Increased Risk of Osteoporosis in Patients With Nephrotic Syndrome. A Nationwide Population-Based Retrospective Cohort Study

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Abstract

Corticosteroid (CS) is commonly used in nephrotic syndrome (NS) and a risk factor for osteoporosis. We evaluated the risk of osteoporosis in patients with nephrotic syndrome using a nationwide population-based dataset. After adjusting for covariates, osteoporosis risk was found to be 3.279 times greater in the NS *cohort* than in the non-NS *cohort,* when measured over 11 years after NS diagnosis. Stratification revealed that age older than 18 years, congestive heart failure, hyperlipidemia, chronic kidney disease, liver cirrhosis, and NS-related disease including diabetes mellitus, hepatitis B infection, hepatitis C infection, lymphoma, and hypothyroidism, increased the risk of osteoporosis is when comparing the NS cohort with the non-NS cohort. Additionally, osteoporosis risk was significantly higher in NS patients with CS use (aHR = 3.397). The risk of osteoporosis in NS patients was positively associated with risk of hip and vertebral fracture (aHR = 2.130 and 2.268, respectively). A significant association exists between NS and subsequent risk for osteoporosis. Therefore NS patients, particularly those treated with CS, should be evaluated for subsequent risk of osteoporosis.

Introduction

Nephrotic syndrome (NS) is defined on the basis of heavy proteinuria, accompanied by hypoalbuminemia, hyperlipidemia, and edema. The mechanidsm of NS can be idiopathic and comprise kidney disease such as minimal-change disease, membranous nephropathy, and focal glomerulosclerosis. Secondary causes include systemic diseases such as diabetes mellitus, systemic lupus erythematosus (SLE), amyloidosis, and cancers, drugs, and infections. [1, 2]The complications of NS are divided into two categories: disease-associated and drug-related complications. Both the disease-associated and drug-related complications of NS could be susceptible to osteoporosis.[3]

Controversy remained as to whether people with NS have an increased risk of developing osteoporotic fractures. The reported prevalence range from 9–60% of osteoporosis among patients with NS. [4–7] Some studies have elucidated that NS is correlated with increased risk of osteoporosis,[6]and that the risk of osteoporosis also increases with increasing age, [8] notwithstanding, others have not.[9] It is unclear that the association between osteoporosis prevalence and NS progression. [6] Data on the risk of osteoporosis in patients with NS and corticosteroids (CS) use are scarce. [6] Therefore, this study used the National Health Insurance Research Database (NHIRD) to determine whether NS is a risk factor for osteoporosis and fracture. Further risk in NS patients who do and do not use CS is additionally evaluated.

Material And Methods

Data source

The nationwide population study retrieved data from the 2000 and 2010 national health insurance research databases (NHIRD) which is a compsulsory single-payer program delineating practically 99.9% population of the country.

NHIRD contains inpatient and outpatient dataset regarding details of diagnoses based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, gender, prescriptions assigned at contracted pharmacies. Researchers can get relevant claims information with scrambled patient identification numbers. The Institutional Review Board of Tri-service general hospital approved this study. All methods were performed in accordance with the relevant guidelines and regulations.

Ethics statement

Patient consent was not required for us to access the NHIRD because of encrypted patient personal information system to protect patient privacy.

Institutional Review Board of the Tri-Service General Hospital approved the study. (TSGHIRB No. 2-105-05-082).

Study participants

Figure 1 depicted the details of study design and specific patient characteristics including inclusion and exclusion criteria. During 2000-2010, 26,614 patients who had been diagnosed with NS (ICD-9-CM code 581) during 2000–2010 been selected in our study. The cohort was confined to at least two NS diagnoses during ambulatory visits or patients who had received at least one NS diagnosis during an inpatient visit. Furthermore, the cohort was circumscribed to patients with ICD-9codes assigned by a nephrologist with appropriate validation.

To ensure the accuracy of the data, we only included cases if they received 2 osteoporosis diagnoses for ambulatory visits or 1 diagnosis in inpatient care and the ICD-9 code was assigned by orthopedists and receiving at least one BMD examination were included in the osteoporotic group. The index date was selected as the date of the first clinical visit for NS. Exclusion criteria were as follows: diagnosis with NS before 2000, osteoporosis (ICD-9-CM code 733) before the index date, incomplete data, and unknown gender. Stratification analysis employed with the ratio of NS to non-NS patients maintained at 1:4 according to age, sex and index date. Using these criteria, 106,456 non-NS patients were identified.

Outcome

The main outcome was a discharge diagnostic claim of osteoporosis (ICD-9-CM code 733) after at least one BMD examination and orthopedist validation. For each participant, follow-up duration was estimated from the index data of osteoporosis diagnosis of uncensored subjects and until date of health insurance policy termination (mostly due to death) or Dec.31,2010 for those who were censored. Aside from analysis of baseline comorbidities, baseline sociodemographic characteristics, we also adjusted environmental factors according to urbanization level and the use of CS.

Statistical analysis

We first compared distribution of age, sex, urbanization, comorbidities and CS use between NS and non-NS cohorts, which were examined using $\chi 2$ test. We then calculated the incidence density of osteoporosis (per 10^5 person-years). NS versus non-NS incidence rate ratio of osteoporosis was examined. We used the univariate and multivariate Cox proportional hazards regression models with adjustment for age, sex, urbanization, hypertension (HTN), diabetes mellitus (DM), congestive heart failure (CHF), stroke, coronary artery disease (CAD), hyperlipidemia, chronic kidney disease (CKD), liver cirrhosis (LC), obesity, chronic obstructive pulmonary disease (COPD), dementia, postmenopause, hyperparathyroidism, alcohol-attributed disease, NS-related disease (including hepatitis B infection (HBV), hepatitis C infection (HCV), human immunodeficiency virus infection (HIV), syphilis, herpes zoster, IgA nephropathy, lymphoma, leukemia, multiple myeloma, neoplasm, amyloidosis, sarcoidosis, SLE, rheumatoid arthritis (RA), *Sjögren's syndrome*, hyperthyroidism, hypothyroidism, and gestational proteinuria), medication including steroid use, relevant fractures(including hip, wrist, vertebral, and rib fracture), season, city location, urbanization, and level of care to calculate *hazard ratio* (HR) with a 95% confidence interval (CI). Kaplan-Meier curved were used to calculate the cumulative proportion of osteoporosis incidence for both groups, and log-rank test was then employed to test differences between curves. We performed statistical analyses with SAS (V.9.3 for Windows), and a two-tailed $P < 0.05$ was considered statistically significant.

Results

Figure 1 shows that the 28,772 patients enrolled between January, 2000 and December, 2010 as inclusion criteria. Osteoporosis was observed in 1,299 of 26,614 NS patients and in 4,094 of 106,456 non-NS patients.

Table 1 compares demographic characteristics and baseline comorbidities between the two cohorts. In the study cohorts, approximately 38% of patients were more than 60 years of age, 17% were 50–59 years old, and 55% were male; the age and sex proportions of the cohorts were similar. The NS cohort had a higher proportion of individuals living in urban areas

(39.04% vs 33.66% of the non-NS cohort; $P < 0.001$). The following comorbidities were significantly more likely in the NS cohort than in the baseline on-NS cohort: HTN (32.12% vs 13.42%;$P < 0.001$), DM (36.01% vs 10.99%; $P < 0.001$), CHF (7.18% vs 2.08%; $P < 0.001$), *hyperlipidemia* (10.17% vs 2.15%; $P < 0.001$), CKD (22.34% vs 3.66%; $P < 0.001$), liver cirrhosis (2.22% vs 1.93%; $P = 0.001$), obesity (0.12% vs 0.03%; $P < 0.001$), HBV (1.98% vs 0.62%; $P < 0.001$), HCV (1.45% vs 0.54%; $P < 0.001$), syphilis (0.07% vs 0.03%; $P = 0.002$), IgA nephropathy (1.10% vs 0.04%; $P < 0.001$), leukemia (0.33% vs 0.13%; $P < 0.001$), multiple myeloma (0.26% vs 0.03%;$P < 0.001$), amyloidosis (0.23% vs 0.01%; $P < 0.001$), SLE (6.81% vs 0.09%; $P < 0.001$), RA (0.33% vs 0.24%;$P < 0.001$), Sjögren's syndrome (0.32% vs 0.05%;$P < 0.001$), hyperthyroidism (0.25% vs 0.15%;$P < 0.001$), hypothyroidism (0.57% vs 0.11%;$P < 0.001$), and gestational proteinuria(0.17% vs 0.00%;$P < 0.001$). Steroid use was predominant in the NS cohort (23.75% vs 22.57%; $P < 0.001$). NS cohort had a higher distribution in the autumn (22.99% vs 22.25%; $P < 0.001$), in the winter (28.46% vs 27.25%; $P < 0.001$), and among people living in northern Taiwan (44.06% vs 39.53%; $P < 0.001$).

Table 1
Demographic characteristics and comorbidities in NS and non-NS cohorts

	Total	NS		
Variables		Yes	No	P -value
Total, n (%)	133,070	26,614 (20.00)	106,456(80.00)	0.999
Age, year	49.55 ± 23.00	49.71 ± 22.58	49.51 ± 23.10	0.204
< 18	14,605 (10.98)	2,921 (10.98)	11,684 (10.98)	0.999
18–29	15,195 (11.42)	3,039 (11.42)	12,156 (11.42)	
30–39	11,775 (8.85)	2,355 (8.85)	9,420 (8.85)	
40–49	17,990 (13.52)	3,598 (13.52)	14,392 (13.52)	
50–59	23,155 (17.40)	4,631 (17.40)	18,524 (17.40)	
≧ 60	50,350 (37.84)	10,070 (37.84)	40.280 (37.84)	
Sex				0.999
Female	59,365(44.61)	11,873 (44.61)	47,492 (44.61)	
Male	73,705 (55.39)	14,741 (55.39)	58,964 (55.39)	
Comorbidity				
Hypertension	22,834(17.16)	8,548(32.12)	14,286 (13.42)	< 0.001*
CHF	4,131 (3.10)	1,912 (7.18)	2,219 (2.08)	< 0.001*
Stroke	7,787 (5.85)	1,176 (4.42)	6,611 (6.21)	< 0.001*
CAD	9,540 (7.17)	1,638 (6.15)	7,902 (7.42)	< 0.001*
Hyperlipidemia	4,994 (3.75)	2,707 (10.17)	2,287 (2.15)	< 0.001*
CKD	9,837 (7.39)	5,946 (22.34)	3,891 (3.66)	< 0.001*
LC	2,641 (1.98)	590 (2.22)	2,051(1.93)	< 0.001*
Obesity	67 (0.05)	32 (0.12)	35 (0.03)	< 0.001*
COPD	7,941 (5.97)	1,130 (4.25)	6,811(6.40)	< 0.001*
Dementia	1,175 (0.88)	174 (0.65)	1,001(0.94)	< 0.001*
Postmenopausal	128 (0.10)	8 (0.03)	120 (0.11)	< 0.001*
Hyperparathyroidism	37 (0.03)	10 (0.04)	27 (0.03)	0.191
Alcohol attributed disease	355 (0.27)	17 (0.06)	338 (0.32)	< 0.001*
Tobacco use disorder	.0 (0.02)	2 (0.01)	28 (0.03)	0.044*
NS related disease				
DM	21,282 (15.99)	9,583 (36.01)	11,699 (10.99)	< 0.001*
HBV	1,192 (0.90)	528 (1.98)	664 (0.62)	< 0.001*
HCV	965 (0.73)	386 (1.45)	579 (0.54)	< 0.001*

	Total	NS		
HIV	19 (0.01)	6 (0.02)	13 (0.01)	0.163
Syphilis	46 (0.03)	18 (0.07)	28 (0.03)	0.002*
Herpes zoster	315 (0.24)	64 (0.24)	251 (0.24)	0.472
IgA nephropathy	336 (0.25)	292 (1.10)	44 (0.04)	< 0.001*
Lymphoma	194 (0.15)	41 (0.15)	153 (0.14)	0.380
Leukemia	228 (0.17)	88 (0.33)	140 (0.13)	< 0.001*
Multiple myeloma	103 (0.08)	68 (0.26)	35 (0.03)	< 0.001*
Neoplasm	11,488 (8.63)	981 (3.69)	10,507 (9.87)	< 0.001*
Amyloidosis	66 (0.05)	60 (0.23)	6 (0.01)	< 0.001*
Sarcoidosis	11 (0.01)	3 (0.01)	8 (0.01)	0.383
SLE	1,903 (1.43)	1,812 (6.81)	91 (0.09)	< 0.001*
RA	346 (0.26)	88 (0.33)	258 (0.24)	0.007*
Sjögren's syndrome	133 (0.10)	85 (0.32)	48 (0.05)	< 0.001*
Hyperthyroidism	224 (0.17)	67 (0.25)	157 (0.15)	< 0.001*
Hypothyroidism	265 (0.20)	151 (0.57)	114 (0.11)	< 0.001*
Gestational proteinuria	49 (0.04)	46 (0.17)	3 (0.00)	< 0.001*
Medication, n (%)				
Steroid use	30,346 (22.80)	6,322 (23.75)	24,024 (22.57)	< 0.001*
Relevant fracture, n (%)				
Hip fracture	1,004 (0.75)	49 (0.18)	955 (0.90)	< 0.001*
Wrist fracture	1,262 (0.95)	12 (0.05)	1,250 (1.17)	< 0.001*
Vertebral fracture	780(0.59)	22 (0.08)	758 (0.71)	< 0.001*
Rib fracture	711 (0.53)	18 (0.07)	693 (0.65)	< 0.001*
Season				< 0.001*
Spring (March-May)	35,413(26.61)	7,078 (26.60)	28,335 (26.62)	
Summer (June-August)	31,269 (23.50)	5,844 (21.96)	25,425 (23.88)	
Autumn (September-November)	29,805 (22.40)	6,118 (22.99)	23,687 (22.25)	
Winter (December-February)	36,583 (27.49)	7,574 (28.46)	29.009 (27.25)	
Location				< 0.001*
Northern Taiwan	53,809 (40.44)	11,727 (44.06)	42,082 (39.53)	
Middle Taiwan	37,855(28.45)	7,001(26.21)	30,854 (28.98)	
Southern Taiwan	33,531 (25.20)	6,494 (24.40)	27.037 (25.40)	

	Total	NS		
Eastern Taiwan	7,260 (5.46)	1,298 (4.88)	5,962 (5.60)	
Outlets Islands	615 (0.46)	94 (0.35)	521 (0.49)	
Urbanization level				< 0.001*
1 (The highest)	46,227 (34.74)	10.390 (39.04)	35,837 (33.66)	
2	57,420 (43.15)	11,813 (44.39)	45,607 (42.84)	
3	9,781 (7.35)	1,312 (4.93)	8,469 (7.96)	
4 (The lowest)	19,642 (14.76)	3,099 (11.64)	16,543 (15.54)	
Level of care				< 0.001*
Medical center	48,856 (36.71)	13,367(50.23)	35,489 (33.34)	
Region hospital	46,783 (35.16)	9,900 (37.20)	36,883 (34.65)	
Local hospital	37,431 (28.13)	3,347 (12.58)	34,084 (32.02)	
Chi-square/Fisher exact test; continue variable: t-test				
*P-value < 0.05				
NS denotes nephrotic syndrome				
DM denotes diabetes mellitus				
CHF denotes congestive heart failure				
CAD denotes coronary artery disease				
CKD denotes chronic kidney disease				
LC denotes liver cirrhosis				
COPD denotes chronic obstructive pulmonary disease				
HBV denotes hepatitis B infection				
HCV denotes hepatitis C infection				
HIV denotes human immunodeficiency virus infection				
SLE denotes Systemic Lupus Erythematosus				
RA denotes rheumatoid arthritis				

Osteoporosis Incidence And Risk

The results revealed that NS cohorts had a 3.279 times (95% CI = 3.054–3.520) higher risk to develop osteoporosis compared with non-NS cohorts with adjustments for age, sex, and comorbidities. (Table 2) During the follow-up period, 1,299 patients in the NS cohorts (4.88%) and 4,094 non-NS participants(3.84%) developed osteoporosis. (Table 3) Males in the NS cohort were at a lower risk for osteoporosis development than females in that cohort (aHR = 0.727; 95% CI = 0.688–0.768; $P < 0.001$). Using age of less than 18 years as reference, the 18–29, 30–39, 40–49,50–59, and ≥ 60 age groups had a higher risk of osteoporosis (aHR = 4.974,3.552,5.839,6.356, and 10.264, respectively). Additionally,

compared to patients without comorbidities, we observed that the risk of osteoporosis was higher in patients who were postmenopausal (aHR = 5.719; 95% CI = 2.775–9.665;*P* < 0.001), and who had alcohol-attributed disease (aHR = 1.870; 95% CI = 1.175–2.976;*P* = 0.008), multiple myeloma (aHR = 5.219; 95% CI = 2.358–11.551;*P* < 0.001), SLE (aHR = 1.729;95% CI = 1.449–2.063;*P* < 0.001), RA (aHR = 2.538; 95% CI = 2.027–3.178;*P* < 0.001), and gestational proteinuria (aHR = 2.344; 95% CI = 2.011–2.731;*P* < 0.001). Use of CS was associated with a higher risk of osteoporosis compared to non-use of CS (aHR = 1.264; 95% CI = 1.102–1.578; *P* = 0.041). Osteoporosis was highly associated with hip and vertebral fracture (aHR = 2.344; 95% CI = 2.011–2.731;*P* < 0.001 and 6.816; 95% CI = 6.095–7.622;*P* < 0.001, respectively).

Table 2
Multivariable Analysis for Osteoporosis at the end of follow-up by using Cox regression

Variables[a]	Crude HR	95% CI	P-value	Adjusted HR	95% CI	P-value
NS[a]	2.587	2.427–2.758	< 0.001*	3.279	3.054–3.520	< 0.001*
Gender						
Male[b]	0.661	0.627–0.698	< 0.001	0.727	0.688–0.768	< 0.001*
Age groups						
18–29	5.330	3.941–7.210	< 0.001*	4.974	3.673–6.737	< 0.001*
30-39[c]	3.484	2.573–4.716	< 0.001*	3.552	2.620–4.815	< 0.001*
40-49[c]	5.079	3.785–6.816	< 0.001*	5.839	4.347–7.843	< 0.001*
50-59[c]	4.916	3.689–6.550	< 0.001*	6.356	4.763–8.483	< 0.001*
≧ 60[c]	6.926	5.261–9.196	< 0.001*	10.264	7.594–13.338	< 0.001*
HTN[a]	0.914	0.858–0.974	0.006*	0.712	0.665–0.763	< 0.001*
CHF[a]	0.677	0.587–0.781	< 0.001*	0.580	0.502–0.670	< 0.001*
Stroke[a]	0.629	0.558–0.708	< 0.001*	0.602	0.537–0.679	< 0.001*
CAD[a]	0.651	0.585–0.725	< 0.001*	0.637	0.571–0.711	< 0.001*
Hyperlipidemia[a]	0.596	0.491–0.725	< 0.001*	0.718	0.578–0.875	0.001*
CKD[a]	1.098	1.004–1.201	0.040*	0.673	0.511–0.741	< 0.001*
LC[a]	0.849	0.720–1.002	0.053	0.976	0.822–1.159	0.799
Obesity	0.953	0.308–2.954	0.934	1.222	0.393–3.797	0.729
COPD[a]	1.085	0.988–1.192	0.086	1.038	0.942–1.142	0.452
Dementia[a]	0.938	0.779–1.142	0.522	0.837	0.687–1.021	0.079
Postmenopausal[a]	5.476	2.944–10.193	< 0.001*	5.719	2.775–9.665	< 0.001*
Hyperparathyroidism[a]	1.296	0.486–3.453	0.604	1.008	0.378–2.691	0.987
Alcohol attributed disease[a]	1.229	0.774–1.953	0.382	1.870	1.175–2.976	0.008*
Tabacco use disorder	0.000	-	0.793	0.000	-	0.775
-NS related disease						

HR = hazard ratio, CI = confidence interval, Adjusted HR: Adjusted for all the variables listed in the table.*P-value < 0.05

a.Without the disease or medication as reference

b.Female as reference

c.Age < 18 year old as reference

Variables[a]	Crude HR	95% CI	P-value	Adjusted HR	95% CI	P-value
DM[a]	0.947	0.886–1.012	0.108	0.800	0.746–0.859	< 0.001*
HBV[a]	0.537	0.400–0.720	< 0.001*	0.605	0.449–0.815	0.001*
HCV[a]	0.475	0.349–0.646	< 0.001*	0.495	0.361–0.677	< 0.001*
HIV[a]	0.835	0.209–3.338	0.798	1.372	0.342–5.498	0.659
Syphilis[a]	0.880	0.220–3.520	0.857	1.077	0.269–4.311	0.917
Herpes zoster[a]	1.044	0.606–1.799	0.876	0.852	0.494–1.470	0.566
IgA nephropathy[a]	0.691	0.223–2.142	0.522	0.640	0.206–1.992	0.441
Lymphoma[a]	0.970	0.574–1.636	0.909	0.932	0.551–1.579	0.793
Leukemia[a]	2.463	1.766–1.434	< 0.001*	0.788	0.394–1.579	0.502
Multiple myeloma[a]	6.624	4.537–9.670	< 0.001*	5.219	2.358–11.551	< 0.001*
Neoplasm[a]	0.619	0.562–0.682	< 0.001*	0.584	0.528–0.645	< 0.001*
Amyloidosis[a]	3.627	1.629–8.079	0.002	0.888	0.389–2.029	0.779
Sarcoidosis	0.000	-	0.899	0	-	0.966
SLE[a]	2.844	2.425–3.336	< 0.001*	1.729	1.449–2.063	< 0.001*
RA	3.486	2.795–4.347	< 0.001*	2.538	2.027–3.178	< 0.001*
Sjögren's syndrome	2.558	1.589–4.119	< 0.001*	1.269	0.782–2.059	0.335
Hyperthyroidism	0.605	0.272–1.348	0.219	0.631	0.283–1.406	0.260
Hypothyroidism	0.771	0.427–1.392	0.388	0.667	0.369–1.206	0.180
Gestational proteinuria	5.243	1.311–20.971	0.019*	2.344	2.011–2.731	< 0.001*
Steroid use[a]	1.222	1.006–1.678	0.046	1.264	1.102–1.578	0.041*
Hip fracture[a]	2.948	2.533–3.430	< 0.001*	2.343	2.011–2.731	< 0.001*
Wrist fracture[a]	1.218	0.940–1.577	0.136	1.010	0.778–1.3100	0.941
Vertebral fracture[a]	8.804	7.898–9.812	< 0.001*	6.816	6.095–7.622	< 0.001*
Rib fracture[a]	0.459	0.267–0.791	0.005*	0.327	0.189–0.564	< 0.001*
HR = hazard ratio, CI = confidence interval, Adjusted HR: Adjusted for all the variables listed in the table.*P-value < 0.05						
a.Without the disease or medication as reference						
b.Female as reference						
c.Age < 18 year old as reference						

Figure 2 shows the Kaplan–Meier curve for the cumulative incidence of osteoporosis between the NS cohort and non-NS cohort after 11 years of follow-up (log rank test; $P < 0.001$). The one-, five-, and 11-year actuarial rates of osteoporosis

were 1.73%, 4.10%,and 4.88% in the NS cohort and 0.88%, 2.62%, and 3.84 % in the non-NS cohort, respectively.

After stratification, the risk of osteoporosis notably increased independent of age status, except in patients younger than 18 years (aHR was highest in the 30–39 years group and lowest in the ≧ 60 years group). The risk of osteoporosis also increased independent of CHF, hyperlipidemia, CKD, LC. We further evaluated the risk of osteoporosis stratified by NS etiology subtypes. A significantly higher risk of osteoporosis was observed in patients with DM, HBV, HCV, lymphoma and hypothyroidism. Additionally, osteoporosis risk was significantly higher in NS patients with corticosteroid (CS) use (aHR = 3.397). The risk of osteoporosis in NS patients was positively associated with risk of hip and vertebral fracture (aHR = 2.130 and 2.268, respectively). (Table 3)

Table 3. Factors of Osteoporosis at the end of the follow-up period stratified by Cox regression

Variables	NS			Non NS			Ratio	Asjusted HR	P-value
Osteoporosis	Event	PYs	Rate	Event	PYs	Rate		(95%CI)	
	1,299	142,320	912.73	4,094	578,734	707.41	1.290	3.279 (3.054-3.520)	<0.001*
Age, year									
<18	14	9,901.05	141.40	36	29,442.38	122.27	1.156	1.170 (0.544-2.517)	0.687
18-29	135	10,592.30	1,274.51	131	29,247.19	447.91	2.845	4.411 (3.284-5.924)	<0.001*
30-39	112	13,393.22	836.24	146	45,505.77	320.84	2.606	5.203 (3.795-7.135)	<0.001*
40-49	133	15,885.28	837.25	267	46,887.28	569.45	1.470	3.381 (2.593-4.409)	<0.001*
50-59	223	27,021.42	825.27	471	85,092.90	553.51	1,491	3.480 (2.856-4.227)	<0.001*
≧60	682	65,527.56	1,040.78	3,043	342,559.21	888.31	1.172	2.978 (2.724-3.257)	<0.001*
Comorbidity									
CHF	88	11,108.09	792.22	107	28,366.36	377.21	2.100	6.721 (4.826-9.362)	**<0.001***
Hyperlipidiemia	54	5,584.38	966.98	49	17,939.91	273.13	3.540	9.062 (5.458-15.047)	**<0.001***
CKD	370	42,315.85	874.38	166	37,409.93	443.73	1,971	4.080 (3.324-5.007)	**<0.001***
LC	49	4,662.33	1,050.98	96	17,917.28	535.80	1.962	4.647 (3.128-6.095)	**<0.001***
NS related disease									

DM	436	49,751.54	876.35	652	111,382.80	585.37	1.497	3.789 (3.287-4.361)	**<0.001***
HBV	16	2,786.79	574.14	29	8,614.80	336.63	1.706	6.207 (2.880-13.379)	**<0.001***
HCV	16	2,014.91	794.08	25	9,288.70	269.14	2.950	6.775 (2.921-15.714)	**<0.001***
Lymphoma	3	322.18	931.16	11	1,569..87	700.69	1.329	6.7229 (4.165-7.026)	**0.002***
HPoT	3	381.47	785.88	8	1,504.18	531.85	1.478	5.305 (1.570-9.110)	**0.022***
Steroid use	559	32,753.91	1,706.67	1,588	124,688.15	1,273.58	1.340	3.397 (3.101-3.623)	**<0.001***
Relevant fracture ,n(%)									
Hip Fx	21	1,129.56	1,859.13	152	6,680.19	2,275.38	0.817	2.130 (1.295-3.503)	**0.003***
Wrist Fx	2	573.99	348.44	56	5,530.58	1,012.55	0.344	0.959 (0.226-4.063)	**0.955**
Vertebral Fx	32	431.33	7,418.91	317	4,867.13	6,513.08	1.139	2.268 (1.513-3.401)	**<0.001***
Rib Fx	4	343.93	1,163.03	9	3,235.38	278.17	4,181	2.737 (0.108-69.419)	0.542

PYs=Person-years; Rate: per 10^5 PYs; Ratio=rate in cases÷ Rate in controls; Adjusted HR= Asjusted Adjusted HR: Adjusted for all the variables listed in Table 3. CI=conficence interval *P-value <0.05

NS denotes nephrotic syndrome

HTN denotes hypertension

DM denotes diabetes mellitus

CHF denotes congestive heart failure

CAD denotes coronary artery disease

CKD denotes chronic kidney disease

LC denotes liver cirrhosis

HBV denotes hepatitis B infection

HCV denotes hepatitis C infection

HPoT denotes hypothyroidism

Discussion

NS was associated with a 3.279-fold increase in the risk of osteoporosis, compared with a non-NS cohort after adjusting for a number of potentially confounding factors. The results of this study are compatible with those of previous studies in relation to the female predominance of osteoporosis (53.19%), but the proportion of the NS cohort in this study that progressed to osteoporosis (4.88%over the 11 years of follow-up) was low compared to the proportions reported by previous studies. [4–7] Patients with NS often demonstrate a number of calcium homeostasis disturbances that attributed to abnormal bone histology, including hypocalcemia, impaired intestinal absorption of calcium, reduced serum vitamin D metabolites such as 25-hydroxyvitamin D [25(OH)D], 1,25-dihydroxyvitamin D [$1,25(OH)_2D$], and elevated levels of immunoreactive parathyroid hormone (PTH).

Loss of a variety of plasma proteins (vitamin D –binding protein) and minerals in the urine, as well as steroid therapy can have great impact on bone integrity.[10]

In a prospective study with 30 NS and 30 control patients conducted by Mohamed GB et al, compared to the control patients, the NS patients demonstrated a significantly lower level of serum OPG and parameters of bone formation (alkaline phosphatase and osteocalcin),conversly, a significantly higher 24-hour urinary Ca. [11] The bone lesions in these patients can be attributed to Vitamin D deficiency and elevated blood levels of PTH.

In the NS cohort, we observed that an age older than 18 years, and especially within the 30–39 years group, had the highest risk of osteoporosis after stratification. In a prospective study by Gulati et al., the authors observed that only about 22% of children with idiopathic NS developed osteoporosis. [6] The authors also concluded older age at onset, lower total calcium intake ($P < 0.0001$), and greater cumulative steroid dose were the main predictive factor for a low BMD ($P < 0.0001$), ($P = 0.005$). A study by Hegarty et al. found that adult survivors of childhood minimal change nephrotic syndrome have significantly reduced forearm trabecular volumetric BMD, placing them at increased fracture risk at this site, indicating a delayed effect of osteoporosis in NS cohorts. [8] Besides, because in the NHIRD we use BMD to define osteoporosis, which may be less accurate than bone mineral content measurements, especially in children, this could have led to an underestimation of the number of patients in the NS cohort who progressed to osteoporosis.[11]

DM is often associated with low levels of insulin, higher glucose levels with higher advanced glycation end-products which precipitate in collagen leading to reduce bone strength. The indirect effect of glycosuria with hypercalciuria leads to decreased levels of calcium in the body and poor bone quality, which hastens bone loss.[12]

Inflammatory cytokines, such as interleukin-1, interleukin-6 and tumor necrosis factor-alpha induced by chronic HBV infection which increase RANKL to stimulate osteoclast formation and bone resorption. Additonally, tumor necrosis factor-alpha can inhibit osteoblast differentiation and promote osteoblast apoptosis. Chronic HCV infection can also induce interleukin-6, which activates osteoclast to increase bone resorption. The combined effects of the aforementioned inflammatory cytokines can eventuating in coupling of decreased bone formation, and increased bone resorption to

diminish the BMD. [13–14] Although the relationship between lymphoma and osteoporosis is unclear, osteopenia and osteoporosis in untreated NHL patients are regarded as a common finding.[15] Mild hypothyroidism is usually observed in NS patients, and results from losses of T4, free T4, T3, free T3, and TBG into the urine.[16] It is proposed that hypothyroidism is correlated with increased risk of fractures with unknown mechanism. Hypothyroidism causes general hypometabolism, with subsequent lowering of bone formation and resorption. The subsequent reduced calciuria may lead to decreased serum osteocalcin and alkaline phosphatase, with elevated parathyroid hormone, which may be a proposed mechanism for osteoporosis.[17] In our study, we observed a prominent deleterious effect of CS on osteoporosis. (aHR = 3.397; 95% CI = 3.101–3.623; $P < 0.001$). In table 3, we observed that the osteoporosis risk was not increased in our pediatric NS cohort (aged younger than 18 years) after stratification. We further evaluated the role of CS in pediatric NS (aged younger than 18 years), using non-NS and non-CS as a reference, and found that use of CS significantly increased the risk of osteoporosis in both the NS cohort (aHR = 1.478; 95% CI = 1.009–1.803; $P = 0.042$) and the non-NS cohort (aHR = 1.315; 95% CI = 1.001–1.698; $P = 0.049$) (Fig. 3).

It is reported that after 12 months' use of more than 7.5 mg/day of prednisone can lead to trabecular bone loss.[18] Glucocorticoid-induced osteoporosis is caused by decreased bone formation and increased bone resorption through the coupling of bone resorption, gastrointestinal calcium absorption and renal tubule excretion imbalance. [19] In NS, CS have been reported to disturb the function of osteoblasts by decreasing the expression of RANKL soluble decoy receptor-OPG, and in contrast, activate the osteoclast by increasing the expression of M-CSF and RANKL. [19–21]

There are several limitations to the present study despite the strength of this cohort study which comprise a large number of Asian patients. First, some adaptable risk factors such as body mass index, dietary habits and family history are not available in NHIRD. Laboratory results such as urine protein level, serum lipid and serum albumin are lacking. Histopathologic changes involved in NS, specifically minimal change disease, membranous nephropathy and focal segmental glomerulosclerosis results are not accessible. Second, bone densitometry results was unavailable thus put validating the diagnosed of osteoporosis in a difficult situdation. Neverheless, diagnostic accuracy was strengthen by limiting the study population to patients with at last one BMD examination and medical care for osteoporosis for more than 2 separate visits. Those physicians who enter the ICD-9 codes of osteoporosis were request to enter accurately subject because of big fines for incorrect entries. Finally, potential biases related to adjustment for confounding variables existed results in a lower quality of statistical analysis of data derived from a retrospective cohort study.

Conclusions

NS patients are at high risk of osteoporosis. Prominent deleterious effect of CS on osteoporosis observed even in pediatric NS cohort (aged younger than 18 years). Early identification of the NS related disease may alert clinical physician about the possible susceptible osteoporosis. Nevertheless, more precise large scale randomized control study need to carry out to support the findings.

Abbreviations

NS, nephrotic syndrome

NHI, The National Health Insurance

NHIRD, The National Health Insurance Research Database

BMD, bone mineral density

DM, diabetes mellitus

CHF, congestive heart failure

CAD, coronary artery disease

COPD, chronic obstructive pulmonary disease

CKD, chronic kidney disease

LC, liver cirrhosis

RA, rheumatoid arthritis

HBV, hepatitis B infection

HCV, hepatitis C infection

HIV, human immunodeficiency virus infection

SLE, systemic lupus erythematosus

CS, corticosteroid

IRR, incidence rate ratio

HR, hazard ratio

CI, confidence interval

Declarations

Disclosures

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Author contributions

C.Y.L, P.C and W.C.C designed and coordinated the study. C.H.C and W.C.C performed statistical analyses and reviewed the manuscript. C.Y.L drafted the manuscript. K.Y.W, T.M.F, F.H.L, C.H.T and C.C.W assisted with the data management and reviewed the manuscript. All authors critically reviewed and approved the final version of the manuscript.

Conflict of interest

The author(s) declare no competing interests.

Data Availability

The data source is included within the manuscript.

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Figures

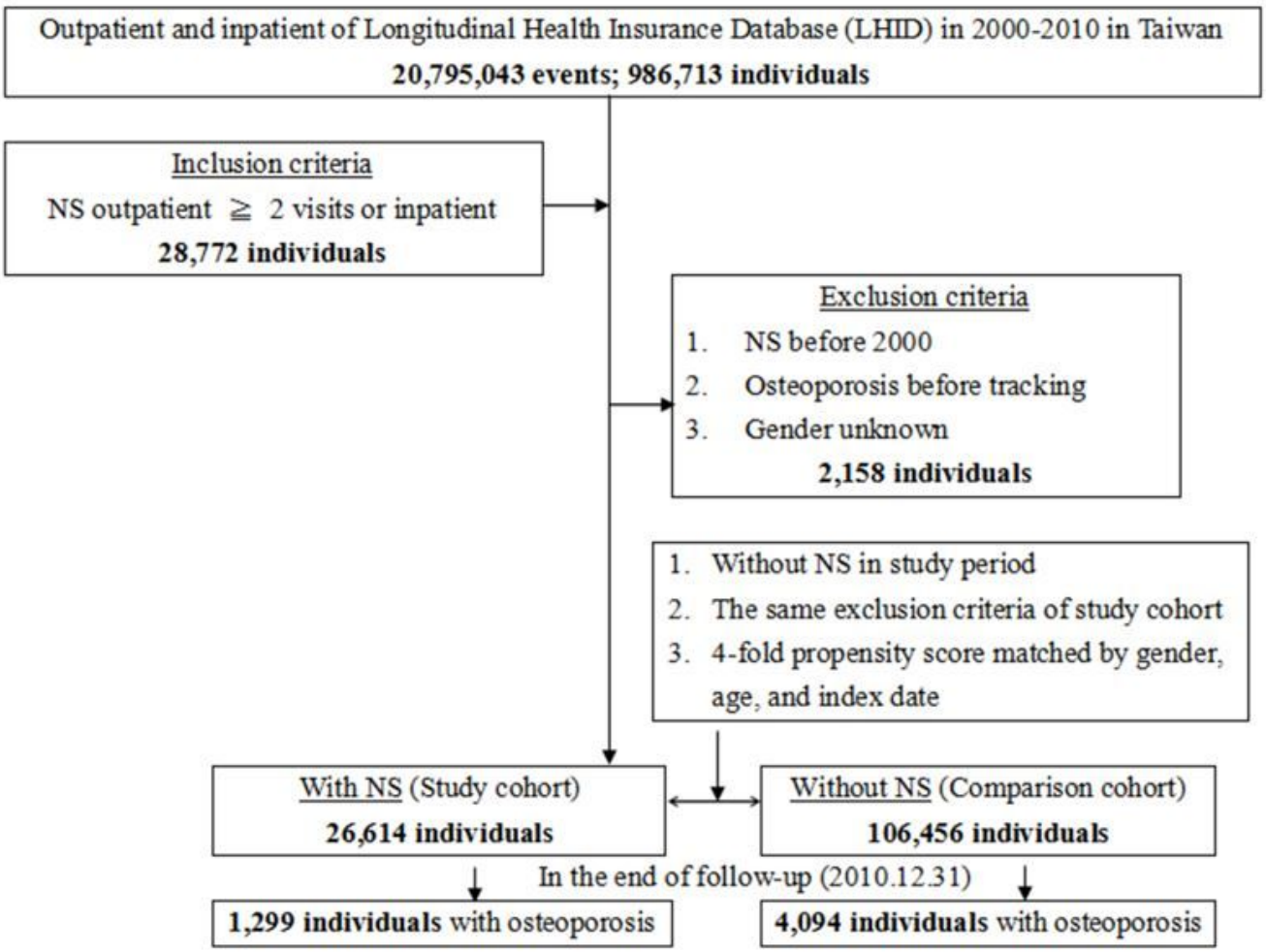


Figure 1

The flowchart of study sample selection from National Health Insurance Research Database in Taiwan NS = Nephrotic syndrome: ICD-9-CM 581 Osteoporosis: ICD-9-CM 733

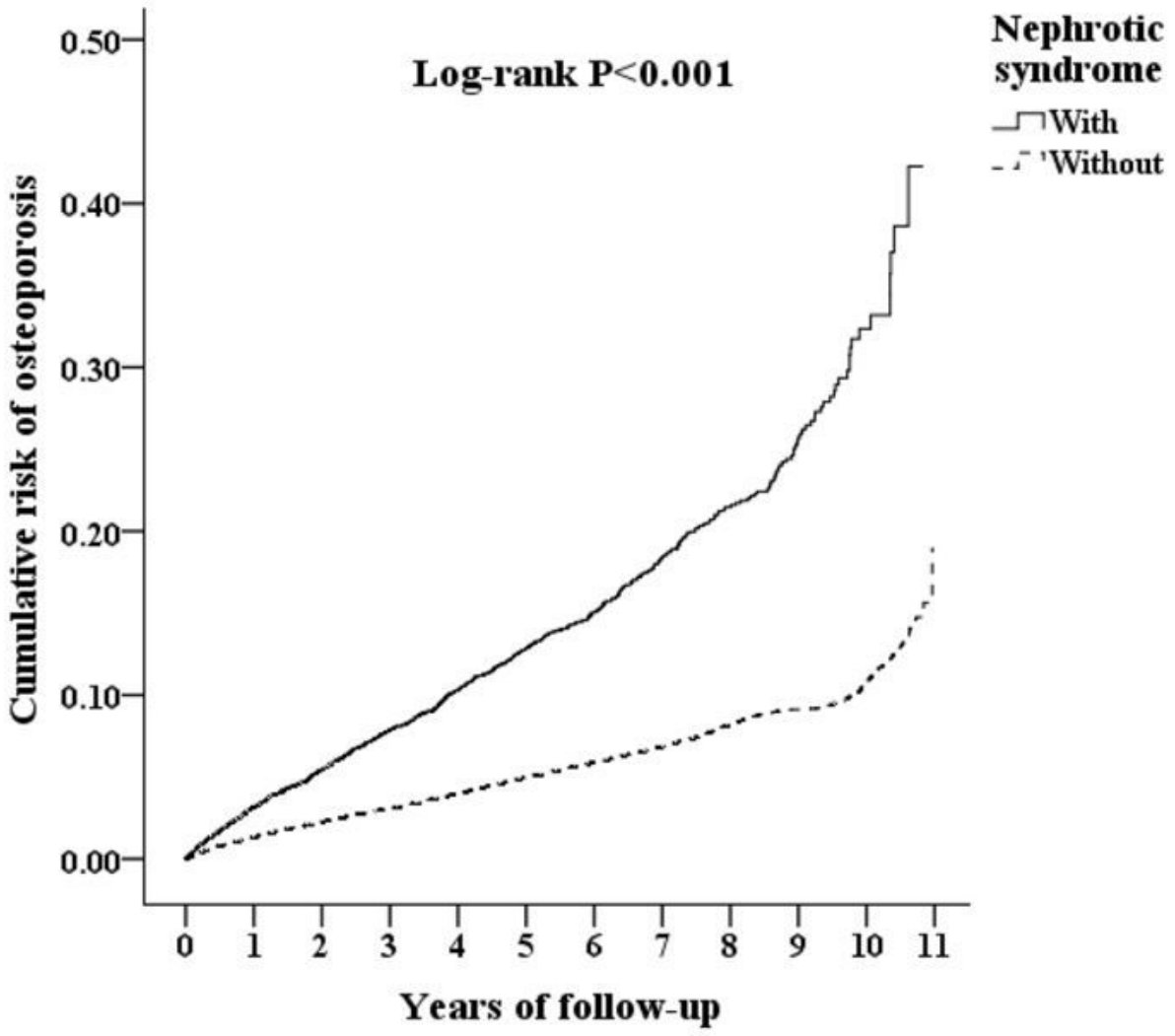
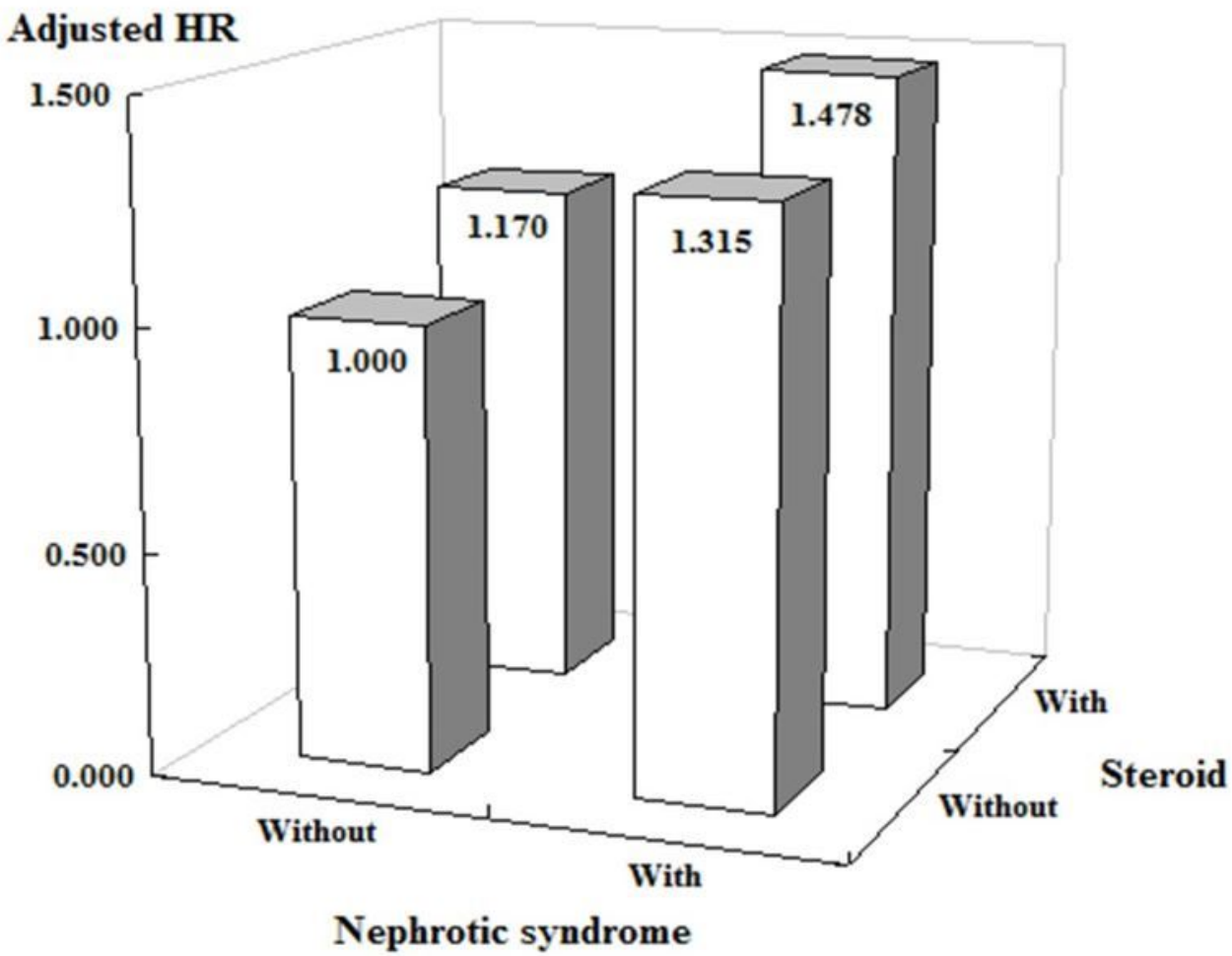


Figure 2

Kaplan-Meier for cumulative risk of osteoporosis over stratified by NS with log-rank test



NS	Steroid	Adjusted HR	95% CI	95% CI	P
Without	Without	Reference			
Without	With	1.315	1.001	1.698	0.049
With	Without	1.170	0.544	2.517	0.687
With	With	1.478	1.009	1.803	0.042

Figure 3

Risk of osteoporosis stratified by NS and steroid aged less than 18 Adjusted HR (Hazard ratio): Adjusted variables listed in Table3. CI = confidence interval Joint effect (Interaction term): NS × steroid, P=0.398