Infections and risk of end-stage renal disease in patients with nephrotic syndrome: a nationwide population-based case-control study

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Background: Infections are a major cause of morbidity in patients with nephrotic syndrome (NS); however, the risk of infections in NS and its subsequent effect on adverse renal outcomes are not well established.

Methods: From 2000–2013 claims data, 4,856 patients with NS were identified from the Taiwanese National Health Insurance Research Database (NHIRD). In the study group, 554 patients progressing to end-stage renal disease (ESRD), as identified during follow-up, were enrolled. In the control group, two patients with NS without progression to ESRD, during the same period, matched with one patient from the study group were included. The correlation between rates of infections and risk of ESRD in patients with NS was estimated using conditional logistic regression analysis.

Results: The proportion of outpatient visits for infections in patients with NS with and without progression to ESRD was 61.2% and 32.8%, respectively, and the proportion of hospitalization due to infections was 28.9% and 1.7%, respectively. The risk of ESRD was higher in patients with frequent outpatient visits for infections (>10 outpatient visits), with a relative risk of 3.20 [95% confidence interval (CI), 1.84–5.57]. Additionally, a significant association was found between severe infections requiring hospitalization and ESRD, with a relative risk of 7.01 (95% CI, 3.65–13.44). Subgroup analysis stratified by sex or age indicated that the risk associated with ESRD was significantly higher in female and elderly patients with NS.

Conclusions: The risk of ESRD in patients with NS was linked to the incidence of infection, especially those requiring hospitalization due to more severe bacterial infections. Implications of study results are important for clinicians who should be aware of the possibility of ESRD development in patients with NS with infectious complications.

Keywords: Nephrotic syndrome (NS); end-stage renal disease (ESRD); infectious; risk; elderly

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Introduction

Nephrotic syndrome (NS) is a common renal disorder characterized by the presence of nephrotic range of proteinuria, hypoalbuminemia, and hyperlipidemia (1,2). In Taiwan, membranous nephropathy is the most common cause of NS, whereas focal segmental glomerulosclerosis is the most common in Brazil and Saudi Arabia (3,4).

Infection is one of the most common complications and is a significant cause of morbidity in patients with NS (5,6). Infection may precipitate episodes or induce relapse during remission in patients with NS. Moreover, NS is often associated with occurrence of infection due to relative immunodeficiency compared with healthy people, resulting in unfavorable responsiveness to therapy (7-9). In this study, we hypothesized that infectious incidents can increase the risk of progression to end-stage renal disease (ESRD) in patients with NS. Although infection is one of the most common complications in patients with NS, data on the occurrence of infection and its effect on renal prognosis in patients with NS are limited.

The association of frequency and severity of infection and the subsequent renal outcome are to be defined. In this study, the occurrence of infections and its effect on renal outcomes in patients with NS were retrospectively analyzed. The aim of this nationwide case-control study was to define risk factors for ESRD and infectious complications in patients with NS.

Methods

Data sources

The National Health Insurance, the health care system in Taiwan, provides national data for medical research, quality of services, clinical practice patterns and accessibility to health care programs. In this study, medical claims data from 2000 to 2013 of the National Health Insurance Research Database (NHIRD) were utilized. The NHIRD contains health care data of the insured population of Taiwan that covers >99% of the 23 million residents (10). The Longitudinal Health Insurance Database, a subset of the NHIRD, comprising 1 million beneficiaries randomly sampled from the NHIRD was used for this research. The study protocol was approved by the Research Ethics Committee of Ditmanson Medical Foundation Chia-yi Christian Hospital (CYCH-IRB-106084).

Study design and population

The diagnosis for NS was based on the International Classification of Diseases, Ninth Revision, Clinical Modification codes (ICD-9-CM code 581). Inclusion criteria for patients enrolment were as follows: at least three NS diagnoses at the time of outpatient services or one NS diagnosis during an admission. Patients suspected of NS due to specific underlying diseases were excluded (ICD-9-CM code 581.81). Finally, 554 patients with NS with ESRD, and 1,108 random non-ESRD controls matched at a ratio of 1:2 during the same observational period were selected (*Figure 1*). The population was categorized according to age as young-aged (<40 years), middle-aged (40–65 years), and old-aged (>65 years) groups. The severity of infection was determined based on outpatient visits for acute respiratory infection (ARI) and hospitalization for more severe bacterial infections. ARI included these diagnostic codes: acute nasopharyngitis (ICD-9-CM code 460), acute respiratory tract infections (ICD-9-CM code 464 and 465), bronchiolitis (ICD-9-CM code 466), and bronchitis (ICD-9-CM code 490). Diagnostic codes for bacterial infections included pneumonia (ICD-9-CM code 486), peritonitis (ICD-9-CM code 567), urinary tract infection (UTI; ICD-9-CM code 599.0), cellulitis (ICD-9-CM code 681 and 682), and bacteremia (ICD-9-CM code 038). The number of outpatient visits were classified into four groups, namely 0, 1–5, 6–10, and >10 visits, and the number of hospitalizations were categorized into two groups: 0 and ≥1.

Potential confounders and outcome variable

Potential confounders considered in this study included comorbidities, such as hypertension (ICD-9-CM codes 401–405), diabetes mellitus (ICD-9-CM code 250), congestive heart failure (CHF; ICD-9-CM code 428), hematuria (ICD-9-CM code 599.7) and acute kidney injury (AKI; ICD-9-CM code 584.9). If these diagnostic codes were included in two or more ambulatory claims 6 months before and after the index date, they were considered as comorbidities. Outcome variables were defined as the presence of at least one inpatient claim or two outpatient claims for ESRD (ICD-9-CM code 585) and the issuance of catastrophic illness cards after NS.

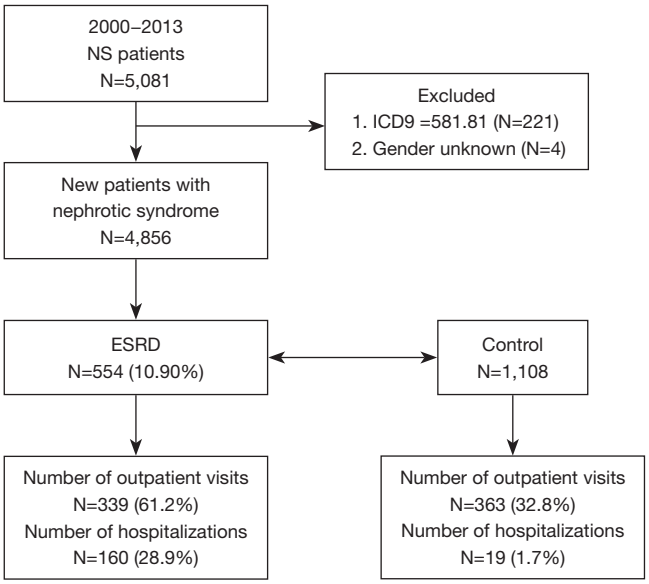

Figure 1 Flow chart showing selection of study subjects. ESRD, end-stage renal disease; NS, nephrotic syndrome; ICD, International Classification of Diseases.

Statistical analysis

Demographic data and ESRD risk between the study and control groups were compared using Pearson's chi-squared test. Conditional logistic regression analyses were performed to calculate the odds ratio (OR) and 95% confidence interval (CI) for having been previously diagnosed with an infection between the two groups. The variables of conditional logistic regression analysis included sex, age, number of outpatient visits, number of hospitalizations, and comorbidities. Further adjustments were performed by stratification of age and sex to evaluate the associations of infection with ESRD. A two-tailed P value of <0.05 was considered statistically significant. All statistical analyses were performed using SAS (version 9.3; SAS institute Inc., Cary, NC, USA).

Results

Clinical characteristics of patients with NS with and without ESRD

A total of 4,856 patients fulfilled the criteria for the diagnosis of NS between 2000 and 2013; of whom, 554 were identified with ESRD and were included in the case group (*Figure 1*). Of the 554 patients, 294 (53.1%) were women and 260 (46.9%) were men. The male to female ratio was 1:1.13. The middle-aged group of 40–65 years (52.7%) was predominantly affected (*Table 1*). A significantly higher proportion of patients with NS with ESRD (22.0%) had more outpatient visits (>10 visits) for ARI compared with patients with NS without ESRD (4.4%). A significantly higher proportion of patients with NS without ESRD (67.2%) had no outpatient visits compared with patients with NS with ESRD (38.8%). Moreover, a significantly higher proportion of patients with NS with ESRD (28.9%) required hospitalization for more severe infections compared with the control group (1.7%). Common causes for hospitalization for infection were UTIs (14.4%), bacteremia (10.3%), and pneumonia (8.8%). Severe infections requiring admissions were significantly associated with a higher risk of ESRD. A trend toward more outpatient visits and inpatient admissions for infections was observed in patients with NS who developed ESRD during the study period.

Risk of ESRD in patients with NS with and without infections

Compared with those with no outpatient visits for infections, the OR associated with ESRD for those with >10 outpatient visits and 6–10 outpatient visits for infections were 3.20 (95% CI, 1.84–5.57) and 2.11 (95% CI, 1.16–3.82), respectively (*Table 2*). Moreover, compared with those who were not hospitalized for infections, the OR associated with ESRD for those hospitalized admissions was 7.01 (95% CI, 3.65–13.44). Our results suggested differences even after adjustment, with higher rates of infections in patients with NS being associated with subsequent adverse renal outcomes. In addition, patients with hypertension, diabetes mellitus, and CHF tended to have an increased risk of associated ESRD (OR: 4.87, 95% CI, 3.30–7.20, OR: 1.87, 95% CI, 1.33–2.63, and OR: 2.95, 95% CI, 1.85–4.73, respectively). Moreover, patients with AKI had a significantly high risk of associated ESRD (OR: 11.40, 95% CI, 5.27–24.65).

Association of ESRD with infections according to sex stratification

Analysis of data stratified according to sex revealed that the risk of ESRD was significantly higher in female patients with >10 outpatient visits (OR: 7.64, 95% CI, 1.77–32.93) than in male patients (*Table 3*). Nevertheless, the OR of ESRD was significantly higher in patients with

Table 1 Baseline demographics and characteristic data of NS patients, group by ESRD

Variables	NS (n=1,662)				P value*
	Non-ESRD		ESRD		
	n=1,108	%	n=554	%	
Gender					<0.001
Female	475	42.9	294	53.1	
Male	633	57.1	260	46.9	
Age					<0.001
Age <40	291	26.3	62	11.2	
40≤ age <65	498	44.9	292	52.7	
Age ≥65	319	28.8	200	36.1	
Number of outpatient visits					
0	745	67.2	215	38.8	<0.001
1–5	259	23.4	154	27.8	
6–10	55	5.0	63	11.4	
>10	49	4.4	122	22.0	
Number of hospitalizations					<0.001
0	1,089	98.3	394	71.1	
≥1	19	1.7	160	28.9	
Comorbidities					
Hypertension	460	41.5	481	86.8	<0.001
Diabetes mellitus	267	24.1	317	57.2	<0.001
CHF	64	5.8	179	32.3	<0.001
Hematuria	69	6.2	57	10.3	0.003
AKI	13	1.2	139	25.1	<0.001

*, Pearson chi-square test. ESRD, end-stage renal disease; NS, nephrotic syndrome; CHF, congestive heart failure; AKI, acute kidney injury.

hospitalizations, both in female (OR: 8.18, 95% CI, 2.21–30.30) and male patients (OR: 4.81, 95% CI, 1.45–15.94). This reveals a consistently significant association between high rates of outpatient visits for infections and ESRD in women, although not significant in men. Furthermore, our results emphasize that the risk of ESRD was significantly associated with hospital admissions for infections in both female and male patients. Additionally, patients with NS with hypertension, CHF, or AKI were observed to have a significantly higher risk of ESRD, irrespective of their sex.

Association of ESRD with infections according to age stratification

Increased OR was found in both middle-aged (40–65 years) and old-aged groups (>65 years) with a higher frequency of outpatient visits (>10 visits), and the risk of ESRD was higher in the old-aged group (OR: 12.58, 95% CI, 2.25–70.22) than in the middle-aged group (OR: 3.82, 95% CI, 1.07–13.64) (*Table 4*). The OR of ESRD was significantly higher in the middle-aged group (40–65 years) with a history of hospital admissions (OR: 27.41, 95%

Table 2 Estimated OR of ESRD associated with infection in NS patients

Variables	OR	95% CI	P value*
Gender			
Female	1.00		
Male	0.93	0.68–1.27	0.657
Age			
Age <40	1.00		
40≤ age <65	1.43	0.90–2.27	0.134
Age ≥65	0.83	0.50–1.40	0.485
Number of outpatient visits			
0	1.00		
1–5	1.12	0.79–1.59	0.533
6–10	2.11	1.16–3.82	0.014
>10	3.20	1.84–5.57	<0.001
Number of hospitalizations			
0	1.00		
≥1	7.01	3.65–13.44	<0.001
Comorbidities			
Hypertension	4.87	3.30–7.20	<0.001
Diabetes mellitus	1.87	1.33–2.63	<0.001
CHF	2.95	1.85–4.73	<0.001
Hematuria	1.50	0.85–2.64	0.159
AKI	11.40	5.27–24.65	<0.001

*, conditional logistic regression. CI, confidence interval; ESRD, end-stage renal disease; NS, nephrotic syndrome; OR, odds ratio; CHF, congestive heart failure; AKI, acute kidney injury.

CI, 2.76–272.08). Moreover, middle-aged patients with hypertension, CHF, and AKI were still observed to have a significantly higher risk of ESRD even after adjustment for confounders. Our results demonstrated a consistently significant association between high rates of outpatient visits for infections and ESRD, and a higher risk was observed, particularly, in elderly patients.

Discussion

Infections have been identified as a possible cause leading to NS. Immune response secondary to viral infection is a potential trigger of relapse in NS. A close association of respiratory tract infection has been noted with the occurrence, relapse, and aggravation of NS (11,12). In this study, an association between the occurrence of infections and ESRD in patients with NS was further observed. Some patients had mild infection, such as ARI, during the course of NS, and more episodes of ARI (>10 times) may be associated with a higher risk of ESRD, especially in female patients. Additionally, a significantly higher risk of ESRD in patients with a history of more serious infections requiring hospitalizations, including pneumonia, peritonitis, UTI, cellulitis, and bacteremia, was noted. These findings demonstrated a higher risk of ESRD in nephrotic patients with either frequent ARI or a history of bacterial infections requiring hospitalization. Our results confirmed the higher prevalence of ESRD in patients with NS with infections compared with those without infections, with the highest risk occurring in patients with more serious infections requiring hospitalization.

Infection is prevalent in people presenting with NS, and majority of infections have been reported to be associated with active disease in nephrotic patients (13). The increased frequency of infections may be due to the loss of immunoglobulins, impaired cellular immunity, and relative malnutrition (14). Studies have reported the relevance of UTI in patients with NS, and it was similar as ARI, both of which are the most frequent infectious triggers of relapse (15,16). In this study, admissions due to various infections, including UTI, was also demonstrated to be significantly associated with a higher risk of ESRD. Control of infection may help remission in some patients, and avoiding potential sources of infection may also reduce adverse renal outcome (17).

The findings of this study revealed a significantly higher prevalence of AKI in patients with NS with progression to ESRD. Occurrence of AKI during an infective episode was known, which is an established independent risk factor for kidney disease progression (18,19). Although AKI is a reversible condition, it may also entail the development of chronic kidney disease in some patients (20). In accordance with these findings, our data demonstrated that AKI has a significant risk of adverse renal outcome. Furthermore, cardiovascular disorders, including hypertension and CHF, were associated with an increased risk of ESRD, as indicated by our results.

A high cumulative dose of prednisone has been reported as a considerable risk factors for severe infections, and small increases in prednisolone dose can prevent relapse in upper respiratory tract infections in patients with NS

Table 3 Estimated OR of ESRD associated with infection in NS patients stratified by gender

Variables	Female			Male		
	OR	95% CI	P value*	OR	95% CI	P value*
Age						
Age <40	1.00			1.00		
40≤ age <65	2.10	0.70–6.27	0.186	1.82	0.79–4.19	0.162
Age ≥65	1.78	0.53–6.05	0.354	1.00	0.42–2.37	0.993
Number of outpatient visits						
0	1.00			1.00		
1–5	0.60	0.28–1.27	0.182	1.20	0.61–2.36	0.598
6–10	0.61	0.18–2.06	0.423	2.45	0.87–6.90	0.090
>10	7.64	1.77–32.93	0.006	2.78	0.98–7.87	0.055
Number of hospitalizations						
0	1.00			1.00		
≥1	8.18	2.21–30.30	0.002	4.81	1.45–15.94	0.010
Comorbidities						
Hypertension	5.03	2.17–11.65	<0.001	5.75	2.65–12.47	<0.001
Diabetes mellitus	1.22	0.59–2.55	0.595	1.73	0.94–3.18	0.076
CHF	5.00	1.46–17.15	0.010	3.84	1.45–10.18	0.007
Hematuria	0.79	0.23–2.67	0.698	2.64	0.83–8.39	0.101
AKI	31.76	3.42–294.67	0.002	12.31	3.33–45.44	<0.001

*, conditional logistic regression. CI, confidence interval; ESRD, end-stage renal disease; NS, nephrotic syndrome; OR, odds ratio; CHF, congestive heart failure; AKI, acute kidney injury.

(21,22). Based on our results, cautious prescription of prednisolone and efforts for reducing episodes of infection may help patients with NS to avoid progression to ESRD. Additionally, these data imply mandatory prophylactic interventions to prevent any infection in children and adults with NS. Some preventive methods have been proposed to reduce the risk of infection in NS in clinical practice (23,24).

In this study, we explored the occurrence of infections in nephrotic cases by using a nationally representative sample. Thereby, we demonstrated that (I) infections are associated with a significantly increased risk of ESRD in nephrotic patients, (II) hospitalization for bacterial infections is a strong risk factor for such morbidity, and (III) cardiovascular disorders and AKI are independent risk factors for kidney disease progression in the majority of patients with NS. Apart from various parameters examined clinically, our study suggests that it can be possible to predict patients with NS who are likely to develop ESRD later. Alternatively, our findings are also in accordance with other studies that suggest decreased kidney function to be associated with a significant high risk of serious infection (25,26). More importantly, NS was characterized by immunological abnormalities with T-cell imbalance and hypogammaglobulinemia, which were involved in the interaction between the virulence of the infecting organism and host defense mechanisms (27,28). The most commonly isolated bacterial species in the UTI were *Escherichia coli* (28%), and *Klebsiella spp*. (22.4%) (29). Moreover, the leading cause of bacterial peritonitis and sepsis in patients with NS was *Streptococcus pneumoniae*, a widespread pathogen that can cause pneumonia and other infectious complications (30). Additional studies to investigate the underlying immunological mechanism and limit infectious complications in patients with NS are required.

Table 4 Estimated OR of ESRD associated with infection in NS patients stratified by age

Variables	40≤ age <65			Age ≥65		
	OR	95% CI	P value*	OR	95% CI	P value*
Gender						
Female	1.00			1.00		
Male	0.84	0.46–1.54	0.574	0.58	0.24–1.40	0.226
Number of outpatient visits						
0	1.00			1.00		
1–5	1.01	0.50–2.05	0.983	1.42	0.50–4.09	0.513
6–10	1.11	0.28–4.51	0.881	3.37	0.85–13.41	0.085
>10	3.82	1.07–13.64	0.039	12.58	2.25–70.22	0.004
Number of hospitalizations						
0	1.00			–	–	–
≥1	27.41	2.76–272.08	0.005	–	–	–
Comorbidities						
Hypertension	6.71	3.27–13.78	<0.001	0.81	0.30–2.18	0.682
Diabetes mellitus	1.42	0.74–2.74	0.292	1.83	0.75–4.47	0.187
CHF	2.93	1.08–7.94	0.03	6.53	2.26–18.93	0.001
Hematuria	1.63	0.59–4.49	0.344	2.60	0.36–18.85	0.344
AKI	8.57	1.84–39.95	0.006	27.61	1.19–640.43	0.039

*, conditional logistic regression. CI, confidence interval; ESRD, end-stage renal disease; NS, nephrotic syndrome; OR, odds ratio; CHF, congestive heart failure; AKI, acute kidney injury.

This is the first study to report that occurrence of infections adversely affect renal prognosis in nephrotic patients. The findings of our study revealed that the incidence of infections was independently associated with an increased rate of ESRD in patients with NS. Patients with NS have a high risk of infections, which are subsequently associated with adverse renal outcomes, especially in female and elderly patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol was approved by the Research Ethics Committee of Ditmanson Medical Foundation Chia-yi Christian Hospital (CYCH-IRB-106084).

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