Increased Risk of End-Stage Renal Disease in Patients With Renal Cell Carcinoma: A 12-Year Nationwide Follow-Up Study

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Abstract: The effect of renal cell carcinoma (RCC) on the risk for end-stage renal disease (ESRD) has not been confirmed. The present population-based study used the claims data from the Taiwan National Health Institutes from 1998 to 2010 to compare the risk for ESRD in patients with and without RCC.

The study cohort consisted of 2940 patients who had newly diagnosed with RCC but no history of ESRD; the control cohort consisted of 23,520 matched patients without RCC. Cox proportional hazard regressions were performed to compute ESRD risk after adjusting for possible confounding factors. Kaplan–Meier analysis and the log-rank test were also used to compare patients and controls.

A total of 119 patients in the RCC group (incidence rate: 119/2940; 4.05%) and 160 patients in the control group (incidence rate: 160/23,520; 0.68%) were diagnosed with ESRD during the follow-up period. After adjusting for potential confounders, the RCC group had an ESRD hazard ratio (HR) of 5.63 [95% confidence interval (CI): 4.37–7.24] relative to the control group. In addition, among patients with RCC, females (adjusted HR: 6.95, 95% CI: 4.82–10.1) had a higher risk for ESRD than males (adjusted HR: 4.79, 95% CI: 3.37–6.82). Finally, there were significant joint effects of chronic kidney disease and diabetes on increasing the risk of ESRD in patients with and without RCC (P < 0.01). The limitations of this study include the retrospective design and the inability to assess methods of treatment and measure the aggressiveness of RCC.

Our data indicates that RCC is an independent risk factor for ESRD, especially in females.

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Abbreviations: CIPR = catastrophic illness patient registry, CKD = chronic kidney disease, ESRD = end-stage renal disease, GFR = glomerular filtration rate, HR = hazard ratio, NHI = National Health Insurance, RCC = renal cell carcinoma.

INTRODUCTION

Previous studies have examined the association between renal cell carcinoma (RCC) and end-stage renal disease (ESRD).19,27 In particular, Maisonneuve et al19 reported that patients with ESRD have increased risk of cancer, but that the increased risk gradually declined with age. Stewart et al27 reported an elevated risk for renal parenchymal cancer in patients undergoing dialysis. However, Mandel and Kjellstrand20 concluded that RCC is an unusual cause of ESRD, occurring in only 0.1%–1% of patients treated by dialysis or transplantation. Epidemiological and clinical evidence has shown links between hypertension, diabetes, obesity, and metabolic syndrome with the onset and progression of chronic kidney disease (CKD).12 However, the complete nature of the association between CKD and RCC has not been thoroughly analyzed.

Patients with RCC may have a higher risk for CKD because of the presence of confounding factors, such as older age, diabetes, hypertension, smoking, and low preoperative glomerular filtration rate (GFR).13,14 In other words, these same risk factors and systemic comorbidities might predispose patients toward renal tumors and CKD.13,17 Additional factors include baseline demographics, genetic factors, environmental factors and habits, comorbid conditions, and preexisting abnormalities in the non-neoplastic kidney parenchyma. Recent reports have shown that RCC is a potential cause and outcome of decreased GFR. In particular, independent predictors of low preoperative GFR in patients with RCC include year of surgery, tumor size, Charlson–Romano index, and hypertension.10,23

The risks of new-onset or exacerbated CKD and development of ESRD after RCC might be linked. Thus, we used multivariable analysis to examine whether patients with RCC have increased risk for ESRD by retrospective use of claims data from the National Health Insurance (NHI) service of Taiwan.
METHODS

Dataset Sources
The Taiwan Bureau of the NHI established a single-payer National Insurance Program in 1995, a program that covers almost the entire population in Taiwan. The NHI Research Databases were derived from this program by the National Health Institutes. We used the inpatient database and the catastrophic illness patient registry (CIPR) for this retrospective cohort study. Nearly all patients with severe illnesses, including those with cancer and those undergoing dialysis, apply for catastrophic illness cards and are exempted from cost sharing. Thus, we validated the diagnosis of diseases through this dataset. These databases included medical claims and the information of each beneficiary from 1996 to 2010. The identification code of each beneficiary was encrypted to ensure privacy. This study was approved by the China Medical University Hospital Institutional Review Board in Taiwan.

Study Individuals
The patients included adults (≥25 y old) with newly diagnosed RCC, based on The International Classification of Diseases, 9th Revision-Clinical Modification (ICD-9-CM), 189.0, from 1998 to 2010. All cases were collected from the CIPR. The date of RCC diagnosis was defined as the index date. The patients were excluded if they were diagnosed with malignancies (ICD-9-CM, 140–188.9 and 189.1–208) or ESRD (ICD-9-CM, 585 from CIPR) before the index date. We used 1:8 matching to select control subjects in order to increase the statistical power of comparisons. Thus, for each case, 8 controls were randomly selected. The cases and controls were matched by age, gender, index year, and index month. All patients were followed from the index date to the date of ESRD diagnosis, to the end of 2010, or the date when they left this program.

Covariate Assessment
The variables in this study included sex, age (25–44, 45–64, and ≥65 y old at the index date), region of residence (northern, central, southern, and eastern Taiwan), occupation (white collar, blue collar, and other), monthly income (≤NT $15,840, NT $15,841–NT $20,100, and >NT $20,100), and presence of comorbidities. We used NT $15,840 as the lowest income level because it is the government-stipulated minimum wage for employees in Taiwan. The comorbidities included hypertension (ICD-9-CM, 401–405), diabetes mellitus (ICD-9-CM, 250), coronary heart disease (ICD-9-CM, 410–414 and 429), atrial fibrillation (ICD-9-CM, 427.3), heart failure (ICD-9-CM, 428), chronic kidney disease (ICD-9-CM, 585), chronic obstructive pulmonary disease (ICD-9-CM, 491), and hyperlipidemia (ICD-9-CM, 272).

TABLE 1. Distribution of Sociodemographic Factors and Comorbidity Between Cohorts With and Without RCC

| Variables                  | RCC       | Non-RCC   | P value |
|---------------------------|-----------|-----------|---------|
|                           | N = 2940  | N = 23,520|         |
| Age                       |           |           | 0.99    |
| 25–44                     | 2552      | 319       |         |
| 45–64                     | 10,352    | 1294      |         |
| ≥65                       | 10,616    | 1327      |         |
| Sex                       |           | 0.99      |         |
| Male                      | 14,480    | 1810      |         |
| Female                    | 9040      | 1130      |         |
| Geographic region         |           | <0.0001   |         |
| Northern                  | 9965      | 802       |         |
| Central                   | 4855      | 375       |         |
| Southern                  | 6496      | 1371      |         |
| Eastern                   | 2203      | 392       |         |
| Occupation                |           | 0.24      |         |
| White collar              | 11,251    | 1447      |         |
| Blue collar               | 9624      | 1188      |         |
| Others                    | 2631      | 304       |         |
| Monthly income, NTD       |           | <0.0001   |         |
| ≤15,840                   | 11,570    | 1494      |         |
| 15,841–20,100             | 1136      | 211       |         |
| >20,100                   | 10,814    | 1235      |         |
| Comorbidity               |           | <0.0001   |         |
| Diabetes                  | 576       | 1811      | <0.0001 |
| Hypertension              | 1164      | 3270      | <0.0001 |
| Coronary heart disease    | 294       | 1586      | <0.0001 |
| Atrial fibrillation       | 57        | 293       | 0.002   |
| Heart failure             | 96        | 454       | <0.0001 |
| Chronic kidney disease    | 53        | 108       | <0.0001 |
| Hyperlipidemia            | 182       | 854       | <0.0001 |

NTD = New Taiwan dollar, RCC = renal cell carcinoma.
429.2), atrial fibrillation (ICD-9-CM, 427.31), CKD (ICD-9-CM, 585), and hyperlipidemia (ICD-9-CM, 272). The comorbidities were defined by the presence of “at least three medical visits” before the index date, based on the inpatient database.

The Taiwan Society of Nephrology launched a nationwide CKD Preventive Project in 2004 and adopted the simplified Modification of Diet in Renal Disease equation to calculate the estimated GFR in late-2005. This provides a five-stage classification of CKD, based on criteria of the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative. The ICD-9 code 585 is consistent with the definition of CKD stages 1–5 and allows for comparisons of the prevalence and incidence of CKD in Taiwan and the United States.

We defined CKD based on the presence of 1 inpatient or 2 outpatient ICD-9 code 585 in the claims data, but without a catastrophic illness registration card for ESRD (which would indicate the need for renal replacement therapy).

Statistical Analysis
A chi-square test was used to assess sociodemographic differences “between the RCC and control cohorts.” The person-years of follow-up was estimated from the index date to the date of ESRD diagnosis, loss to follow-up, death, or the end of 2010. We estimated the overall cumulative incidence densities and calculated the incidence rate ratios (per 100,000 person-years) and 95% confidence intervals (CIs) with stratification by gender using the Poisson regression model. Kaplan–Meier analysis was used to plot the cumulative incidence for ESRD and the log-rank test was used to test the difference between the two cohorts. The hazard ratios (HRs) and 95% CIs for ESRD were measured using Cox proportional hazards regression. The interaction of RCC and CKD with ESRD was estimated. The trend test was employed Cox proportional hazards regression. All data analyses were conducted using the SAS (ver. 9.3) statistical package for Windows (SAS Institute, Cary, NC), and the significant level was set at 0.05 in a two-sided test.

RESULTS
Significant Demographic Differences of RCC and Control Cohorts
We included 2940 RCC and 23,519 control subjects in this retrospective cohort study (Table 1). Compared with the control cohort, more RCC group lived in the southern areas and had monthly income ≤20,100. In addition, the RCC group had more comorbidities than the control group, the most common of which were hypertension, diabetes, and coronary heart disease.

Positive Association of RCC and ESRD Risk
Table 2 compares the incidences and HRs of ESRD risk of the two cohorts. The mean follow-up duration was 2.8 years in the RCC group and 3.7 years in the control group (P = 0.0002, data not shown). The results of the multivariate analysis indicate a 5.63-fold increased risk of ESRD in the RCC group compared with the control group. Compared with the control cohort, more patients in the RCC cohort developed ESRD in all 3 age groups (crude HRs: 7.53–54.8). Among patients with RCC, the mean follow-up duration was 3.4 years for males and 3.2 years for females (P = 0.61, data not shown). Further stratified by sex, uniform association existed between RCC and ESRD risk (Figure 1; P < 0.0001). After adjusting for other factors, the association was stronger for females (HR: 7.06, 95% CI: 4.90–10.2) than for males (HR: 4.76, 95% CI: 3.34–6.78) (Table 2). In addition, for patients without comorbidities, the RCC group had a 5.5–7-fold increased risk of ESRD compared with the control group.

Synergistic Effects of RCC and Comorbidities on ESRD Risk
Next, we compared patients with and without RCC and evaluated the potential risk factors for prediction of ESRD (Table 3). Old age (≥65 y old), diabetes, and CKD were...
significantly associated with ESRD incidence in patients with and without RCC. In addition, female sex was a significant predictor of ESRD in the RCC group and hypertension was a significant predictor of ESRD in the non-RCC group. Finally, we examined the combined effects of RCC with age, CKD, and diabetes on the risk for ESRD (Table 4). Each of these factors increased the risk of ESRD in patients with and without RCC (*P < 0.0001 for all comparisons). Examination of the interaction of factors associated with ESRD indicated that there were significant synergistic interactions of CKD and RCC and of diabetes and RCC (interaction *P < 0.005 for both). In other words, the joint effects of CKD and RCC and of diabetes and RCC were significantly greater than the combined independent effects.

**DISCUSSION**

This study is the first large-scale study to examine the renal outcome in patients with RCC over a 12-year follow-up period. This study has three novel findings. First, we found that male and female patients with RCC in Taiwan had increased risk for ESRD. Second, females with RCC had higher risk for ESRD than males. Third, patients with RCC along with CKD or diabetes were more likely to have ESRD.

CKD is common in patients who have received therapy for RCC, because therapy often involves nephrectomy and administration of an antivascular endothelial growth factor.8 The loss of a functioning renal mass after nephrectomy induces compensatory renal growth. 24,25,28 Adaptive renal hypertrophy occurs immediately after nephrectomy and the subsequent decrease in GFR is transient and subclinical.4,11 However, some nephrectomy patients experience clinically evident ESRD. Information on ESRD after nephrectomy is limited. Our study provides some evidence of an increased incidence of CKD after nephrectomy because of RCC. This may be explained by volume depletion (from nausea/vomiting, diarrhea, overdiuresis, malignant ascites, or pleural effusions), sepsis, or cardiac involvement, which sensitize the kidney to nephrotoxins by induction of a prerenal state.22 Moreover, several reports indicated an association between RCC and other renal diseases, such as acute and chronic glomerulonephritis.22 Previous studies reported that

| TABLE 2. Comparisons of the Incidence Rate Ratios and Hazard Ratios of ESRD in Cohorts With and Without RCC |
| --- |
| | Non-RCC | RCC |
| Variables | Cases | PY | Rate | Cases | PY | Rate | Crude HRs (95% CI) | Multivariate-HRs (95% CI) |
| All | 160 | 101,611 | 1.57 | 119 | 9464 | 12.57 | 8.24 (6.50–10.5) *** | 5.63 (4.37–7.24) *** |
| Age | | | | | | | | |
| 25–44 | 1 | 1187 | 0.09 | 6 | 1192 | 5.03 | 54.8 (6.59–456) *** | 41.8 (4.57–383) ** |
| 45–64 | 53 | 46,063 | 1.15 | 42 | 4321 | 9.72 | 8.52 (5.68–12.8) *** | 4.05 (2.54–6.45) *** |
| ≥65 | 106 | 44,360 | 2.39 | 71 | 3951 | 17.97 | 7.53 (5.57–10.2) *** | 5.57 (4.07–7.64) *** |
| Sex | | | | | | | | |
| Male | 91 | 59,598 | 1.53 | 57 | 5545 | 10.28 | 6.74 (4.84–9.40) *** | 4.76 (3.34–6.78) *** |
| Female | 69 | 42,013 | 1.64 | 62 | 3919 | 15.82 | 9.58 (6.79–13.5) *** | 7.06 (4.90–10.2) *** |
| Comorbidity | | | | | | | | |
| Diabetes | | | | | | | | |
| No | 112 | 95,792 | 1.17 | 82 | 8033 | 10.21 | 8.80 (6.62–11.7) *** | 7.15 (5.27–9.70) *** |
| Yes | 48 | 5819 | 8.25 | 37 | 1431 | 25.85 | 3.14 (2.04–4.82) *** | 2.98 (1.90–4.68) *** |
| Hypertension | | | | | | | | |
| No | 104 | 90,875 | 1.14 | 65 | 6251 | 10.40 | 9.15 (6.71–12.5) *** | 6.77 (4.83–9.50) *** |
| Yes | 56 | 10,735 | 5.22 | 54 | 3213 | 16.81 | 3.26 (2.24–4.74) *** | 3.61 (2.45–5.32) *** |
| Coronary heart disease | | | | | | | | |
| No | 135 | 96,217 | 1.40 | 107 | 8691 | 12.31 | 8.83 (6.85–11.4) *** | 6.28 (4.79–8.23) *** |
| Yes | 25 | 5394 | 6.44 | 12 | 772 | 15.54 | 3.34 (1.67–6.65) *** | 2.49 (1.22–5.07) *** |
| Atrial fibrillation | | | | | | | | |
| No | 157 | 100,742 | 1.56 | 118 | 9348 | 12.62 | 8.09 (6.37–10.3) *** | 5.65 (4.38–7.29) *** |
| Yes | 3 | 869 | 3.45 | 1 | 116 | 8.62 | 2.49 (0.29–24.0) | 3.40 (0.17–67.3) |
| Heart failure | | | | | | | | |
| No | 1153 | 100,336 | 1.52 | 113 | 9244 | 12.22 | 8.04 (6.30–10.3) *** | 5.53 (4.26–7.17) *** |
| Yes | 7 | 1274 | 5.49 | 6 | 220 | 27.29 | 4.83 (1.62–14.4) *** | 3.79 (1.17–12.3) |
| Chronic kidney disease | | | | | | | | |
| No | 146 | 101,401 | 1.44 | 100 | 9343 | 10.70 | 7.53 (5.83–9.71) *** | 5.74 (4.39–7.51) *** |
| Yes | 14 | 210 | 6.68 | 19 | 121 | 157.36 | 2.60 (1.30–5.22) ** | 2.13 (0.94–4.81) |
| Hyperlipidemia | | | | | | | | |
| No | 143 | 98,908 | 1.45 | 109 | 8994 | 12.12 | 8.42 (6.56–10.8) *** | 5.87 (4.48–7.68) *** |
| Yes | 17 | 2703 | 6.29 | 10 | 470 | 21.30 | 3.33 (1.52–7.29) ** | 3.46 (1.53–7.79) ** |

CI = confidence interval, ESRD = end-stage renal disease, HR = hazard ratio, IRR = incidence rate ratio, PY = person-years, RCC = renal cell carcinoma.

*P < 0.05.
**P < 0.01.
***P < 0.0001.
membranous glomerulonephritis is the glomerular lesion most often associated with RCC.9,21 Other studies reported that minimal change nephropathy, immunoglobulin A glomerulonephritis, membranoproliferative glomerulonephritis, and rapidly progressive glomerulonephritis were rarely associated with RCC.1–3,5,9,15,18,21,26,30 In the present study, we found that RCC is associated with an increased risk for ESRD. This might be explained by the presence of the above factors in our patients with RCC.

We also found that females with RCC had higher risk for ESRD than males with RCC. In Western countries, females with RCC have better survival rates after radical and partial nephrectomy than males, although the reason for this survival advantage is unclear.29 Lee et al17 demonstrated that Korean females with RCC had significantly better survival rates than males. Korean females with RCC also had a lower proportion of clear cell histology and a higher proportion of chromophobe histology.17 Moreover, a study in China

| Variables | Crude HRs (95% CI) | Multivariate HRs (95% CI) | Interaction P value |
|-----------|-------------------|--------------------------|-------------------|
| RCC CKD*  | Case no./N         |                          | 0.002             |
| No        | No                | 146/23,412               | 1.00              |
| Yes       | No                | 100/2887                 | 7.47 (5.79–9.64)** |
|           | Yes               | 14/108                   | 47.6 (27.4–82.7)**|
|           | No                | 19/53                    | 112 (69.1–180)**  |
|           | Yes               | 112 (69.1–180)**         |                   |
| P for trend | <0.0001             | <0.0001                   | 0.0001            |
| RCC DM†   | Case no./N         |                          |                   |
| No        | No                | 112/21,709               | 1.00              |
| Yes       | No                | 82/2364                  | 8.78 (6.60–11.7)**|
|           | Yes               | 48/1811                  | 7.12 (5.07–10.0)**|
|           | No                | 37/576                   | 22.5 (15.5–32.7)**|
| P for trend | <0.0001              | <0.0001                   | 0.0001            |
| RCC Age ≥ 65‡ | Case no./N      |                          | 0.42             |
| No        | No                | 54/12,904                | 1.00              |
| Yes       | No                | 48/1613                  | 9.25 (6.26–13.6)**|
|           | Yes               | 106/10,616               | 2.52 (1.82–3.50)**|
|           | Yes               | 71/1327                  | 19.0 (13.3–27.1)**|

*Multivariate model, adjusted for sex, monthly income, and comorbidities (including diabetes, chronic kidney disease, hypertension, coronary heart disease, heart failure, and hyperlipidemia).
†Multivariate model, adjusted for age, sex, monthly income, and comorbidities (including diabetes, hypertension, coronary heart disease, heart failure, and hyperlipidemia).
‡Multivariate model, adjusted for age, sex, monthly income, and comorbidities (including chronic kidney disease, hypertension, coronary heart disease, heart failure, and hyperlipidemia).
indicated that females with RCC had lower stage and grade tumors than males. Thus, it is possible that females with RCC had higher risk for ESRD simply because they had a survival advantage over males with RCC.

Limited information is available concerning the prognostic effect of renal survival for patients with RCC. Our study shows that CKD, diabetes, and old age are statistically significant independent prognostic factors for poor renal outcome. Advanced age and diabetes are well-known risk factors for the progression of CKD. Thus, as expected, our multivariate analysis found that old age and diabetes are associated with ESRD in patients with RCC. After adjusting for these confounding variables, we found that the presence of CKD is also associated with higher risk for ESRD in patients with RCC. This has not been previously reported for patients with RCC.

The current study has several limitations. First, we used a retrospective cohort design by the analysis of existing claims data. The results of clinical tests, anthropometric and laboratory examinations, and health behavior of the patients were not available in the claims data. Thus, we were unable to examine the association of abnormal levels of laboratory markers, such as hemoglobin or albumin, with ESRD. However, the existing claims data enabled us to perform a natural history study on other comorbidities that may be associated with renal outcome. Second, we were unable to assess patients with RCC who received clinical diagnoses of RCC but were not given surgery. The operation techniques, such as open and laparoscopic surgery, and the status of adjuvant chemotherapy were not evaluated, and this might have affected the subsequent renal outcome following the diagnosis of RCC. Third, information on the aggressiveness of RCC was not available in the inpatient claims database. Thus, we were unable to measure whether the RCC aggressiveness is associated with ESRD. In addition, episodes of acute kidney injury during the follow-up period might have affected the accuracy of accumulated incidence in the study and control cohorts. However, the strength of this study is its use of a nationwide population-based sample that effectively enabled us to collect representative patients with ESRD. Further studies of this issue should be conducted with long-term follow-up in order to elucidate the mechanism of ESRD development in patients with RCC based on additional biological and clinical information.

In conclusion, RCC is an independent risk factor for ESRD, and the relationship between them is stronger in females than in males. The diagnosis and treatment of CKD after the diagnosis of RCC, as well as surveillance of renal function and adjustment of drug regimens that may impair renal function, brings together the nephrologist and a team of specialists who are all caring for this group of patients. We expect that such a multimodal approach will increase the survival rate and improve the quality of life of patients with RCC.

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