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Chronic Kidney Disease is Associated With Upper Tract Urothelial Carcinoma

A Nationwide Population-Based Cohort Study in Taiwan

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Abstract: Increased urinary tract malignancy has been reported in end-stage renal disease (ESRD). However, little is known about chronic kidney disease (CKD). This study is designed to explore the association between CKD and upper tract urothelial carcinoma (UTUC).

Using Taiwan's Longitudinal Health Insurance Database, we studied CKD patients between January 2000 and December 2011. The non-CKD controls were selected at a ratio of 4:1 and frequency matched by gender, age group, and index date. We used the chi-square test and *t* test to analyze the sociodemographic information and comorbidities. Cox regression analysis was used to calculate the hazard ratio (HR) and 95% confidence interval (CI).

The selected cases included 45,321 CKD cases and 181,284 controls. A significantly higher incidence of UTUC was noted in the CKD group (0.22% vs 0.07%, $P < 0.001$). In univariate analysis, CKD, female gender, age, hypertension, hematuria, repeated urinary tract infection, bladder cancer, and ESRD were all associated with UTUC. In multivariate analysis, only CKD, female gender, age, hematuria, bladder cancer, and ESRD were significantly associated. The HR for CKD was 1.63 (95% CI: 1.26–2.13). Females had a higher HR of 1.38 (95% CI: 1.11–1.71). After excluding those patients who progressed to dialysis or kidney transplantation, the risk for CKD was still high, with an HR of 1.72 (95% CI: 1.33–2.33).

CKD is a significant factor associated with UTUC. We should pay attention to the possibility of UTUC for CKD patients before they progress to ESRD.

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Abbreviations: CI = confidence interval, CID = Catastrophic Illness Database, CKD = chronic kidney disease, ESRD = end-stage renal disease, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, 9th revision, Clinical Modification, IRB = Institutional Review Board, LHID = Longitudinal Health Insurance Database, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, TSN = Taiwan Society of Nephrology, UTI = urinary tract infection, UTUC = upper tract urothelial carcinoma.

INTRODUCTION

The incidence of chronic kidney disease (CKD) is an increasingly challenging problem worldwide. CKD is the predecessor of end-stage renal disease (ESRD). There is substantial evidence demonstrating higher incidence rates of urinary tract malignancy in patients with ESRD.[1–4] Port et al reviewed 4,161 ESRD patients and found a 5 times the normal incidence of renal cancer.[1] Two large case review studies indicated a higher incidence rate of urothelial carcinoma in Taiwanese patients with ESRD compared to the general population.[2,3] Another study found that the overall adjusted hazard ratio (HR) for urinary tract cancer in ESRD patients was between 10.5 and 11.1 compared to patients without ESRD.[4]

Previous studies have indicated a high prevalence of CKD in upper tract urothelial carcinoma (UTUC) patients (51–58.6%).[5–7] On the contrary, there are some emerging evidences for an excess risk of cancer in patients in the CKD stage.[8–10] Therefore, we hypothesize that carcinogenesis may occur at the CKD stage and the association between CKD and UTUC gradually increases as CKD progresses to ESRD.

The prevalence rate of CKD in Taiwan was as high as 11.9%.[11] Thus, Taiwan has a large population of CKD patients. Moreover, since Taiwan has a National Health Insurance (NHI) system with almost 100% coverage, Taiwan is an ideal study setting for exploring the association between CKD and UTUC. We postulate that it might be more representative to conduct a population-based cohort study than an institution-based study in order to elucidate the relationship between the 2 diseases. The aim of this study is to examine the association between CKD and UTUC.

MATERIALS AND METHODS

Data Source

We retrieved patient data from Taiwan's Longitudinal Health Insurance Database (LHID2000), which was validated for its representativity of all beneficiaries of Taiwan's NHI in 2000. The NHI in Taiwan is a national health insurance program launched by the Taiwanese government in 1995. More than 96% of Taiwanese citizens are covered by this system.[12]

In LHID2000, the original claim data of 1,000,000 patients were randomly sampled from Taiwan's National Health Insurance Research Database (NHIRD) in the year 2000. The LHID2000 provided information about both outpatient and inpatient visits. They included the diagnosis and procedure codes (coded in the International Classification of Diseases, 9th revision, Clinical Modification [ICD-9-CM]), usage of medical resources, and sociodemographic information (age, gender, residence, and insured income). The Catastrophic Illness Database (CID) in NHIRD was another data source for this study. It is a registry of all catastrophic illnesses (e.g., malignancies and long-term dialysis) bulleted by NHIRD. Patients' medical records are submitted to an expert review board, and once the application for registration in CID is approved, the patient is exempt from any copayment for related medical services. All personal identification information in LHID2000 and CID were anonymized and encrypted. By using encrypted identification numbers, all parts of the LHID2000 and CID can be linked, allowing researchers to trace patients' medical histories and follow their prognoses after the index date of disease. Access to NHIRD is approved by the Review Committee of the National Health Research Institute (registered number: NHIRD-101-549). This study has been approved by Institutional Review Board (IRB) of Ditmanson Chia-Yi Christian Hospital (IRB No: 104002). Because of the encryption of personal identification information, this study was remitted from full review by IRB.

Study Subjects and Design

The CKD and control groups were observed from January 1, 1997, to December 31, 2011, to examine the association between CKD and UTUC in Taiwan. The CKD group included all of the prevalent cases with a diagnosis of CKD (ICD-9-CM codes: 403.00, 403.10, 403.90, 404.00, 404.10, 404.11, 404.90, 404.91, 582, and 585) in LHID2000 during the study period. The date of the first diagnosis of CKD was defined as the index date. Patients were excluded if dialysis (defined as being registered in CID for dialysis) or kidney transplantation (ICD-9-CM code v42.0) or UTUC (ICD-9-CM code 1891, 1892 and being registered in CID) were recorded before their index date. The control group was randomly selected from the remaining beneficiaries of LHID2000 who had not been diagnosed with CKD, no history of dialysis, kidney transplantation, or UTUC before the year they were enrolled. The controls were frequency matched to the CKD patients by age group ($\pm$5 years) and sex in a ratio of 4:1. The index date of controls was assigned as the first date of the year they were enrolled. Both groups were followed from their index date to the date of UTUC occurrence or death, whichever came first. If the study subjects died without a prior history of UTUC during the follow-up period, their status was censored.

Comorbidities, including diabetes mellitus, hypertension, hematuria, repeated urinary tract infection (UTI), bladder cancer, and ESRD, were included. Diagnoses of these comorbidities from the year before the index date to the end of observations were all included as covariates in this study. In addition, several villages in southwestern and northeastern Taiwan, which were reported as arseniasis-endemic areas, were also identified.[13,14] The urbanization level of living was classified into 4 levels according to the study by Liu et al.[15]

DEFINITION

Chronic kidney disease (CKD) is a general term for heterogeneous disorders affecting the structure and function of the kidney.[16] As it is an important public health issue in Taiwan, the Taiwan Society of Nephrology (TSN) launched a nationwide CKD Preventive Project in 2004. As of late 2005, the TSN adopted the simplified Modification of Diet in Renal Disease equation to calculate the estimated glomerular filtration rate.[17,18] The CKD stage was classified according to the National Kidney Foundation's Kidney Disease Outcome Quality Initiative.[19]

According to Hwang et al, diabetes mellitus (43.2%), chronic glomerulonephritis (25.1%), hypertension (8.3%), and chronic interstitial nephritis (2.8%) are 4 major renal diseases underlying ESRD.[20] In the definition of CKD, we included CKD (ICD-9-CM code 585), chronic glomerulonephritis (ICD-9-CM code 582), hypertensive chronic kidney disease (ICD-9-CM code 403.00, 403.10, and 403.90), and hypertensive heart and chronic kidney disease (ICD-9-CM code 404.00, 404.01, 404.10, 404.11, 404.90, and 404.91). Diabetes nephropathy is classified as ICD-9-CM code 585. We excluded ESRD patients who required dialysis. This definition encompassed most identifiable etiologies of CKD in clinical practice.

Statistical Analysis

We used the chi-square test and *t*-test to inspect the differences between the CKD and control groups in terms of all sociodemographic information and comorbidities. The chi-square test was also used to compare the differences in the cumulative incidence of kidney transplantation, dialysis, UTUC, and mortality in both groups. Univariable and multivariable Cox proportional regression analyses were used to examine the association between CKD and risk of UTUC. The adjusted HR and 95% CI were estimated after adjusting for age, gender, urbanization level, insured income, geographic area, diabetes mellitus, hypertension, hematuria, repeated UTI, bladder cancer, arseniasis-endemic areas, and ESRD. A subgroup analysis was further conducted to examine the association between pre-end-stage CKD and the risk of UTUC. In the subgroup analysis, the CKD group only included CKD patients who had not undergone dialysis or kidney transplantation during the study period. A P value of <0.05 was considered statistically significant. Data management and data analyses were performed using SAS/STAT® software, version 9.3 for Windows (SAS Institute Inc, Cary, NC).

RESULTS

A total of 45,321 CKD cases and 181,284 controls were analyzed in this study. There were 17,059 patients diagnosed with CKD (ICD-9-CM code 585), 18,839 patients with chronic glomerulonephritis (ICD-9-CM code 582), 2,489 patients with hypertensive chronic kidney disease (ICD-9-CM code 403.00, 403.10, and 403.90), 2,934 patients with hypertensive heart and chronic kidney disease (ICD-9-CM code 404.00, 404.01, 404.10, 404.11, 404.90, and 404.91), and 4,000 patients with at least 2 above-mentioned diagnoses as shown in the supplementary Table 1, http://links.lww.com/MD/A896. More than half of the subjects were >60 years of age. Table 1 lists the sociodemographic characteristics, comorbidities, and outcomes of all included subjects. The patients in the CKD group were more likely to have a lower socioeconomic status, live in urbanized areas, live in central and southern Taiwan, and live in an arseniasis-endemic area (Table 1). Comorbidities, including diabetes mellitus, hypertension, hematuria, repeated UTI, and bladder cancer, were more prevalent in the CKD group than in the control group (all P values < 0.001). In CKD group, we

TABLE 1. Sociodemographic Characteristics, Comorbidities and Outcomes for Patients with CKD and Control Group Patients in Taiwan (n = 226,605)

Variable	CKD Group (n = 45,321)	Control Group (n = 181,284)	*P* Value
Time for follow-ups, y (Mean ± SD)	8.7 ± 3.4	9.2 ± 3.4	< 0.001*
Age, y, n (%)			
Mean ± SD	59.0 ± 18.4	58.1 ± 18.7	< 0.001*
<20	1468 (3.2)	5872 (3.2)	1.00
20–39	5684 (12.5)	22736 (12.5)	
40–59	14292 (31.5)	57168 (31.5)	
60–79	18943 (41.8)	75772 (41.8)	
≧80	4934 (10.9)	19736 (10.9)	
Gender			
Male	23935 (52.8)	95740 (52.8)	1.00
Female	21386 (47.2)	85544 (47.2)	
Urbanization			
I (Highest)	12582 (27.9)	51738 (28.7)	0.01
II	12648 (28.0)	49894 (27.7)	
III	7702 (17.1)	30673 (17.0)	
IV (Lowest)	12203 (27.0)	48043 (26.6)	
Insured income, USD$			
> 794	6192 (13.7)	25938 (14.3)	< 0.001
503–794	19193 (42.4)	75545 (41.7)	
0–503	7441 (16.4)	30573 (16.9)	
0	12495 (27.6)	49228 (27.2)	
Geographic area			
North	19390 (42.8)	83383 (46.0)	< 0.001
Central	11490 (25.4)	42570 (23.5)	
South	13101 (28.9)	48839 (26.9)	
East and offshore	1339 (3.0)	6490 (3.6)	
Arseniasis-endemic area	363 (0.8)	1220 (0.7)	0.003
Comorbidities			
Diabetes Mellitus	21141 (46.7)	44023 (24.3)	<0.001
Hypertension	33184 (73.2)	82039 (45.3)	<0.001
Hematuria	1367 (3.0)	2052 (1.1)	<0.001
Repeated UTI	4335 (9.6)	6027 (3.3)	<0.001
Bladder cancer	669 (1.5)	988 (0.6)	<0.001
Outcomes of the CKD and control groups			
UTUC (%)	101 (0.22)	124 (0.07)	<0.001
Dialysis (%)	4816 (10.6)	219 (0.12)	<0.001
Kidney transplantation (%)	197 (0.43)	0 (0)	<0.001
Mortality (%)	37 (0.08)	98 (0.05)	<0.001

P-values were estimated by using the chi-square test, unless otherwise specified.

CKD = chronic kidney disease, USD = United Stated dollars, UTI = urinary tract infection, UTUC = upper tract urothelial carcinoma.

*Student's *t* test.Exchange rate between USD$ and NT$ (New Taiwan Dollar): 31.5:1.

further compared the association between DM and UTUC. The statistics were not significant as shown in the supplementary Table 2, http://links.lww.com/MD/A896. During the study period, 101 CKD patients developed UTUC, including 43 patients with bladder cancer. A significantly higher incidence of UTUC was noted in the CKD group (0.22% vs 0.07%, $P < 0.001$). The chronic glomerulonephritis was responsible for most UTUC cases in CKD group (please see supplementary Table 3, http://links.lww.com/MD/A896). Approximately 10.6% of the CKD patients progressed to ESRD requiring dialysis, and 0.43% received kidney transplantation. A significantly higher mortality rate was noted in the CKD group than in the non-CKD group.

Risk Factors Associated with UTUC

Further analysis using the Cox proportional hazard model is presented in Table 2. Using univariate analysis, we found that CKD, female gender, age, hypertension, hematuria, repeated UTI, bladder cancer, and ESRD were all associated with UTUC. In multivariate analysis, the CKD group had a 1.63-fold higher risk of UTUC than the non-CKD group after adjusting for sociodemographic characteristics and comorbidities (adjusted HR: 1.63, 95% CI: 1.26–2.13). Female gender, older age, hematuria, bladder cancer, and ESRD were associated with higher risks. Among these factors, bladder cancer had the highest hazard ratio (HR: 12.98, 95% CI: 8.97–18.78). A 1-year increase in age was associated with an elevated risk of UTUC (HR: 1.01, 95% CI: 1.00–1.02).

Subgroup Analysis

In the subgroup analysis, we excluded CKD patients who had progressed to dialysis or had undergone kidney transplantation during the study period. The results were calculated using multivariate analysis and are listed in Table 2. The patients in the CKD group still had an escalated risk of UTUC (HR: 1.72, 95% CI: 1.33–2.33). Sex, age, hematuria, and bladder cancer were all significantly correlated with UTUC. Interestingly, the HRs for all the aforementioned variables, except for gender, were attenuated compared with those in overall analysis. Because the bladder cancer was a well-known risk factor for UTUC, we further excluded CKD patients with history of bladder cancer and performed the multivariate analysis. We still found the risk of UTUC in these CKD patients remained significantly higher (HR: 1.84, 95% CI: 1.42–2.39).

DISCUSSION

This was a nationwide, population-based cohort study. During the mean follow-up period of 9.1 years, we confirmed that CKD patients had an elevated risk of UTUC compared with non-CKD patients.

Because there is well-established evidence of increased malignancy risk in ESRD and kidney transplantation patients, we excluded those CKD patients who had already progressed to ESRD or were given kidney transplantation to further elucidate the association between CKD and malignancy. After exclusion, the risk remained significantly higher (HR: 1.72, 95% CI: 1.33–2.23). As time and the underlying renal disease progress, we think the risk for UTUC may increase.

The prevalence rate of CKD in this study was lower than that in previous study,[11] which identified cases from medical screening program. Many early stage CKD patients are asymptomatic and unaware to their renal diseases,[16,18] Whereas the CKD cases identified in this study were those patients who already had renal symptoms or signs and searched for medical service. Though the CKD prevalence rate of this study could be underestimated, we think the association between CKD and UTUC would be more accurate.

The epidemiology of UTUC in Taiwan is quite different from that in the West. First, UTUC is a rare disease in the West and accounts for only 5% of all urothelial carcinomas,[21] but

TABLE 2. Risk Factors Associated With the Risk of UTUC in Cox Proportional Hazard Model

	Overall Analysis (n = 226,605)		Subgroup Analysis* (n = 221,532)
Variables	**cHR (95% CI)**	**aHR (95% CI)**	**aHR (95% CI)**
Group			
CKD	2.61 (2.11–3.23)	1.63 (1.26–2.13)	1.72 (1.33–2.23)
Control	Ref.	Ref.	Ref.
Gender			
Female	1.25 (1.02–1.62)	1.38 (1.11–1.71)	1.35 (1.08–1.72)
Male	Ref.	Ref.	Ref.
Age, per 1 year increase	1.01 (1.01–1.02)	1.01 (1.00–1.02)	1.01 (1.00–1.02)
Urbanization level of residence			
I (Highest)	0.92 (0.67–1.22)	0.96 (0.68–1.35)	0.95 (0.66–1.38)
II	1.07 (0.81–1.40)	1.07 (0.79–1.46)	0.99 (0.71–1.39)
III	0.84 (0.60–1.18)	0.88 (0.62–1.26)	0.94 (0.64–1.36)
IV (Lowest)	Ref.	Ref.	Ref.
Monthly insured income, USD			
> 794	0.85 (0.60–1.20)	1.10 (0.76–1.59)	1.16 (0.78–1.72)
>503–794	0.87 (0.67–1.12)	0.91 (0.69–1.18)	0.85 (0.63–1.15)
>0–503	1.06 (0.79–1.44)	1.15 (0.85–1.57)	1.24 (0.89–1.72)
0	Ref.	Ref.	Ref.
Geographic area of residence			
Northern	0.83 (0.46–1.49)	0.82 (0.44–1.53)	0.81 (0.42–1.56)
Central	0.79 (0.43–1.46)	0.77 (0.42–1.42)	0.79 (0.42–1.51)
Southern	1.11 (0.61–2.00)	1.03 (0.56–1.89)	0.97 (0.51–1.84)
Eastern	Ref.	Ref.	Ref.
Diabetes	1.21 (0.98–1.51)	0.87 (0.69–1.10)	0.94 (0.72–1.22)
Hypertension	1.47 (1.19–1.82)	0.91 (0.71–1.16)	0.98 (0.76–1.27)
Hematuria	10.14 (7.52–13.67)	2.13 (1.43–3.17)	2.20 (1.37–3.52)
Repeated UTI	2.20 (1.57–3.09)	1.27 (0.89–1.80)	1.27 (0.84–1.92)
Bladder cancer	28.57 (21.83–37.38)	12.98 (8.97–18.78)	12.30 (7.97–18.98)
Arseniasis-endemic area	2.03 (0.84–4.90)	1.70 (0.68–4.21)	2.13 (0.85–5.34)
ESRD	7.80 (5.85–10.40)	3.38 (2.38–4.81)	Not included

Death from other causes led to censorship of data.

Exchange rate of New Taiwan Dollar: USD = 31.5: 1.

aHR = adjusted hazard ratio, cHR = crude hazard ratio, CI = confidence interval, CKD = chronic kidney disease, ESRD = end-stage renal disease, Ref. = reference group, USD = United States dollars, UTI = urinary tract infection, UTUC = upper tract urothelial carcinoma.

*Exclude patients with dialysis or kidney transplantation.

UTUC occurrence in Taiwan is as high as 31% of all urothelial carcinomas.[22] Second, the male-to-female ratio (M/F ratio) of UTUC is between 2:1 and 4:1 in the West,[23,24] but the M/F ratio is 1:1.3 in Taiwan.[25] Although there were fewer females than males with CKD in this study (47.2% vs 52.8%, Table 1), female CKD patients had a significantly higher risk for UTUC (Table 2). The finding of females with a higher risk for UTUC is in accordance with previous investigations conducted in the East.[4,7,11,22,26]

The exact etiology of this gender disparity in UTUC has not been clearly described. In Taiwan, herbal medication is prescribed to women 58.1% of the time compared to 41.9% for men.[27] More female Chinese herbal nephropathies have been diagnosed.[28] In the study by Chang et al, the authors report that the use of Chinese herbs, especially if they contain aristolochic acid or compound analgesics, may contribute to the development of urothelial carcinoma.[29] A population-based study also revealed that the use of aristolochic acid-containing Chinese herbal products is associated with a dose-dependent increased risk of urinary tract cancer.[12] We hypothesize that the discrepancy between genders in the West and the East may be due to differences in culture, lifestyle, diet, and drug use. Of course, the underlying mechanisms for gender variability in UTUC need further studies to clarify.

CKD is associated with an increased risk of bladder cancer recurrence in patients with UTUC who have been treated by nephroureterectomy.[30] In addition, the aggressiveness of UTUC increases with the severity of CKD.[31] This study also found that CKD patients with bladder cancer had a 13-fold higher risk of UTUC (Table 2). In subgroup analysis, the risk remained significantly higher ($P < 0.001$ in Table 2). In addition, we found that the risk of UTUC was 1.8 -fold in CKD patients without bladder cancer. We may suggest there is an interaction between CKD and urothelial carcinoma and they may share similar risk factors.

Hung et al have demonstrated an association between CKD severity and UTUC aggressiveness.[31] Though the risk for UTUC in CKD patients was only 0.22% in this present study, it was 3 times higher than that in non-CKD patients. Therefore, preventing CKD progression is still an important issue, because it may also decrease the risk of UTUC.

In our study, aging, male gender, and lower socioeconomic status were associated with CKD, which is in agreement with previous studies.[11,32,33] We found that most CKD patients lived in urbanized areas. CKD patients require more medical care. In urbanized areas, there are more medical resources, which may explain the concentration of CKD patients in these areas. Increased levels of hematuria and repeated UTIs were noted

in the CKD group, which may be either consequences of CKD or the early signs of urothelial carcinoma. We also observed significantly higher rates of diabetes mellitus and hypertension in the CKD group. In developed countries, CKD is generally associated with old age, diabetes mellitus, and hypertension.[16] The increased prevalence of microvascular diseases, including neurological and renal disorders, is associated with arsenic ingestion.[34] This association might explain why more CKD patients were found in arseniasis-endemic areas in this study, though the association between the inhabitants living in arseniasis-endemic areas and UTUC was not significant upon multivariate analysis.

This study has some limitations. First, some clinical information, such as laboratory data, and pathology tumor staging, were not available in Taiwan NHIRD. Therefore, we could not classify the severity of CKD or UTUC. It was also difficult to know whether observed CKD was due to the obstructive nature of UTUC. This is a common methodological limitation when using administrative databases. However, we have tried to control many potential confounding factors, including diabetes mellitus, hypertension, hematuria, repeated UTI, bladder cancer, and arseniasis-endemic areas with multivariable statistical analyses. Second, smoking history, the severity of proteinuria, the habitual use of Chinese herbal medicine and medication that CKD patients took were not attainable in the NHIRD. All these factors may contribute to the pathogenesis of CKD and UTUC. Therefore, the association between CKD and UTUC in our study could be negatively affected. We would recommend further studies to investigate these potential confounding factors. Third, we included prevalent cases with the diagnosis of CKD but not newly diagnosed cases. Therefore, it was unable to estimate the possible onset of UTUC among CKD patients. Fourth, the diagnosis of CKD and other comorbidities were based on ICD-9-CM codes. Many previous population-based studies used ICD-9-CM codes have validated this approach.[4,12,35,36] In Taiwan, the NHI Bureau regularly scrutinized the charts and audited the medical charges to prevent malpractices and inadequate medical expenses. Misclassification was possible, but was most likely to be minimal.

CONCLUSIONS

This was a large-scale and long-term follow-up study. We demonstrated that CKD patients have an elevated risk for UTUC compared with non-CKD patients. Excluding CKD patients who had progressed to dialysis or underwent kidney transplantation, the risk remained high. Female CKD patients had a significantly higher risk for UTUC. In addition to ESRD patients, CKD patients should also be carefully monitored for UTUC, especially patients presenting with hematuria.

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