, the patients with CSCR had a mean age of 38 years and an age range of 24–49 years.[33] These demographic results were also mirrored in our cohort study. The overall statistical risk of developing CSCR

Table 4

Sensitivity test for factors (steroid usage) of central serous chorioretinopathy by using Cox regression

NS subgroup	Events	PYs	Rate (per 10^5 PYs)	Adjusted HR	95% CI	95% CI	*p*
Without NS	64	191 682.79	33.39				
1 month before CSCR, without steroid	48	155 416.20	30.88	Reference			
1 month before CSCR, with steroid	16	36 266.59	44.12	1.425	0.994	2.059	0.057
Frequency of steroid use: 1	4	9275.24	43.13	1.391	0.972	2.007	0.074
Frequency of steroid use: 2	8	17 929.75	44.62	1.444	1.106	2.083	<0.001
Frequency of steroid use: 3	4	9061.60	44.14	1.428	1.002	2.062	0.048
Frequency of steroid use: 4	0	0.00	–	–	–	–	–
With NS	74	166 250.72	44.51				
1 month before CSCR, without steroid	54	125 642.94	42.98	Reference			
1 month before CSCR, with steroid	20	40 607.78	49.25	1.149	0.802	1.670	0.204
Frequency of steroid use: 1	3	8992.60	33.36	0.779	0.568	1.128	0.488
Frequency of steroid use: 2	9	18 962.01	47.46	1.108	0.774	1.602	0.326
Frequency of steroid use: 3	6	10 341.12	58.02	1.352	0.949	1.955	0.081
Frequency of steroid use: 4	2	2312.05	86.50	2.010	1.397	2.906	<0.001

Adjusted for the variables listed in Table 2. Frequency was measured by week.

Adjusted HR = Adjusted hazard ratio; CSCR = central serous chorioretinopathy; CI = confidence interval; NS = nephrotic syndrome; PYs = Person-years.

in both groups decreased significantly after age 50 (aHR = 0.422 [$p = 0.007$] and 0.349 [$p < 0.001$] for the 50–59 and ≥60 years age group, respectively) (Table 2); hence, younger patients (18–29 years age group) had a higher risk of developing CSCR than in older patients in our study. However, the age range of NS can vary in different etiologies. In our study cohort, patients with NS had a mean age of 62.5 ± 16.0 years with over 85% of the patients aged over 40 years (18.61%, 23.41%, and 41.83% for the 40–49, 50–59, and ≥60 years age group, respectively) at endpoint. This specific age group also mirrored the typical age range for adult NS in Taiwan (44.6 ± 18.8 years in minimal change disease, 50.4 ± 17.1 years in focal segmental glomerulosclerosis, and 58.1 ± 13.7 years in membranous nephropathy).[35] Interestingly, with a relatively older age distribution than the classic age range of CSCR, we also found that patients with NS had a significantly increased risk of developing CSCR in ≥40 years age group than those without NS (aHR = 3.345, 5.421, and 4.957 for the 40–49, 50–59, and ≥60 years age group, respectively [all $p < 0.001$]) (Table 3). This may imply that even though patients over 40 years might have a lesser risk of developing CSCR than younger patients, but when diagnosed NS, the risk of developing CSCR in such age group would increase significantly than those without NS. Owing to the diversity of etiologies and patient characteristics of NS, further study may need to clarify the underlined relationship between this specific age group of NS in the risk of developing CSCR.

In a real-world setting with its own complexity and additional compound factors, such as multiple comorbidities, the association between NS and the subsequent risk of developing CSCR should intuitively be difficult to perceive. However, a nationwide population-based study in Taiwan has demonstrated a significantly increased risk of developing CSCR in ESRD patients.[36] Given that NS is one of the most common etiologies of ESRD, our results have demonstrated consistent findings corroborating the report that patients with NS have an increased risk (aHR = 3.349) of developing CSCR. Moreover, there was a statistically significant correlation between NS and ESRD in our study that more patients were diagnosed ESRD at endpoint with NS (206 patients [1.39%]) than without (16 patients [0.11%]). However, all patients in both cohorts which eventually developed CSCR do not have ESRD (Table 3). This may either imply that our patients with NS were not that severe or that our study subjects did not have enough time to progress to ESRD before the incidence of CSCR. Hence, we can conclude that NS does not need to progress to ESRD to provide an increased risk for developing CSCR. And, given that diabetic nephropathy is the one of the most common NS causing ESRD in Taiwan,[8,37,38] it is reasonable to expect that DM would be somehow associated with the development of CSCR in patients with NS. Surprisingly, in our study, patients with NS and subsequent CSCR mostly did not have any other comorbidities; only one out of 74 patients had DM as comorbidities (Table 3). Moreover, the univariate and multivariate analyses showed no statistical relationship between CSCR and comorbidities (DM, HTN, CKD, peptic ulcer, psychiatric disease, allergic respiratory diseases, CAD, and ESRD) in both cohort groups (Table 3). Combining these results, it is reasonable to assume that CSCR may have a more straightforward relationship with "primary" NS unlike the secondary causes associated with comorbidities such as DM.

One of the most common "primary" NS in adults is membranous nephropathy in Taiwan.[35] Membranous nephropathy is a glomerulopathy characterized by subepithelial immune-complex deposit and thickening of the glomerular basement membrane;[39] with the histological similarity between the kidney and choroid,[40] it has been reported to be related to CSCR.[19] Another glomerular disease, membranoproliferative glomerulonephritis (MPGN) type II, which could sometimes present with NS, has also been repeatedly reported to be associated with CSCR in several case reports.[19–22] MPGN type II, also referred to as dense deposit disease, is characterized by electron-dense deposits in the glomerular basement membrane (GBM). In a new classification of MPGN using immunofluorescence microscopy, MPGN type II is classified under complement 3 (C3) glomerulopathies, which is a term encompassing all 3 types of MPGN with immune complex-mediated and complement-mediated mechanisms, and it is characterized by C3 deposits in the mesangium, subendothelial, and subepithelial capillary walls of the glomerulus.[41] The current hypothesis for glomerular damage in C3 glomerulopathy is focused on the activation of alternative complement pathway, which resulted from immune complex deposits in the glomerular basement membrane.[42] Due to the structural similarity between the glomerular epithelium-GBM-capillary tuft interface and the RPE-Bruch membrane-choriocapillaris interface, C3 glomerulopathy has been known to be associated with drusen-like deposits in Bruch's membrane in the literature.[40,43–45] Interestingly, in a pilot study of proteomics and metabolomics, proteins, and metabolites of the subretinal fluid extracted from a patient with CSCR revealed an upregulation of C3 and complement factor H (CFH)-related proteins.[46] Moreover, there has been increasing evidences on the genetic susceptibility of CFH

gene variants as a risk factor in CSCR patients.[14,47,48] These associations reinforced the idea that the dysfunction of the alternative complement pathway may be a more common molecular mechanism in the development of CSCR and C3 glomerulopathies. Further studies are needed to clarify the relationship between these interlinked pathophysiologies.

Patients with NS were usually treated symptomatically for the presenting heavy proteinuria, edema, hyperlipidemia, and its complications.[49] In addition, immunosuppressive therapy, especially corticosteroid treatments, usually oral or systemic administration, have long been used in treating various primary NS, such as minimal change disease, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, and membranous nephropathy.[24,50–52] On the other hand, corticosteroid usage, despite its route of administration and duration, has been listed as an associated risk factor for developing CSCR.[25,26] Hence, to exclude this confounding factor of steroid usage in NS patient, we further analyzed our dataset for patient with a history of prescription corticosteroids 1 month before the development of CSCR. Most patients in our study developed CSCR after a mean 5.11 ± 3.83 years of being diagnosed with NS and did not have a history of steroid usage 1-month before the development of CSCR (73% in study group and 75% in control group). These NS patients may consider relative stable in their disease process.[24] And for patient with a history of steroid usage, there was a statistical significance in risk of developing CSCR in the study group compared with the control (aHR = 3.521, p <0.001). However, considering the additional effect in the risk of developing CSCR, the frequency of steroid usage was examined in NS patients, and the results in Table 4 demonstrate the relationship between the risk of developing CSCR and NS was independent to prior steroid usage, except in long-duration usage. Therefore, NS, despite commonly treated with corticosteroid, can be independently associated with an increasing risk of developing CSCR without the confounding factor of corticosteroid usage. Furthermore, we also found that with the risk of developing CSCR in NS patients would gradually increase along with a longer duration of steroid usage and eventually get a statistical difference. Hence, physicians treating NS patients with long-duration corticosteroids should be aware of the increasing risk of developing CSCR, which could cause a significant visual disturbance.

Our current study has several limitations. First, this was a retrospective study utilizing a computerized database for comparison cohort analysis. Second, the NHIRD database only includes the original registration and claims data for each beneficiary. Due to the pseudonymization nature of the database, the medical charts or image reviews for confirming the accuracy of the diagnoses of both CSCR and NS are lacking. Third, the diagnosis of CSCR is challenging even for ophthalmologists, especially for more clinically ambiguous cases; hence, the possible misdiagnosis of CSCR may have led to further misclassification bias in our study. Fourth, the NHIRD mainly contained Taiwanese population; hence, the ethnic variation may have limited the application of our study results to other populations. Fifth, due to the study design, the control group included patients without NS during the entire study period. This may have constituted a healthier population than the general population, resulting in selection bias in the control cohort and overestimating the statistical relationship between both groups. Sixth, owing to the diversity of the underlined etiologies of NS, our study was difficult to conclude the exact and direct mechanism between CSCR and all kinds of NS. However, our purpose was to raise the concern of increased risk of developing CSCR in NS patients and advocated ophthalmic screening in such patients with an acute onset of visual disturbance to prevent persistent vision loss.

However, our study has several strengths. The NHI system is mandatory for every Taiwan citizen; hence, the data collected from the NHIRD and analyzed are for a nationwide population that is incomparable to any other epidemiological study elsewhere, with a large number of cases and high statistical power. Besides, the study participants with NS have high statistical significance in having hyperlipidemia and CKD compared with the control group, which signifies the inherent relationship between hyperlipidemia/CKD and NS, confirming the diagnostic accuracy of the study group. Moreover, utilizing the NHIRD database, our study encompassed a 14-year follow-up period. This enabled the analysis of the cumulative risk of developing CSCR in patients with NS, which is certainly a more time- and cost-effective study design than a cross-sectional cohort study.

In conclusion, the data in our study showed that patients with NS have an increased risk of developing CSCR 3 times more than those without NS. Furthermore, there is an even higher risk to develop CSCR for NS patient under corticosteroid treatment. Therefore, clinicians who treat patient with NS should consider refer them to ophthalmologist for CSCR evaluation if the patient complained about recent visual disturbance. This study is the first nationwide population-based study to describe the association between NS and CSCR.

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