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Vesicoureteral reflux is associated with increased risk of chronic kidney disease

A nationwide cohort study

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Abstract

The association between vesicoureteral reflux (VUR) and chronic kidney disease (CKD) risk remains unestablished. We investigated the incidence of CKD in children with VUR in Taiwan and evaluated whether they had a higher risk of CKD than the general population. A nationwide population-based cohort study was conducted among children with VUR identified using Taiwan's National Health Insurance Research Database from 2000 to 2013. VUR was defined according to the International Classification of Diseases, Ninth Revision, Clinical Modification codes. We identified the children with VUR and randomly selected comparison children according to a 1:1 ratio, matching them by age, gender, index year and comorbidity using data from the National Health Insurance Research Database. In total, 8648 children with VUR and 8648 comparison children were included. All children were followed from the study date until a diagnosis of CKD, termination of insurance, or the end of 2013. Cox proportional hazards regressions were performed to compare the hazard ratios for CKD between the 2 cohorts. Incident cases of CKD were identified. After adjustment for potential confounders, the study cohort was independently associated with a higher risk of CKD (adjusted hazard ratio, 3.78; 95% confidence interval, 2.10–7.18). This population-based cohort study indicated that children with VUR have a higher risk of CKD than those without VUR.

Abbreviations: aHR = adjusted hazard ratio, CI = confidence interval, CKD = chronic kidney disease, HR = hazard ratio, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, UTI = urinary tract infection, VUR = vesicoureteral reflux.

Keywords: chronic kidney injury, cohort study, vesicoureteral reflux

1. Introduction

Chronic kidney disease (CKD) is complex in children, exerting a high financial cost for the healthcare system and increasing substantial morbidity and mortality. CKD refers to a condition related to irreversible kidney damage that can further progress to loss of kidney function.[1,2] It is not only affecting the health of the patient during childhood but also having a significant impact on the life of the adult that this child will become. According to epidemiologic reports, the prevalence of CKD in children has increased along with the incidence of dialysis and renal transplant recipients. It is believed that the numbers of pediatric CKD are still under-diagnosed and under-reported due to the limited information on the epidemiology of the early stages of CKD in the pediatric population, as it is often asymptomatic. The overall incidence rates of moderate to severe CKD for Europe and Latin America are estimated to be around 11 to 12 per million of the age-related population (pmarp) and 2.8 to 15.8 pmarp. The worldwide median incidence is about 9 pmarp, according to specific reports on the CKD epidemiology in children who are requiring renal replacement therapy.[3–5] The etiologies of CKD are often complex and multifactorial. Among the patients, congenital anomalies of the kidney and urology tract, steroid-resistant nephrotic syndrome, and chronic glomerulonephritis are the most common factors that contribute to increased risk of CKD.[1,3,5]

KLC and FYC contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are publicly available.

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Vesicoureteral reflux (VUR) is referred to retrograde flow of urine from the bladder into the upper urinary tract. The diagnosis and clinical significance of VUR in children were defined in 1960, and the classification following grades based on voiding cystourethrography was established in 1985.[6,7] VUR is one of the most common urological diagnoses in the pediatric population, with an estimated prevalence of 0.4% to 1.8% in the general pediatric population, affecting approximately 30% of children with a history of urinary tract infection (UTI) and 17.2% in children with normal kidneys.[8–11] For many years, VUR has been considered a risk factor for UTI, acute pyelonephritis, and renal parenchymal damage but whether children VUR contributes to the risk of CKD remained unclear.[10,11] As a result, this large population-based cohort study investigated the association of children VUR and the risk of CKD. Herein, Taiwan's National Health Insurance Research Database (NHIRD) was utilized for statistical analysis to compare the risk of CKD between patients with VUR and those without VUR between 2000 to 2013.

2. Methods

2.1. Data source

The data source we used for this nationwide population-based retrospective cohort study were retrieved from the NHIRD. The Taiwan government initiated the National Health Insurance (NHI) program in 1995 to provide comprehensive health care to all residents (https://nhird.nhri.edu.tw/). The NHIRD has been released to researchers in an electronically encrypted form since 1999. The NHIRD contains medical information, including records on outpatient visits, emergency department visits, hospital admission, drug prescriptions, sex, date of birth, and diagnoses coded in the format of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). For this cohort study, we used a hospitalization dataset that contains inpatients claims files and a registry of beneficiaries.[12]

2.2. Ethics statement

The NHIRD ensures patient information encryption and only provides researchers with nameless numbers associated with required data. As a result, the informed consent form of the patients is not necessary for the current study. This study has been approved by the Institutional Review Board of China Medical University (CMUH104-REC2-115- CR-4) to exempt from requiring informed consent to access the NHIRD.

2.3. Study population

The case-cohort comprised all patients diagnosed with VUR (ICD-9-CM 593.7) aged 18 years and younger between January 1, 2000, and December 31, 2013. The date of the first VUR diagnosis served as the index date. We excluded patients diagnosed with CKD (ICD-9-CM code 585) before the index date and whose demographic information was absent in the NHIRD. For comparison cohorts, we randomly selected patients without VUR diagnosis from the hospitalization dataset under the same study criteria and matched them by propensity score method with 1:1 ratio according to age group, sex, index year of VUR, and comorbidity. The underlying comorbidities we considered as confounding factors in the present study included in this study were diabetes mellitus (ICD-9-CM code 250), hypertension (ICD-9-CM code 401–405), kidneys infection (ICD-9-CM code 590), hydronephrosis (ICD-9-CM code 591), cystitis (ICD-9-CM code 595), urinary tract infection (ICD-9-CM code 599), bladder cancer (ICD-9-CM code 188), and kidney cancer (ICD-9-CM code 189) because the risk of CKD could be significant influenced by these disease entities.

2.4. Outcome and comorbidities

The study outcome was the occurrence of CKD (ICD-9-CM 584–586). Both VUR and non-VUR cohorts were followed up until a diagnosis of CKD, termination of insurance, or until December 31, 2013.

Table 1

Baseline demographic characteristics among patients with and without vesicoureteral reflux.

	Before PS match					After PS match				
	Non-vesicoureteral reflux (n = 5,342,022)		Vesicoureteral reflux (n = 10,326)			Non-vesicoureteral reflux (n = 8648)		Vesicoureteral reflux (n = 8648)		
Characteristics	n	%	n	%	*P* value	n	%	n	%	*P* value
Age, yr†										
<1	22,3686	4.19	5929	57.42	<.0001	3497	40.44	4252	49.17	<.0001
1–5	958,750	17.95	2733	26.47		3422	39.57	2732	31.59	
>5	4,159,586	77.87	1664	16.11		1729	19.99	1664	19.24	
Mean ± SD*	9.83 ± 5.13		2.26 ± 3.15		<.0001	2.85 ± 3.45		2.66 ± 3.29		.004
Gender†										
Male	2,574,437	48.19	4510	43.68	<.0001	4070	47.06	4158	48.08	.19
Female	2,767,539	51.81	5816	56.32		4578	52.94	4490	51.92	
Comorbidity†										
Diabetes mellitus	88,714	1.66	4207	40.74	<.0001	3580	41.40	3428	39.64	.05
Hypertension	109,140	2.04	5154	49.91	<.0001	4358	50.39	4181	48.35	.02
Kidneys infection	20,338	0.38	928	8.99	<.0001	638	7.38	842	9.74	<.0001
Hydronephrosis	20,958	0.39	970	9.39	<.0001	694	8.02	832	9.62	.01
Cystitis	1746	0.03	70	0.68	<.0001	41	0.47	64	0.74	.04
Urinary tract infection	134,360	2.52	9041	87.56	<.0001	7451	86.16	7363	85.15	.12
Bladder cancer	122	0.00	3	0.03	.0005	1	0.01	2	0.02	.56
Kidney cancer	164	0.00	3	0.03	.006	0	0.00	2	0.02	.16
Follow-up duration, year*	7.43 ± 4.00		7.32 ± 3.89		.0005	7.04 ± 4.02		7.32 ± 3.89		.002

Data shown as n (%) or mean ± SD.

*Two sample *t* test.

†Chi-squared test.

2.5. Statistical analysis

Differences in demographic characteristics, namely age group, sex, and comorbidities, between patients with and those without VUR were examined using the chi-square test. Differences in the mean age and mean follow-up period was computed using the Student *t* test. We used the Kaplan–Meier method to plot CKD cumulative incidence curves for the VUR and non-VUR cohorts and tested the difference with a log-rank test. The overall age-, sex-, and comorbidity-specific incidence of CKD (per 10,000 person-years) were estimated. Univariate and multivariate Cox proportional hazard regression models were used for estimating hazard ratios (HRs) and 95% confidence intervals (CIs) to assess the effects of VUR on the risk of CKD.[12] The multivariate models were simultaneously adjusted for age, sex, and comorbidities, namely diabetes mellitus, hypertension, kidney infection, hydronephrosis, cystitis, and UTI. SAS 9.4 software (SAS Institute, Cary, NC) was used for data management and statistical analysis. A 2-sided *P* value < .05 indicated statistical significance.[12]

3. Results

3.1. Baseline characteristics of the study population

We identified 8648 VUR patients and 8648 matched non-VUR controls with similar age, sex, and comorbidity distributions (Table 1). The mean (standard deviation) ages of the VUR and non-VUR cohorts were 2.66 (±3.29) and 2.85 (±3.45) years, respectively. The majority of VUR patients were in the age group < 1 year (49.17%), followed by 1–5 years (31.59%) and >5 years (19.24%). In the VUR patients, 51.92% were females. The distribution of comorbidities between the VUR and non-VUR cohorts was balanced after matching. A slightly higher prevalence of kidney infection (9.74% vs 7.38%), hydronephrosis (9.62% vs 8.02%), and cystitis (0.74% vs 0.47%) were observed in patients with VUR than in the non-VUR patients ($P < .05$).

3.2. Comparison of incidence and HRs of CKD associated with VUR and other covariates

A total of 63,320 person-years and 60,076 person-years were followed up in the VUR and non-VUR cohorts. The overall incidence rate of CKD was 8.05 per 10,000 person-years in patients with VUR and 2.16 per 10,000 person-years in non-VUR patients, respectively. The crude HR of CKD was 3.74 (95% CI 2.04–6.89) in patients with VUR compared with that in non-VUR patients. After adjustments for age, sex, and comorbidities, the adjusted hazard ratio (aHR) was 3.78 (95% CI 2.10–7.18). The incidence of CKD increased with age. Compared with patients aged 1 year, the risk of CKD development was 1.47-fold higher in those aged 1 to 5 years (95% CIs 0.96–3.26) and 2.99-fold higher in those aged > 5 years (95% CIs 1.59–5.62). Regardless of VUR, female patients exhibited a significantly higher incidence of CKD than male patients did, with the aHR was 2.18 (95% CI 1.27–3.73). Cox proportional hazard regression analyses also showed other independent predictors of CKD, including diabetes mellitus (aHR 2.27; 95%

Table 2

Hazard ratios and 95% CIs of chronic kidney disease associated with vesicoureteral reflux patients.

	Chronic kidney disease (n = 72)				
Variables	**Event**	**PY**	**IR**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**
Vesicoureteral reflux					
No	13	60,076	2.16	1 (reference)	1 (reference)
Yes	51	63,320	8.05	3.74 (2.04–6.89)***	3.78 (2.10–7.18)***
Age, yr					
<1	21	55,787	3.76	1 (reference)	1 (reference)
1–5	22	44,524	4.94	1.32 (0.72–2.39)	1.47 (0.96–3.26)
>5	21	23,086	9.10	2.41 (1.31–4.41)**	2.99 (1.59–5.62)***
Gender					
Male	15	58,498	2.56	1 (reference)	–
Female	49	64,899	7.55	1.72 (1.03–2.88)*	2.18 (1.27–3.73)**
Comorbidity					
Diabetes mellitus					
No	32	83,910	3.81	1 (reference)	1 (reference)
Yes	32	39,487	8.10	2.04 (1.25–3.35)**	2.27 (1.31–3.95)**
Hypertension					
No	37	76,156	4.86	1 (reference)	1 (reference)
Yes	27	47,241	5.72	1.11 (0.67–1.84)	1.15 (0.67–1.99)
Kidneys infection					
No	52	115,386	4.51	1 (reference)	1 (reference)
Yes	12	8010	14.98	3.20 (1.70–6.01)***	3.79 (1.70–7.55)***
Hydronephrosis					
No	58	115,786	5.01	1 (reference)	1 (reference)
Yes	6	7610	7.88	1.48 (0.63–3.44)	0.90 (0.22–1.63)
Cystitis					
No	64	122,651	5.22	1 (reference)	1 (reference)
Yes	0	746	0.00	–	–
Urinary tract infection					
No	15	19,109	7.85	1 (reference)	1 (reference)
Yes	49	104,288	4.70	0.59 (0.33–1.06)	0.45 (0.23–1.07)

aHR adjusted for age, sex, diabetes mellitus, hypertension, kidneys infection, hydronephrosis, cystitis and urinary tract infection.

CI = confidence interval, HR = hazard ratio, IR = incidence rate, per 10,000 person-years, PY = person-years.

*$P < .05$

**$P < .01$

***$P < .001$.

CI 1.31–3.95) and kidneys infection (aHR 3.79; 95% CI 1.70–7.55) (Table 2).

3.3. HRs of CKD stratified by age, gender, diabetes, hypertension, kidneys infection, hydronephrosis, cystitis and UTI.

The age-specific risk of CKD for VUR to the comparison cohort was significantly higher in patients aged 1 to 5 with the aHR of 4.43 (95% CI = 1.62–12.09) and patients aged > 5 with the aHR of 5.29 (95% CI = 1.81–17.96). The sex-specific risk of CKD was found only in the female subgroup with the aHR of 5.15 (95% CI = 2.42–12.42). It indicates that VUR remained significantly associated with a higher risk of CKD in all subgroups stratified by comorbidities for patients with diabetes mellitus, hypertension and urinary tract infections (Table 3).

3.4. Cumulative incidence of CKD using the Kaplan–Meier method

According to the log-rank test, CKD's cumulative incidence was significantly higher in patients with VUR than in patients without VUR ($P < .001$, Fig. 1).

4. Discussion

Although the link between CKD and VUR is well established,[10,11,13–17] data regarding the association between CKD and VUR in children remain limited. The present population-based cohort study conducted using Taiwan's NHIRD revealed a high CKD risk among children with VUR. Our findings reveal a 3.78-fold increased risk of CKD in the VUR cohort compared with the non-VUR cohort. In this population-based study, we demonstrated that CKD is highly associated with VUR in children aged > 1 year.

The relationship between CKD and VUR is not a new concept, but the mechanism of CKD development in patients with VUR is complex and has to be elucidated. Various theories and hypotheses have been proposed to explain the link between VUR and CKD. Studies conducted by Smellie et al and Goldraich et al reported that all grades of VUR would cause renal scarring with a greater tendency for scarring to develop with more severe VUR. Extensive renal scarring may progress to further renal injury with subsequent decreased renal function and result in CKD.[18–21] In addition, VUR will cause retention of urine in the urinary system. The urine retention in the kidney might induce a generalized parenchymal thinning and atrophy of the papillae in the kidney, which later affect kidney function.[22] When the flow of urine is obstructed in the developing kidney, it is believed that a series of abnormalities included arrested of glomerular maturation, glomerulosclerosis, ischemia, and necrosis of some tubular cells, apoptosis of other tubular and collecting duct cells, interstitial inflammation, proliferation, and fibrosis, and tubular dilatation and atrophy will occur, which subsequently lead to CKD.[22–25]

Similar to previous reports,[10,11,13–17] we revealed an increased risk of CKD in children with VUR than in the non-VUR group. Nonetheless, our female VUR patients had a higher risk of CKD than the non-VUR group, which differs

Table 3

HRs and 95% CIs of chronic kidney disease associated with vesicoureteral reflux stratified by age, gender and comorbidities.

	Vesicoureteral reflux							
	No			Yes				
Variables	Event	PY	IR	Event	PY	IR	Crude HR (95% CI)	Adjusted HR (95% CI)
All	13	60,076	2.16	51	63,320	8.05	3.74 (2.04–6.89)***	3.78 (2.10–7.18)***
Age, yr								
<1	5	25,344	1.97	16	30,442	5.26	2.66 (1.01–7.25)*	2.48 (0.90–6.81)
1–5	5	24,319	2.06	17	20,204	8.41	4.12 (1.52–11.17)**	4.43 (1.62–12.09)**
>5	3	10,413	2.88	18	12,673	14.20	4.94 (1.45–16.82)**	5.29 (1.81–17.76)**
Gender								
Male	6	27,955	2.15	16	30,542	5.24	2.46 (1.02–6.31)*	2.32 (0.90–5.96)
Female	7	32,121	2.18	35	32,778	10.68	4.90 (2.18–11.04)***	5.15 (2.42–12.42)***
Comorbidity								
Diabetes mellitus								
No	8	40,582	1.97	24	43,328	5.54	2.81 (1.27–6.27)**	2.74 (1.12–6.12)*
Yes	5	19,494	2.56	27	19,992	13.51	5.32 (2.05–13.83)***	5.46 (2.09–14.23)***
Hypertension								
No	9	36,886	2.44	28	39,269	7.13	2.91 (1.38–6.18)**	2.79 (1.32–5.92)**
Yes	4	23,190	1.72	23	24,051	9.56	5.69 (1.97–16.45)***	5.77 (1.99–16.76)***
Kidneys infection								
No	11	56,913	1.93	41	58,473	7.01	3.65 (1.87–7.10)***	3.64 (1.87–7.10)***
Yes	2	3163	6.32	10	4847	20.63	3.40 (0.75–15.54)	4.11 (0.88–19.16)
Hydronephrosis								
No	13	56,950	2.28	45	58,836	7.65	3.37 (1.82–6.26)***	3.26 (1.76–6.05)***
Yes	0	3126	0.00	6	4484	13.38	–	–
Cystitis								
No	13	59,761	2.18	51	62,889	8.11	3.75 (2.04–6.91)***	3.68 (2.00–6.78)***
Yes	0	315	0.00	0	430	0.00	–	–
Urinary tract infection								
No	3	8947	3.35	12	10,162	11.81	3.51 (1.02–12.46)*	3.87 (1.09–13.81)*
Yes	10	51,129	1.96	39	53,158	7.34	3.79 (1.89–7.59)***	3.70 (1.84–7.42)***

aHR adjusted for age, sex, diabetes mellitus, hypertension, kidneys infection, hydronephrosis, cystitis and urinary tract infection.

CI = confidence interval, HR = hazard ratio, IR = incidence rate, per 10,000 person-years, PY = person-years.

*$P < .05$

**$P < .01$

***$P < .001$.

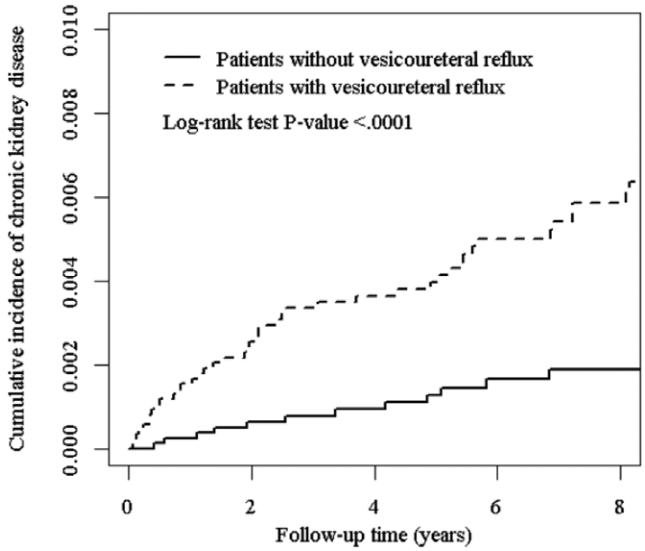

Figure 1. The cumulative incidence of chronic kidney disease for the patient with and without vesicoureteral reflux.

from the previous reports,[11,13] showing that the male gender is the CKD risk factor in VUR patients. Another study by Silva et al showed that the probability of CKD according to gender was remarkably divergent during follow-up. It revealed a greater risk of renal impairment in boys with diagnosis in the first year after the diagnosis of VUR, while the risk of CKD for girls exceeded that for boys on a long-term basis. These findings were explained by Silva et al[10] with 2 different gender-related mechanisms involved in the genesis of renal impairment, congenital renal hypoplasia prevalent in boys and acquired renal scarring in girls.

CKD is consistently associated with several comorbidities of VUR. The HR increased to 2.27 in patients with diabetes, and 3.79 in patients with kidney infections, implying that these comorbidities increase CKD risk in patients with VUR (Table 3). Few studies and literature[26–28] have mentioned that VUR alone might not be the only reason for the deterioration of kidneys that induced CKD. As a result, clinicians should treat the comorbidities to reduce the risk and severity of CKD potentially.

The NHI was adopted in 1996, all the citizens in Taiwan and foreigner who resides in Taiwan for employment purpose are compulsory to enroll in this program except for those who lose their insurance eligibility.[29,30] The medical care is provided to all Taiwan residents who undercovered by this system with the characteristics of low co-payments and good accessibility. The NHIRD is a reliable and effective database to provide population-based studies with sex- and age-matched groups as the complete database of health records, NHI claim, and administrative data are well managed by the NHI since the first day of implementation. As a result, it is an advantage of the present investigation by using this population-based dataset that enabled us to trace all the cases of VUR and CKD during the study period. This large sample size afforded us a considerable statistical advantage in detecting actual differences between the 2 cohorts. Moreover, the diagnosis of CKD and VUR are reliable. Like all other electronic health databases, the diagnoses of the patients in this study are coded by medical specialists according to ICD-9 codes, who meet the standard clinical diagnostic criteria consisting of typical clinical symptoms and signs, laboratory data, and radiologic findings. Medical specialists are required to precisely coordinate the associated disease with the ICD-9 codes for the medical reimbursements managed by the Bureau of NHI. Therefore, the diagnosis of CKD and VUR are reliable.

4.2. Limitation

Some potential limitations warrant a mention. First, the NHIRD does not provide detailed clinical information, laboratory data, such as blood urea nitrogen, creatinine level, glomerular filtration rate, radiologic findings for VUR, and lack of information on CKD severity. Thus, the grades of VUR and CKD could not be identified accurately. Second, clinical information regarding the disease course and treatment strategy of VUR was not obtained. Since VUR is often co-existed with UTI, antibiotics treatment might be prescribed. However, several antibiotics are potentially nephrotoxic and they might cause CKD, which could be a confounding factor in this study. Additionally, many children with a history of VUR underwent surgical treatment, which may have attenuated the pathological effects of VUR on CKD. Finally, the study's fundamental limitation with the potential bias resulting from possible unknown cofounder factors due to the nature of the retrospective observational study has its methodological limitations even though a meticulous study design has been made.

5. Conclusion

In conclusion, the risk of developing CKD was significantly increased in children with VUR. Additional studies on screening and early intervention are required to prevent subsequent complications of CKD in patients with VUR.

Author contributions

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