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Dialysis and the risk of early urological cancer

A nationwide population-based cohort study in Taiwan

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Abstract

Patients with end-stage renal disease (ESRD) are predisposed to a higher risk of developing malignancies. This study aimed to explore the association between chronic dialysis with ESRD treated and the subsequent development of urothelial cell carcinoma or renal cell carcinoma (UC/RCC). Data spanning 13 years were retrieved from Taiwan's National Health Insurance Research Database. A total of 11,820 patients with ESRD undergoing maintenance dialysis between January 1, 2000, and December 31, 2013, and 35,460 controls matched for sex, age, and index year, were identified. After adjusting for confounding factors, Cox proportional hazards analysis was performed to compare the risk of UC/RCC during the 13-year follow-up period, and Kaplan–Meier analysis was used to evaluate the cumulative UC/RCC incidence between the ESRD and non-ESRD cohorts. The average time before developing UC/RCC was 4.18 years after dialysis initiation in the ESRD group compared to 5.39 years in the control group. After adjusting for sex, age, monthly income, urbanization level, geographic region, and comorbidities, the hazard ratio for UC/RCC was 1.186 (95% confidence interval, 1.071–1.448; $P = .005$). Stratified by age, the odds ratios (ORs) for developing UC/RCC were 2.105, 1.498, 1.371, and 0.925 among patients with ESRD aged 40 to 49, 50 to 59, 60 to 69, and ≥ 70 years, respectively. Stratification by comorbidities revealed ORs of 1.204, 1.179, 1.186,1.172, 1.211, and 1.210 for patients without diabetes mellitus, hyperlipidemia, obesity, coronary artery disease, chronic obstructive pulmonary disease, and hematuria, respectively. The mean time to UC/RCC occurrence was 4.18 years after dialysis. Furthermore, younger male patients undergoing dialysis with fewer comorbidities were at higher risk of developing UC/RCC. Early or more intensive surveillance for urological cancers post-dialysis initiation is recommended for patients undergoing dialysis with longer life expectancies or a higher likelihood of undergoing renal transplantation.

Abbreviations: CCI = Charlson comorbidity index, CI = confidence interval, CKD = chronic kidney disease, ESRD = end-stage renal disease, HD = hemodialysis, HR = hazard ratio, ICD-9-CM = International classification of diseases, ninth revision, clinical modification, LHID = longitudinal health insurance database, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, OR = odds ratios, PD = peritoneal dialysis, PSM = propensity score matching, RCC = renal cell carcinoma, UC = urothelial carcinoma.

Keywords: chronic dialysis, renal cell carcinoma, urological cancer, urothelial cell carcinoma

1. Introduction

Several studies[1] have documented disparities in the incidence rates of various malignancies between patients with end-stage renal disease (ESRD) and the general population. In particular, urological malignancies are more prevalent among patients treated with regular hemodialysis (HD) or peritoneal

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The authors have no conflicts of interest to disclose.

The data are available from the National Health Insurance Research Database (NHIRD), Taiwan. However, due to legal restrictions imposed by the Personal Information Protection Act, the data are not publicly available. Requests for access to the data can be submitted to the NHIRD as formal proposals.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Tri-Service General Hospital, Taiwan (IRB approval No. TSGH-IRB No. E202316007). Informed consent statement was not applicable.

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dialysis (PD) across different racial populations.[2–4] Potential pathophysiological mechanisms include immune system disturbances, chronic infection with oncogenic viruses, chronic inflammation, nutritional deficiencies, impaired DNA repair, accumulation of carcinogenic compounds, and reduced antioxidant capacity.[5,6] Despite these findings, a standardized cancer screening protocol for ESRD patients has not yet been established. Previous studies have suggested that cancer screening in patients undergoing dialysis may not be cost-effective or provide survival-benefits.[7,8] Malignancy is one of a leading cause of death in patients undergoing dialysis. In Japan, 9.1% of deaths in patients who underwent HD were attributed to malignancies, ranking third after cardiac failure (27.2%) and infectious diseases (20.3%).[9] The heterogeneous nature of the population with ESRD includes patients of varying ages and comorbidities. Identifying patients who would benefit from a more aggressive cancer surveillance protocol is essential. More and more evidence advice against routine cancer screening in dialysis patients with limited life expectancy, but recommends individualized assessment based on cancer risk and life expectancy.[10,11] This study aimed to assess the time to onset of urothelial carcinoma (UC) and renal cell carcinoma (RCC) following dialysis initiation in patients with ESRD, and to identify dialysis subgroups at elevated risk for urological malignancies.

2. Materials and methods

2.1. Database

We utilized the Taiwan Longitudinal Health Insurance Database (LHID), a dataset randomly sampled from the National Health Insurance Research Database (NHIRD), maintained by the Taiwan National Health Research Institute. The NHI program, covering 99.9% of Taiwan population (a population size nearing 23.2 million as recorded in 2012), collects claims and registration data from nearly all medical institutions nationwide.

The LHID includes data on outpatients, emergency department patients, and inpatients. The LHID contains data randomly collected from 1,685,500 insured individuals, encompassing 25,789,508 medical events from January 1, 2000, to December 31, 2013. The demographic composition and features of individuals in the LHID cohort exhibited a normal distribution.

2.2. Study design and patient setting

Patients from the LHID who were diagnosed with ESRD (ICD-9-CM code 585) and underwent maintenance dialysis – HD (procedure code 39.95) or PD (procedure code 54.98) – between 2000 and 2013 were included. Patients who received regular renal replacement therapy before the index date, had a prior diagnosis of UC or RCC (ICD-9-CM codes 188–189), were aged < 20 years, or had unknown sex were excluded.

To minimize selection bias and enhance group comparability, we applied propensity score matching to select non-ESRD controls in a 1:3 ratio based on age, sex, and index year. Propensity scores were estimated using logistic regression with key baseline characteristics, and nearest neighbor matching without replacement was performed to ensure similarity between groups. The matching ratio was chosen to balance statistical power and representativeness. The selection process is summarized in Figure 1.

The LHID provides comprehensive data on sex, age, income level, hospital level, dates of medical events, urbanization level, geographic location, and other comorbidities. Urbanization levels were determined according to population-based indicators. Level 1 included areas with populations ≥ 1,250,000 and featured major political, economic, cultural, and metropolitan functions. Level 2 referred to regions with 500,000–1,249,999 inhabitants,

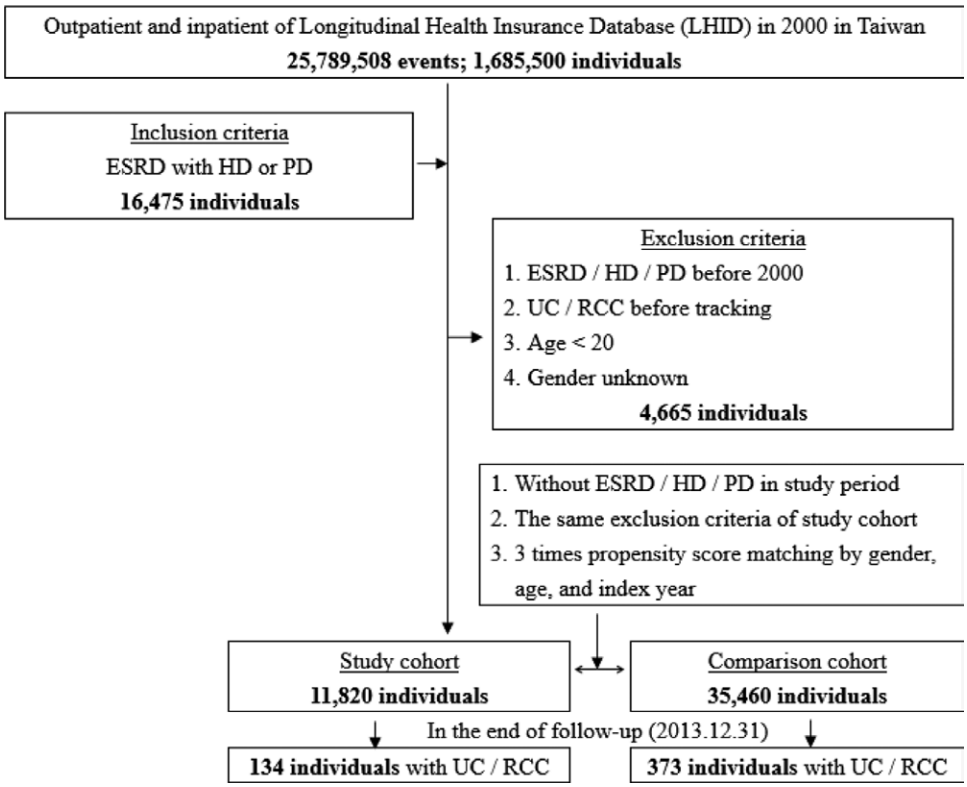

Figure 1. Flowchart showing the process of participant selection from the National Health Insurance Research Database of Taiwan. ESRD; ICD-9-CM, 585; HD: ICD-9-CM OP39.95; PD: ICD-9-CM OP54.98; (UC)/RCC: ICD-9-CM 188 to 189. ESRD = end-stage renal disease, HD = hemodialysis, PD = peritoneal dialysis, RCC = renal cell carcinoma, UC = urothelial carcinoma

generally having secondary centers. Level 3 covered areas with 150,000 to 499,999 people, while Level 4 encompassed regions with fewer than 149,999 residents. In Taiwan, patients diagnosed with a catastrophic disease by the Ministry of Health and Welfare can submit relevant medical documentation to apply for a certificate of catastrophic illness. This certificate exempts patients from paying deductibles for outpatient and inpatient treatments related to a specified disease during the validity period. For subgroup analysis, UC/RCC was classified under ICD-9-CM 188 to 189 and further divided into bladder malignant neoplasm (ICD-9-CM 188), kidney malignant neoplasm (ICD-9-CM 189.0), renal pelvic malignant neoplasm (ICD-9-CM 189.1), ureter malignant neoplasm (ICD-9-CM 189.2), and other urothelial cell malignant neoplasms (ICD-9-CM 189.3–189.9).

Data on patients with the following comorbidities were extracted using the corresponding ICD-9-CM codes: hypertension (ICD-9-CM codes 401–405), diabetes mellitus (DM; ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), obesity (ICD-9-CM code 278), chronic obstructive pulmonary disease (COPD; ICD-9-CM codes 490–496), coronary artery disease (CAD; ICD-9-CM codes 410–414), and hematuria (ICD-9-CM code 599.7).

Of the 1,685,500 patients in the LHID group, 16,475 with ESRD on HD or PD were enrolled in this study. All participants were at least 20 years old and had been newly diagnosed with ESRD requiring HD or PD since 2000. After excluding 4665 patients, 11,820 were selected for subsequent analyses. At the end of the follow-up period (December 31, 2013), UC/RCC was diagnosed in 134 patients with ESRD in the maintenance dialysis group and in 373 patients in the non-ESRD group. A flow chart of the study is shown in Figure 1.

2.3. Ethical consideration

This study utilized data from the LHID, a de-identified secondary database extracted from the NHIRD. Since the dataset is fully anonymized before release, individual informed consent was waived in accordance with national ethical regulations. This study was approved by the Institutional Review Board of the Tri-Service General Hospital, Taiwan, Republic of China (approval no. TSGH-IRB No. E202316007).

2.4. Statistical analysis

Statistical analyses were performed using the SPSS software version 20 (IBM Corp., Armonk). The chi-square test and Fisher exact test were used to compare categorical variables, while the Student *t* test was used to compare continuous variables between the ESRD and non-ESRD groups. Kaplan–Meier curve analysis and log-rank tests were used to assess the cumulative risk of subsequent UC/RCC. The hazard ratios (HRs) of UC/RCC and other relevant parameters were determined using a multivariate Cox regression analysis. Statistical significance was set at $P < .05$. This study used data from the LHID, an administrative claims database where diagnostic and procedural codes are mandatory for reimbursement. Consequently, missing data for key clinical variables were minimal. Previous validation studies of the NHIRD have reported a missing data rate of <1% for primary diagnostic codes. In this study, a completeness analysis confirmed that missingness was negligible for primary exposure and outcome variables. To ensure valid outcome ascertainment, individuals without follow-up (i.e., without any tracking records) were excluded. However, information on lifestyle factors and laboratory results was not available and is acknowledged as a study limitation.

3. Results

Table 1 summarizes the demographic profile and clinical characteristics of the cohort included in this study. Among the 11,820 patients in the ESRD group, 49.73% were male. Compared to the control group, the study participants tended to have lower rates of hypertension, hyperlipidemia, CAD, and COPD ($P < .001$). Most patients were diagnosed in northern Taiwan, which has a concentration of urbanization levels 1 and 2 cities, and were predominantly treated in medical centers. Among the patients with ESRD (n = 11,820), 9045 (76.52%) underwent follow-up in the Department of Nephrology. At the end of the follow-up period, 507 patients (1.07%) developed UC/RCC: 134 (1.13%) in the study group and 373 (1.05%) in the control group. (Table S1, Supplemental Digital Content, https://links.lww.com/MD/O921) The patients tended to have a higher risk of developing UC/RCC at the end of follow-up than the control group ($P = .011$).

Figure 2 presents the Kaplan–Meier analysis of the cumulative incidence of UC/RCC among individuals aged ≥ 20 years stratified into ESRD and non-ESRD groups using the log-rank test. Over the 8-year follow-up period, the difference in incidence between the 2 groups was significant (log-rank test = 0.05) (Table S3, Supplemental Digital Content, https://links.lww.com/MD/O923).

Table 2 shows the results of Cox regression analysis of the risk factors associated with UC/RCC development. The crude HR was 1.372 (95% CI: 1.126–1.672, $P = .002$). After adjusting for age, sex, comorbidities, geographical area of residence, urbanization level of residence, and monthly income, the adjusted HR (aHR) was 1.186 (95% CI: 1.071–1.448, $P = .005$). Male patients (aged 30–39, 40–49, 50–59, and 60–69 years) with hematuria undergoing dialysis had a higher risk of developing UC/RCC, whereas patients undergoing dialysis with comorbid DM, hypertension, hyperlipidemia, COPD, and CAD had a lower risk of developing UC/RCC. Furthermore, patients undergoing dialysis living in urbanized areas and who were followed up in the Department of Nephrology had a higher risk of being diagnosed with UC/RCC.

In the stratified analysis comparing patients with and without ESRD (Table 3), the overall incidence rates of UC/RCC were 262.98 per 100,000 person-years and 189.34 per 100, 000 person-years in the ESRD and non-ESRD groups, respectively. The aHR was 1.186 ($P = .005$).

Male patients, those with hypertension, and those aged 40 to 49, 50 to 59, and 60 to 69 years in the ESRD group exhibited a higher risk of developing UC/RCC, with aHRs of 2.215, 1.472, 2.105, 1.498, and 1.371, respectively.

Patients without DM, hyperlipidemia, obesity, CAD, COPD, hematuria, ESRD, or dialysis were more likely to be diagnosed with UC/RCC, with aHRs of 1.407 ($P = .039$), 1.179 ($P = .017$), 1.186 ($P = .005$), 1.172 ($P = .031$), 1.211 ($P = .046$), and 1.210 ($P = .026$), respectively.

In the subgroup analysis (Table 4), 134 of 11,820 patients in the ESRD group developed UC/RCC. Of these, 74 (55.22%) had a malignant bladder neoplasm, 30 (22.39%) had a malignant kidney neoplasm, 12 (8.96%) had a malignant renal pelvic neoplasm, 8 (5.97%) had a malignant ureter neoplasm, and 10 (7.46%) had other urothelial cell malignant neoplasms. In the control group, 373 of the 35,460 patients developed UC/RCC, including 200 (53.62%) with bladder malignant neoplasms, 96 (25.74%) with kidney malignant neoplasms, 27 (7.24%) with renal malignant neoplasms, 24 (6.43%) with ureter malignant neoplasms, and 26 (6.97%) with other urothelial cell malignant neoplasms. The ESRD group had a higher risk of developing bladder malignant neoplasms (aHR: 1.223; $P = .05$), renal pelvis malignant neoplasms (aHR: 1.468, $P < .001$), and other urothelial malignant neoplasms (aHR: 1.277, $P = .013$) than the non-ESRD group. The incidence rates of malignant neoplasms in the kidneys and ureters were higher, although these trends were not significant.

We also compared the risk of developing UC/RCC between patients undergoing PD (46.3%, n = 62) and those undergoing HD (53.7%, n = 72). The overall incidence of UC/RCC was

Table 1

Baseline characteristics of the study group.

Group	Total		Study cohort		Comparison cohort		
Variables	**n**	**%**	**n**	**%**	**n**	**%**	***P***
Total	47,280		11,820	25.00	35,460	75.00	
Gender							
Male	23,512	49.73	5878	49.73	17,634	49.73	.999
Female	23,768	50.27	5942	50.27	17,826	50.27	
Age (yr)	57.51 ± 17.22		57.81 ± 17.28		57.42 ± 17.20		.574
Age group (yr)							
20 to 29	3560	7.53	890	7.53	2670	7.53	.999
30 to 39	5668	11.99	1417	11.99	4251	11.99	
40 to 49	7100	15.02	1775	15.02	5325	15.02	
50 to 59	6632	14.03	1658	14.03	4974	14.03	
60 to 69	10,132	21.43	2533	21.43	7599	21.43	
≥70	14,188	30.01	3547	30.01	10,641	30.01	
Low income							
Without	46,774	98.93	11,687	98.87	35,087	98.95	.268
With	506	1.07	133	1.13	373	1.05	
Catastrophic illness							
Without	42,532	89.96	9503	80.40	33,029	93.14	<.001
With	4748	10.04	2317	19.60	2431	6.86	
DM							
Without	41,643	88.08	10,420	88.16	31,223	88.05	.387
With	5637	11.92	1400	11.84	4237	11.95	
HT							
Without	40,771	86.23	10,625	89.89	30,146	85.01	<.001
With	6509	13.77	1195	10.11	5314	14.99	
Hyperlipidemia							
Without	45,935	97.16	11,669	98.72	34,266	96.63	<.001
With	1345	2.84	151	1.28	1194	3.37	
Obesity							
Without	47,270	99.98	11,818	99.98	35,452	99.98	.526
With	10	0.02	2	0.02	8	0.02	
CAD							
Without	43,625	92.27	11,096	93.87	32,529	91.73	<.001
With	3655	7.73	724	6.13	2931	8.27	
COPD							
Without	42,917	90.77	11,080	93.74	31,837	89.78	<.001
With	4363	9.23	740	6.26	3623	10.22	
Hematuria							
Without	47,069	99.55	11,773	99.60	35,296	99.54	.201
With	211	0.45	47	0.40	164	0.46	
Outpatient location							
Northern Taiwan	18,737	39.63	4694	39.71	14,043	39.60	.002
Middle Taiwan	12,691	26.84	3204	27.11	9487	26.75	
Southern Taiwan	12,736	26.94	3146	26.62	9590	27.04	
Eastern Taiwan	2865	6.06	740	6.26	2125	5.99	
Outlying islands	251	0.53	36	0.30	215	0.61	
Urbanization level							
1 (highest)	16,456	34.81	4495	38.03	11,961	33.73	<.001
2	19,945	42.18	5235	44.29	14,710	41.48	
3	3370	7.13	608	5.14	2762	7.79	
4 (lowest)	7509	15.88	1482	12.54	6027	17.00	
Follow-up in the Department of Nephrology							
Without	30,339	64.17	2775	23.48	27,564	77.73	<.001
With	16,941	35.83	9045	76.52	7896	22.27	
Insured premium (NT$)							
<18,000	40,730	86.15	10,610	89.76	30,120	84.94	<.001
18,000 to 34,999	5240	11.08	990	8.38	4250	11.99	
≥35,000	1310	2.77	220	1.86	1090	3.07	

P-value (categorical variable: chi-square/Fisher exact test; continuous variable: *t*-test).

CAD = coronary artery disease, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus.

262.98 per 100,000 person-years in the ESRD group, while it was only 189.34 per 100,000 person-years in the non-ESRD group. In our study cohort, the HD group had an incidence of 271.74 per 100,000 person-years (aHR = 1.225, $P = .001$), whereas the PD group had an incidence of 253.49 per 100,000 person-years (aHR = 1.149, $P = .008$). The HD group had a slightly higher incidence of UC/RCC than the PD group did (Table 5).

The mean follow-up duration was 9.18 ± 4.69 years (range, 0.01–13.99) for all patients. The average duration to UC/RCC occurrence after patient enrollment was 5.24 ± 4.05 years (range, 0.1–13.74). In the ESRD group, the average duration to

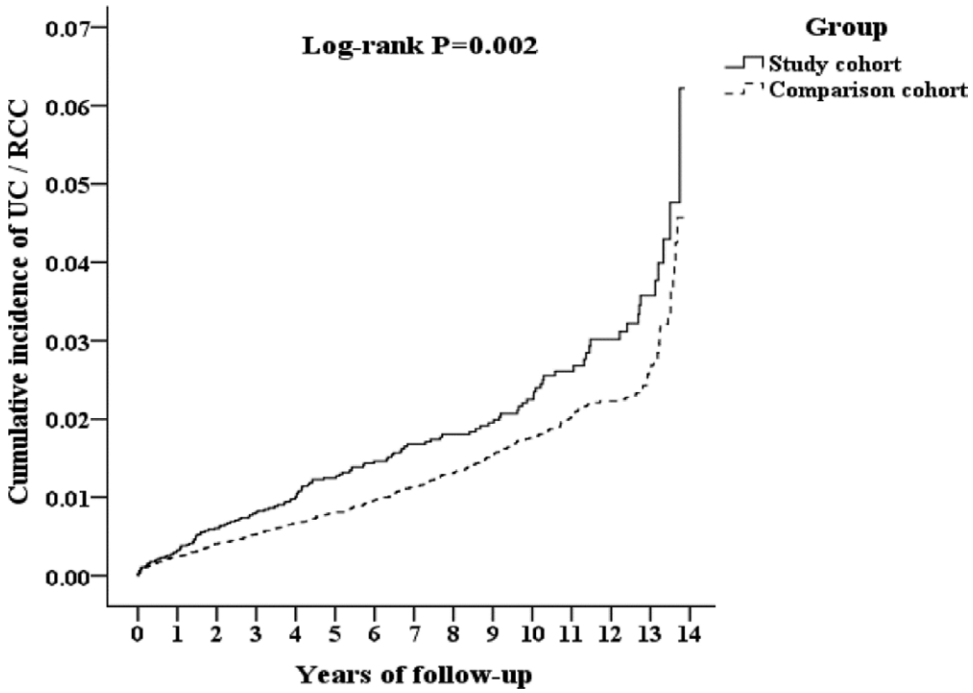

Figure 2. Kaplan–Meier analysis of the cumulative incidence of UC/RCC among patients aged ≥ 20 years stratified by group using the log-rank test. RCC = renal cell carcinoma, UC = urothelial carcinoma.

UC/RCC occurrence was 4.18 ± 4.06 years (range, 0.1–13.74); in the non-ESRD group, the average duration to UC/RCC occurrence was 5.39 ± 4.04 years (range, 0.14–13.68) (Table S2-1 and S2-2, Supplemental Digital Content, https://links.lww.com/MD/O922).

4. Discussion

Patients with ESRD undergoing dialysis are widely known to have an increased risk of cancer and cancer-related mortality compared with the general population. Although various types of cancers have been observed in different regions, most studies have demonstrated higher urological cancer incidence, including UC/RCC.[3,5,6,12] Our population-based cohort study, with a mean follow-up of 9.18 years, found that patients with ESRD undergoing chronic dialysis had a higher risk (aHR = 1.186) of developing UC/RCC than those without ESRD. Moreover, the mean duration to UC/RCC occurrence in the ESRD group was shorter than that in the non-ESRD group (4.18 ± 4.06 years vs 5.39 ± 4.04 years). Over the tracking period of 8 years, the incidence of UC/RCC differed significantly between the 2 groups ($P = .05$).

In our subgroup analysis, the ESRD group had a significantly higher incidence of malignant bladder neoplasms, malignant neoplasms of the renal pelvis, and other malignant neoplasms than the non-ESRD group did. Higher incidence trends were observed in the ESRD groups with malignant neoplasms in the kidneys and ureters, but the p-values were not considered significant.

Previous studies[13–16] have reported inconsistent findings regarding the cancer risk between patients undergoing HD and PD. In our study, patients with ESRD who underwent HD or PD were at a higher risk of developing urological cancer than those in the non-ESRD group; however, no significant difference was observed between the HD and PD groups. Furthermore, the mean durations to the development of urological cancer were 4.11 ± 3.97 years in the HD group and 4.39 ± 4.20 years in the PD group.

In both groups, the incidence rate of UC/RCC was proportional to age; however, this increased excess risk declined with increasing age up to 70 years. Compared with the control group, the risk of UC/RCC in the ESRD group gradually decreased with age: 30 to 39 years: aHR = 0.553 (74.43 vs 32.94, $P = .527$), 40 to 49 years: aHR = 2.105 (164.13 vs 57.08, $P = .007$), 50 to 59 years: aHR = 1.498 (276.58 vs 131.90, $P = .014$), 60 to 69 years: aHR = 1.371 (450.94 vs 228.46, $P = .022$), and ≥ 70 years: aHR = 0.925 (256.85 vs 234.86, $P = .587$). Patients with ESRD aged 40 to 70 years had a significantly higher incidence of developing malignancies than controls.

In our study, the highest risk of developing UC/RCC in the ESRD group was observed in patients aged 60 to 69 years (450.94/100,000 person-years). In patients with ESRD aged ≥ 70 years, the incidence rate dropped (256.85/100,000 person-years), and the aHR decreased further (aHR = 0.925) compared to the non-ESRD group, although this difference was not significant ($P = .587$). A potential reason for this decline could be the higher mortality rate of older patients. The presence of ESRD and comorbidities in older individuals undergoing dialysis may result in death from other causes such as cardiovascular and infectious diseases, which are the leading causes of death in patients undergoing dialysis.[9,17,18] The higher death rate in the ESRD group aged ≥ 70 years can be attributed to death as a competing risk. In this age group, patients with ESRD were far more likely to die than to develop cancer as they grew older.[19] Other studies have reported similar findings.[20–23] These results indicate that cancer evaluation and prevention efforts should focus on younger patients.

A French study[24] demonstrated that the risk of developing cancer in the Poitou-Charentes region was higher among patients undergoing dialysis without DM than among those with DM. The authors proposed that common pro-tumor factors (chronic inflammation, DNA mutations, etc) contribute to this association, but without additive effects in patients with DM, who may benefit from closer medical follow-up and the potential protective role of metformin.[25–27] In contrast, our study revealed that the risk of developing UC/RCC was lower in patients undergoing dialysis with DM, HT, hyperlipidemia,

Table 2

Factors associated with UC/RCC development based on Cox regression analysis.

Variables	Crude HR	95% CI	95% CI	*P*	Adjusted HR	95% CI	95% CI	*P*
Group								
Comparison cohort	Reference				Reference			
Study cohort	1.372	1.126	1.672	.002	1.186	1.071	1.448	.005
Gender								
Male	1.450	1.215	1.730	<.001	1.424	1.192	1.702	<.001
Female	Reference				Reference			
Age group (yr)								
20 to 29	0.000	–	–	.879	0.000	–	–	.908
30 to 39	0.189	0.089	0.399	<.001	0.181	0.085	0.386	<.001
40 to 49	0.356	0.228	0.563	<.001	0.291	0.184	0.459	<.001
50 to 59	0.689	0.518	0.916	.010	0.568	0.426	0.758	<.001
60 to 69	1.144	0.923	1.418	.220	0.983	0.791	1.221	.875
≥70	Reference				Reference			
Low income								
Without	Reference				Reference			
With	0.784	0.406	1.516	.470	1.341	0.688	2.615	.389
Catastrophic illness								
Without	Reference				Reference			
With	4.030	3.385	4.797	<.001	3.440	2.866	4.128	<.001
Tumor stage								
0	Reference				Reference			
1	1.265	1.001	1.745	.040	1.102	1.003	1.643	.033
2	1.644	1.254	2.568	.001	1.550	1.065	2.012	<.001
3	5.469	0.454	9.898	.897	4.565	0.469	8.804	.798
DM								
Without	Reference				Reference			
With	0.713	0.559	0.909	.006	0.705	0.550	0.903	.006
HT								
Without	Reference				Reference			
With	0.693	0.554	0.867	.001	0.762	0.605	0.960	.021
Hyperlipidemia								
Without	Reference				Reference			
With	0.131	0.033	0.524	.004	0.205	0.051	0.927	.026
Obesity								
Without	Reference				Reference			
With	0.000	–	–	.760	0.000	–	–	.981
CAD								
Without	Reference				Reference			
With	0.493	0.337	0.721	<.001	0.578	0.393	0.848	.005
COPD								
Without	Reference				Reference			
With	0.385	0.276	0.539	<.001	0.318	0.227	0.446	<.001
Hematuria								
Without	Reference				Reference			
With	7.270	4.596	11.496	<.001	6.928	4.369	10.985	<.001
Location								
Northern Taiwan	Reference				Multicollinearity with urbanization level			
Middle Taiwan	0.830	0.663	1.039	.104	Multicollinearity with urbanization level			
Southern Taiwan	1.106	0.890	1.365	.347	Multicollinearity with urbanization level			
Eastern Taiwan	0.837	0.573	1.222	.357	Multicollinearity with urbanization level			
Outlying islands	0.503	0.071	3.589	.493	Multicollinearity with urbanization level			
Urbanization level								
1 (Highest)	2.013	1.488	2.724	<.001	1.807	1.334	2.447	<.001
2	1.862	1.391	2.492	<.001	1.766	1.319	2.365	<.001
3	0.902	0.535	1.519	.698	0.946	0.561	1.595	.836
4 (Lowest)	Reference				Reference			
Follow-up in the Department of Nephrology								
Without	Reference				Reference			
With	2.055	1.721	2.453	<.001	1.316	1.092	1.586	.004

Adjusted HR = adjusted hazard ratio: adjusted for the variables listed in table.

CAD = coronary artery disease, CI = = confidence interval, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, HR = hazard ratio, HT = hypertension, RCC = renal cell carcinoma, UC = urothelial carcinoma.

CAD, and COPD than in those without. These results are consistent with those of a similar study conducted in Taiwan.[15] Furthermore, recent studies have reported the potential anti-inflammatory and anticancer effects of statins,[28] steroids,[29] and antihypertensive agents.[30] However, well-designed clinical trials are needed to validate these findings.

In the general population, the American Urological Association guidelines recommend different evaluation strategies for patients with asymptomatic microscopic hematuria, based on risk factors.[31] In patients undergoing dialysis, hematuria is a significant risk factor for UC/RCC and warrants further evaluation, including cystoscopy and upper urinary tract

Table 3

Factors associated with UC/RCC development stratified by variables listed in the table using Cox regression analysis.

	Study cohort			Comparison cohort							
Variables	**Event**	**PYs**	**Rate (per 10^5 PYs)**	**Event**	**PYs**	**Rate (per 10^5 PYs)**	**Ratio**	**Adjusted HR**	**95% CI**	**95% CI**	***P***
Total	134	50,954.74	262.98	373	197,001.06	189.34	1.389	1.186	1.071	1.448	.005
Gender											
Male	75	24,390.60	307.50	137	98,666.65	138.85	2.215	1.412	1.053	1.895	.021
Female	59	26,564.14	222.10	236	98,334.41	240.00	0.925	0.979	0.741	1.294	.884
Age group (yr)											
20 to 29	0	673.32	0.00	0	1945.67	0.00	–	–	–	–	–
30 to 39	3	4030.64	74.43	4	12,141.97	32.94	2.259	0.553	0.088	3.468	.527
40 to 49	10	6092.76	164.13	10	17,517.79	57.08	2.875	2.105	1.030	5.336	.007
50 to 59	21	7592.62	276.58	35	26,535.04	131.90	2.097	1.498	1.060	2.610	.014
60 to 69	38	8426.85	450.94	76	33,266.60	228.46	1.974	1.371	1.019	2.044	.022
≥70	62	24,138.55	256.85	248	105,593.99	234.86	1.094	0.925	0.699	1.225	.587
Low income											
Without	4	49,454.59	8.09	5	188,454.12	2.65	3.049	1.171	0.957	1.434	.126
With	130	1500.15	8665.80	368	8546.94	4305.63	2.013	2.438	0.623	9.547	.201
Catastrophic illness											
Without	84	37,181.36	225.92	179	118,757.69	150.73	1.499	1.048	0.765	1.435	.576
With	50	13,773.38	363.02	194	78,243.37	247.94	1.464	1.248	1.059	1.625	.019
Tumor stage											
0	0	50,310.59	0.00	0	194,989.48	0.00	–	–	–	–	–
1	101	525.74	19,211.02	297	1725.56	17,211.80	1.116	1.184	1.010	1.295	.003
2	33	107.71	30,637.82	75	281.61	26,632.58	1.150	1.201	1.095	1.454	.014
3	0	10.70	0.00	1	4.41	22,675.74	0.000	0.000	–	–	.897
DM											
Without	118	42,160.87	279.88	312	156,815.78	198.96	1.407	1.204	1.071	1.491	.039
With	16	8793.87	181.94	61	40,185.28	151.80	1.199	1.098	0.627	1.921	.744
HT											
Without	107	40,329.81	265.31	305	147,276.91	207.09	1.281	1.126	0.901	1.408	.296
With	27	10,624.93	254.12	68	49,724.15	136.75	1.858	1.472	1.033	2.322	.036
Hyperlipidemia											
Without	133	49,773.77	267.21	372	191,016.88	194.75	1.372	1.179	1.065	1.441	.017
With	1	1180.97	84.68	1	5984.18	16.71	5.067	0.491	0.025	2.930	.899
Obesity											
Without	134	50,936.55	263.07	373	196,911.57	189.43	1.389	1.186	1.071	1.448	.005
With	0	18.19	0.00	0	89.49	0.00	–	–	–	–	–
CAD											
Without	126	46,488.18	271.04	353	175,361.89	201.30	1.346	1.172	1.045	1.440	.031
With	8	4466.56	179.11	20	21,639.17	92.42	1.938	1.683	0.707	4.007	.239
COPD											
Without	127	43,221.14	293.84	343	162,660.99	210.87	1.393	1.211	1.005	1.488	.046
With	7	7733.60	90.51	30	34,340.07	87.36	1.036	1.059	0.371	1.987	.722
Hematuria											
Without	131	50,687.08	258.45	357	195,969.06	182.17	1.419	1.210	1.078	1.482	.026
With	3	267.66	1120.82	16	1032.00	1550.39	0.723	0.416	0.109	1.587	.199
Urbanization level											
1 (highest)	47	15,255.82	308.08	132	58,250.20	226.61	1.360	1.096	0.781	1.537	.597
2	71	23,367.27	303.84	183	88,764.10	206.16	1.474	1.299	1.048	1.714	.007
3	3	3140.87	95.51	16	17,271.99	92.64	1.031	1.017	0.197	2.489	.582
4 (lowest)	13	9190.78	141.45	42	32,714.77	128.38	1.102	1.091	0.580	2.052	.787
Follow-up in the Department of Nephrology											
Without	59	33,235.47	177.52	236	149,516.54	157.84	1.125	1.027	0.770	1.369	.786
With	75	17,719.27	423.27	137	47,484.52	288.52	1.467	1.355	1.017	1.806	.035

Adjusted HR = adjusted hazard ratio: adjusted for the variables listed in Table 2.

CAD = coronary artery disease, CI = confidence interval, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, HT = hypertension, PYs = person-years, RCC = renal cell carcinoma, UC = urothelial carcinoma.

imaging studies, such as sonography or computed tomography. Our study also found that hematuria was a strong risk factor for developing UC/RCC among patients undergoing dialysis, with an aHR of 6.928 (95% CI: 4.369–10.985; $P < .001$). However, in the ESRD group that developed UC/RCC, only 3 of the 134 patients presented with hematuria. If the evaluation is delayed until hematuria develops, it will likely miss or delay the diagnosis in most cases of UC/RCC in patients undergoing chronic dialysis. Additionally, patients undergoing dialysis who reside in urbanized areas and are regularly followed up in outpatient departments are more likely to be diagnosed with UC/RCC, highlighting the importance of surveillance.

Currently, cancer screening is not routinely recommended for patients undergoing chronic dialysis because of their limited life expectancy and lack of cost-effectiveness, even with a higher incidence of malignancies in this population.[32,33] The global prevalence of ESRD is increasing, primarily because of the improved survival rates of patients with ESRD, better risk factor assessments, easier access to dialysis, and enhanced care programs.[34–36] Many studies have also demonstrated improved cumulative survival rates and extended life

Table 4

Factors associated with UC/RCC development stratified by subgroup using Cox regression analysis.

	Study cohort			Comparison cohort			Ratio	Adjusted HR	95% CI		95% CI	*P*
	Event	PYs	Rate (per 10^5 PYs)	Event	PYs	Rate (per 10^5 PYs)						
Total	134	50,954.74	262.98	373	197,001.06	189.34	1.389	1.186	1.071	1.448	.005	
Bladder malignant neoplasm	74	50,954.74	145.23	200	197,001.06	101.52	1.430	1.223	1.105	1.499	.001	
Kidney malignant neoplasm	30	50,954.74	58.88	96	197,001.06	48.73	1.208	1.032	0.986	1.335	.059	
Renal pelvis malignant neoplasm	12	50,954.74	23.55	27	197,001.06	13.71	1.718	1.468	1.321	1.780	<.001	
Ureter malignant neoplasm	8	50,954.74	15.70	24	197,001.06	12.18	1.289	1.100	0.999	1.356	.051	
Other urothelial malignant neoplasm	10	50,954.74	19.63	26	197,001.06	13.20	1.487	1.277	1.024	1.395	.013	

Adjusted HR = adjusted hazard ratio: adjusted for the variables listed in Table 2.

CI = confidence interval, PYs = person-years, RCC = renal cell carcinoma, UC = urothelial carcinoma.

Table 5

Factors associated with UC/RCC development stratified by subgroup using Cox regression analysis.

	Study cohort			Comparison cohort			Ratio	Adjusted HR	95% CI	95% CI	*P*
	Event	PYs	Rate (per 10^5 PYs)	Event	PYs	Rate (per 10^5 PYs)					
Total	134	50,954.74	262.98	373	197,001.06	189.34	1.389	1.186	1.071	1.448	.005
HD	72	26,496.32	271.74	373	197,001.06	189.34	1.435	1.225	1.124	1.501	.001
PD	62	24,458.42	253.49	373	197,001.06	189.34	1.339	1.149	1.039	1.396	.008

Adjusted HR = adjusted hazard ratio: adjusted for the variables listed in Table 2.

CI = confidence interval, HD = hemodialysis, PD = peritoneal dialysis, PYs = person-years, RCC = renal cell carcinoma, UC = urothelial carcinoma.

expectancies after dialysis initiation, especially in younger patients.[37,38] With longer life expectancy, patients are more likely to receive a renal transplant, which is associated with improved survival outcomes posttransplantation.[39,40] A more proactive surveillance strategy for urological malignancies in younger patients could facilitate earlier and less invasive interventions, help identify higher-risk patients prior to transplantation, and potentially enhance long-term outcomes. Malignancies of the urinary organs remain one of the most lethal cancers in patients undergoing dialysis.[4] Some clinicians recommend periodic screening only for transplantation candidates or for patients with a longer expected survival. Typically, initial screening is performed approximately 3 years after dialysis initiation and includes radiological studies conducted at intervals ranging from yearly to every 2 to 3 years. However, these guidelines are not evidence based.[10] Our study suggests that early surveillance may benefit these patients based on the evidence gathered.

The American Society of Nephrology (ASN) recommends against routine cancer screening in dialysis patients with limited life expectancy who are ineligible for kidney transplantation, advocating instead for a personalized strategy based on individual cancer risk and estimated survival.[11] For patients with longer expected lifespans (younger, fewer comorbidities, transplant candidates), we recommend less invasive screenings – such as kidney sonography, urinalysis, and urine cytology – at intervals of 1 to 3 years depending on risk (hypertension, obesity, smoking, occupational carcinogens, specific drugs or herbs, arsenic exposure, and racial/ethnic susceptibility).[41,42] CT scans and cystoscopy should be reserved for positive preliminary results to minimize unnecessary risks. Since early-stage RCC and bladder UC can be effectively treated with minimally invasive approaches, such as radiofrequency ablation for solitary small renal tumors[43] and transurethral resection of bladder tumors, early detection and intervention increase opportunities for renal transplantation, reduce advanced-stage tumor-related morbidity, and more importantly improve posttransplant outcomes.[44,45] The proposed screening approach may hold promise, but its effectiveness remains to be confirmed by prospective clinical trials before general recommendation.

4.1. Strengths and limitations

Our study has several strengths. First, the National Health Administration in Taiwan ensures accurate diagnosis and appropriate treatment by regularly reviewing patient charts. Treatment protocols were standardized, and diagnoses were thoroughly verified. Second, we employed a comprehensive nationwide longitudinal database spanning 14 years. The NHI system was established in Taiwan in 1995, which enabled us to conduct a longitudinal analysis of sequential events. Patients diagnosed with urological cancer before the index date were excluded to reduce the potential bias typical of cross-sectional studies. Third, the coverage rate in Taiwan is approximately 99%, allowing for a large sample size that ensures high statistical power. Due to the nature of the claims database, missing data for key clinical variables was minimal, as reimbursement regulations require complete diagnostic coding. Finally, a key strength of this study is the consistency of the findings after adjusting for confounders, suggesting that the results are both convincing and reliable.

However, this study has some limitations. First, it was based on retrospective statistical analysis of claims data. Although missingness in diagnostic and procedural data was minimal, information on laboratory results and certain lifestyle factors was not available, which remains a study limitation. Moreover, some traditional risk factors related to urological cancer, such as smoking, exposure to specific chemicals, family history of cancer, and genetic information, were not included in the database. The association between patient characteristics and clinical outcomes has not been comprehensively investigated. Second, this study was conducted in an ethnically homogeneous Asian population, which may limit the external validity and applicability of the findings to other racial or ethnic groups. Third, disease identification was based on diagnostic codes, which introduces the potential for misclassification bias due to variability in coding practices among physicians and institutions involved in health insurance claims in Taiwan.

5. Conclusion

Renal replacement therapy in patients undergoing chronic dialysis is associated with an elevated risk and earlier onset of urological malignancies. This risk is notably elevated in younger patients with fewer comorbidities, who also have longer life expectancy and greater transplant potential. A more proactive and risk-adapted urological cancer evaluation strategy following dialysis initiation may support earlier detection, timely intervention, and improved long-term clinical outcomes in this population.

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