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Clinical-Kidney cancer

Diabetes and kidney cancer survival in patients undergoing nephrectomy: A Canadian multi-center, propensity score analysis

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ABSTRACT

Introduction: Diabetes has been associated with worse survival outcomes in various malignancies; however, there are conflicting data in kidney cancer. Determining whether diabetes is associated with survival in kidney cancer may help guide treatment in a comorbid patient population.

Methods: We used the Canadian Kidney Cancer information system database to identify patients undergoing partial or radical nephrectomy between 1989 and 2017 for localized renal cell carcinoma at 16 institutions across Canada. We derived inverse probability of treatment weights (IPTW) from a propensity score model based on various clinical, surgical, and pathological characteristics. We used Cox proportional hazard models to evaluate the association between diabetes and cancer-specific and overall survival, in the sample weighted by the IPTW.

Results: 4828 patients met inclusion criteria, of whom 948 (19.6%) were diabetic. Median follow-up in those without death was 26.6 months (interquartile range 9.7−53.8). Among the entire cohort, 901 deaths were from any cause, and 299 deaths from kidney cancer. Before propensity score methods, diabetics were older, more likely to have comorbidities and clear cell histopathology. After propensity score adjustment, all characteristics were balanced between groups (standardized difference <0.10). IPTW-adjusted Cox proportional hazard models demonstrated no significant association between diabetes and cancer-specific (hazard ratio 1.13, 95% confidence interval 0.78−1.62), or overall survival (hazard ratio 1.14, 95% confidence interval 0.94−1.38).

Conclusions: Our multi-centre study found that diabetes and nondiabetics have similar survival following nephrectomy for kidney cancer.

Keywords: Kidney neoplasms; Diabetes mellitus; Survival; Propensity score; Nephrectomy

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1. Introduction

In 2015, there were an estimated 425,000 incident cases of kidney cancer and 89,000 kidney cancer deaths worldwide [1]. Furthermore, it is estimated that the incidence of kidney cancer is increasing by approximately 2% per year [2]. This increasing incidence is thought to be partly due to an increased prevalence of obesity and hypertension, established risk factors for kidney cancer [3], and the increasing use of diagnostic imaging [4].

A diagnosis of kidney cancer often coexists alongside various comorbidities, and comorbidity burden has been shown to be associated with survival in kidney cancer [5]. Although diabetes status is often included as a component of the comorbidity burden assessment, this particular comorbidity been shown to be an independent predictor of reduced survival in various malignancies such as such as breast cancer [6] and colorectal cancer [7]. In other malignancies, such as lung [8] and prostate [9] cancer, diabetes has not been associated with survival. There are conflicting data in kidney cancer [10−15].

In addition to generally having a greater comorbidity burden, the diabetic state may contribute to worse survival among cancer patients because hyperinsulinemia and hyperglycemia can result in increased cell growth, metastasis, and chemoresistance [16−18]. Determining whether diabetes is associated with survival may help inform prognosis in a comorbid population and may optimize management by arranging closer follow-up or considering adjuvant treatments for these patients. Given that diabetes is increasing in incidence and prevalence worldwide [19], and has been shown to be associated with an increased risk of kidney cancer [20], understanding this association will be clinically relevant for this increasing proportion of kidney cancer patients. To address this topic, we performed a multi-center study to evaluate the association between diabetes and survival in patients undergoing partial or radical nephrectomy for clinically localized kidney cancer.

2. Patients and Methods

2.1. Patients and Data Sources

We conducted a multi-centre cohort study using the national Canadian Kidney Cancer information system (CKCis). This collaborative, multi-institutional kidney cancer database collects both retrospective and prospective data across 16 Canadian tertiary academic centers. CKCis was started in 2011. Patients diagnosed prior to 2011 were included through retrospective review of medical records. Patients diagnosed as of January 1, 2011 were prospectively accrued. All participating hospitals received review board approval prior to contributing to CKCis. This study was approved by the University Health Network Research Ethics Board.

We included patients undergoing radical or partial nephrectomy for unilateral, clinically nonmetastatic renal cell carcinoma between 1989 and 2017. Patients undergoing nephrectomy may have previously been managed with surveillance.

Clinical, surgical, and pathological characteristics, including diabetes status at the time of diagnosis were abstracted from the medical record.

2.2. Outcome Measures

The outcomes of interest were kidney cancer-specific survival (CSS) and overall survival (OS). Deaths occurring within 30 days of surgery were considered cancer-related mortality [21]. All survival times were measured from the date of nephrectomy.

2.3. Statistical Analysis

Baseline patient characteristics were compared between diabetics and nondiabetics using the Wilcoxon rank sum test for continuous variables and the chi-square test or Fisher's exact test for categorical variables.

We used propensity score methods to reduce confounding due to differences in the distributions of measured covariates between diabetics and nondiabetics. Propensity score methods allow for comparison of outcomes among groups of patients with balanced baseline characteristics, where only the exposure (in this case diabetes status) is different [22].

To estimate the propensity score, we modeled the distribution of diabetes status given the observed covariates using logistic regression. The covariates included in the model were patient characteristics (age, sex, history of hypertension, coronary artery disease, myocardial infarction, peripheral vascular disease, chronic obstructive pulmonary disease, congestive heart failure, cerebrovascular disease, chronic kidney disease, other previous cancer), surgical characteristics (year of nephrectomy, type of surgery [radical vs. partial]), and pathological characteristics (tumor stage, nodal stage, histology). We chose these variables a priori because of their potential impact on the outcomes of interest [23]. All covariates were modeled as categorical variables, except age, which was modeled using restricted cubic splines with 5 knots. Year of nephrectomy was dichotomized to 1989−2010 vs. 2011−2017, based on when CKCis became prospective.

After deriving the propensity scores, we calculated the inverse probability of treatment weights (IPTW) for all patients. IPTW uses weighting based on the propensity score to create a sample wherein the distribution of baseline covariates measured is independent of exposure group. To reduce the IPTW variance, the weights were stabilized by multiplying by the marginal probability of receiving the exposure that was actually received. To ensure that our propensity score methods had achieved the intended balance on measured characteristics [22], comparisons between the groups in the IPTW-weighted sample were made using standardized differences, with a threshold of greater than 10% implying a clinically meaningful difference [24].

We constructed IPTW-adjusted survival curves for each outcome, then calculated the relative and absolute rate differences of the survival estimates at 2 and 5 years. For CSS, patients were censored at noncancer death or at last follow-up. For OS, patients were censored at last follow-up. IPTW-weighted Cox proportional hazard models were then used to estimate the hazard of each outcome. This was done by regressing the hazard of the occurrence of the outcome on exposure status (diabetic vs. nondiabetic) in the IPTW-weighted sample. We used the cumulative score statistic to evaluate the Cox proportional hazards assumption, which was found to hold for all outcomes.

3. Results

3.1. Cohort Characteristics

We excluded patients (n=107) with a previous history of nephrectomy, missing pT or pN stage, histology inconsistent with renal cell carcinoma, history of von Hippel−Lindau, and incomplete follow-up information. Of the remaining 4,828 patients between 1989 and 2017 that met inclusion criteria, 948 (19.6%) were diabetic. Cohort characteristics are outlined in Table 1. Median follow-up in those without death was 26.6 months (interquartile range 9.7−53.8). In the full cohort, there were 901 deaths from any cause, and 299 deaths from kidney cancer. Before propensity score methods, diabetics were older, more likely to have a history of concomitant comorbidities, and more likely to have clear cell histology. Diabetes was more common in the contemporary (2011−2017) surgical cohort. After propensity score methods were applied, all characteristics were balanced between groups (standardized difference <10%), as outlined in Table 1.

3.2. Cancer-specific Survival

The IPTW-adjusted CSS curves are illustrated in Fig. 1. CSS at 2 years was 96% in both diabetics and nondiabetics. By 5 years postnephrectomy, CSS was 91% in diabetics and 92% in nondiabetics. When we compared diabetics to nondiabetics, relative and absolute risk differences in CSS were −0.1% and −0.1% at 2 years, and −1.2 % and −1.1% at 5 years, respectively. IPTW-adjusted Cox proportional hazard models also demonstrated no significant association between diabetes and cancer-specific survival (hazard ratio 1.13, 95% CI 0.78−1.62).

3.3. OS

The IPTW-adjusted OS curves are illustrated in Fig. 2. OS at 2 years was 90% in both diabetics and nondiabetics. By 5 years postnephrectomy, OS was 76% in diabetics and 78% in nondiabetics. When we compared diabetics to nondiabetics, the relative and absolute risk differences in OS were −0.2% and −0.2% at 2 years, and −2.8 and −2.1% at 5 years, respectively. IPTW-adjusted Cox proportional hazard models demonstrated no significant association between diabetes and OS (hazard ratio 1.14, 95% CI 0.94−1.38).

3.4. Posthoc Analyses

A sensitivity analysis adjusting for BMI (data available in 50% of patients) and a subgroup analysis based on cohort era (prospective vs. retrospective) demonstrated similar results to the primary analyses (results available on request).

4. Discussion

Diabetes is increasing in incidence and prevalence worldwide [19], and may itself be an independent risk factor for kidney cancer [20]. As such, the proportion of patients with these two conditions is expected to increase over time, a finding that was demonstrated in this study. In addition to the increasing incidence of diabetes, the increasing proportion of diabetics may be due to improved screening for the disease and documentation of comorbidities. It is therefore clinically relevant to understand whether diabetes is associated with kidney cancer survival outcomes to help determine the optimal treatment approach in this comorbid population. Our large, multi-center cohort study found that diabetes was not significantly associated with cancer-specific or overall survival in patients undergoing radical or partial nephrectomy for clinically localized kidney cancer, suggesting that diabetics, in this context, should be managed similarly to nondiabetics.

Diabetes has been associated with worse survival outcomes in various malignancies including breast and colorectal cancer [6,7]. However, in other malignancies, such as lung and prostate cancer [8,9], there has been no significant association between diabetes and survival outcomes, suggesting that the influence of diabetes on survival may vary depending on the type of malignancy. In kidney cancer, however, there are still conflicting data.

A meta-analysis published in 2013 evaluating the association between diabetes and kidney cancer survival included 8 cohort studies and found that diabetes was not significantly associated with CSS [10]. A subsequent meta-analysis published in 2015 included 18 cohort studies, evaluated multiple kidney cancer survival outcomes, and found that diabetes was associated with significantly worse recurrence-free survival, CSS, and OS [11]. However, there are some limitations to this meta-analysis that preclude interpretation of their results. For example, several of the included studies did not adjust for comorbidity burden, a factor that has been associated with survival among kidney cancer patients [5]; given that diabetics tend to have more comorbidities than nondiabetics, as demonstrated in this

Table 1
Baseline characteristics of 4,828 patients undergoing a nephrectomy for unilateral, sporadic, M0, renal cell carcinoma

Variable	Diabetics (*n*=948)	Nondiabetics (*n*=3,880)	*P* value (unadjusted comparison)	Sample weighted by IPTW standardized difference (%)
Patient characteristics				
Age at nephrectomy, years (median [IQR])	60 (17)	64 (13)	<0.0001	5.0
Sex (*n*[%])			0.51	1.0
Male	635 (67)	2555 (66)		
Female	313 (33)	1325 (34)		
Comorbidities (*n* [%])				
Hypertension	733 (77)	1693 (44)	<0.0001	1.7
Coronary artery disease	131 (14)	250 (6)	<0.0001	4.3
Myocardial infarction	82 (9)	135 (3)	<0.0001	2.1
Peripheral vascular disease	24 (3)	34 (1)	<0.0001	0.1
Chronic obstructive pulmonary disease	94 (10)	233 (6)	<0.0001	0.8
Congestive heart failure	16 (2)	39 (1)	0.08	0.8
Cerebrovascular disease	54 (6)	74 (2)	<0.0001	0.4
Chronic kidney disease	129 (14)	228 (6)	<0.0001	0.7
Prior malignancy	136 (14)	449 (12)	0.019	0.9
Surgical characteristics				
Year of surgery (*n*[%])			0.014	1.9
1989−2010	197 (17)	954 (83)		
2011−2017	751 (20)	2926 (80)		
Type of surgery (*n*[%])			0.94	2.3
Partial nephrectomy	459 (48)	1873 (48)		
Radical nephrectomy	489 (52)	2007 (52)		
Pathological characteristics				
Pathological tumor stage (*n* [%])			0.15	2.2
pT1	604 (64)	2472 (64)		
pT2	76 (8)	396 (10)		
pT3	261 (28)	981 (25)		
pT4	7 (1)	31 (1)		
Pathological nodal stage (*n* [%])			0.36	0.7
pNX/0	926 (98)	3769 (97)		
pN+	22 (2)	111 (3)		
Disease histology (*n* [%])			0.007	3.6
Chromophobe renal cell carcinoma	45 (5)	312 (8)		
Papillary renal cell carcinoma	129 (14)	600 (15)		
Clear cell renal cell carcinoma	745 (79)	2826 (73)		
Other renal cell carcinoma	29 (3)	142 (4)		

IPTW: inverse probability of treatment weights.

study, failure to account for this factor would bias risk estimates towards reduced survival among diabetics. Furthermore, although this meta-analysis appropriately used random-effects models for CSS and OS, they did not include prediction intervals. Prediction intervals are important in random-effects models to account for potential between-study heterogeneity [25], as is common in meta-analyses due to differences in patient demographics, follow-up, and other factors. Finally, not every study that met inclusion criteria was included in the pooled estimate, and since the publication of this meta-analysis, additional studies have been published that found no association between diabetes and kidney cancer survival [12,13].

While our study found no survival differences among diabetics and nondiabetics undergoing nephrectomy, our study found that kidney cancer patients with diabetes were more likely to have clear cell carcinoma, an aggressive subtype of kidney cancer [26]. This finding has been previously demonstrated [12]. Although these data are yet to be confirmed in other series, evaluating the association between diabetes and kidney cancer survival outcomes may demonstrate a biased risk estimate of reduced survival in diabetics if histology is not accounted for. Indeed, several studies which demonstrated that diabetes is an independent adverse survival prognostic factor did not adjust for histology [14,15].

There are several potential explanations for the lack of survival difference among diabetics and nondiabetics with kidney cancer. As mentioned above, previous studies that found a survival difference did not adjust for comorbidity burden or histology. As these negative prognostic factors may be more common among diabetics, adjusting for them, as was done in our study, may extinguish the association between diabetes and kidney cancer survival that has been observed by others. Another potential explanation for the lack of survival difference found in our study is the inability

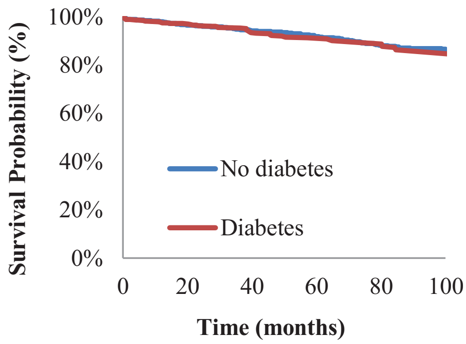

Fig. 1. IPTW-adjusted survival curves comparing CSS among diabetics and nondiabetics.

to account for medication use as this information is also not captured in the database. Metformin is a commonly prescribed medication among diabetics that has recently gained interest in the oncology community for its putative antineoplastic properties. Therefore, if metformin were to confer a survival advantage in kidney cancer, the direction bias in this study would be towards improved survival in diabetics since only they would be exposed to the medication. However, studies demonstrating an association between metformin and improved survival in kidney cancer [27−29] have been prone to several important limitations [30] and it is difficult to interpret their findings. Conversely, other studies have shown no protective benefit of metformin in kidney cancer [31,32], including a recent population-based study that evaluated cumulative use metformin [33]. As such, it remains unclear how accounting for medication use would influence the results of this study.

Given that our study did not find survival differences among diabetics and nondiabetics, the clinical implication of this is that diabetes status should not influence management in patients undergoing nephrectomy. This is an important notion as a previous population-based study from the Netherlands found that diabetics were treated less aggressively for various malignancies, even after adjusting for age, stage, and gender [34]. In kidney cancer, however, this same study found that diabetics were just as likely as nondiabetics to undergo surgery. The results of our study support the role of surgery in diabetic patients with kidney cancer.

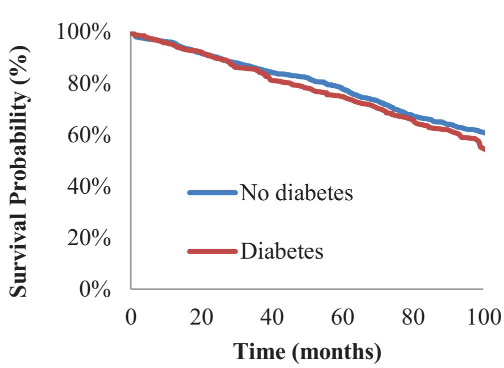

Fig. 2. IPTW-adjusted survival curves comparing OS among diabetics and nondiabetics.

Our study is strengthened by its multi-center design, thereby increasing sample size and reducing selection bias. Furthermore, treatment heterogeneity across centers is reduced to some extent as the Canadian healthcare system provides universal access to care. Nonetheless, the findings of our study is limited to Canadian patients that were treated at tertiary academic centers. Our results are also strengthened by our ability to control for various patient, surgical, and pathological factors. Controlling for these factors, particularly comorbidity burden and histology for the reasons outlined above, is important to understand the independent association of diabetes with kidney cancer survival outcomes. Finally, we used propensity score methods to further reduce confounding and compare groups that were balanced on measured baseline characteristics.

Our study also has limitations. First, our study could not control for diabetes severity as this information, such as serum HbA1c levels, is not captured in the CKCis database. However, a previous study adjusting for a surrogate of diabetes severity (requiring the use of antidiabetic medication) found no association between diabetes severity and kidney cancer survival [12]. Similarly, we could not control for triglyceride levels, which may be associated with kidney cancer survival [35]. Second, we did not have information on the possibility of diabetes being diagnosed during follow-up among the nondiabetic cohort. To the best of our knowledge, no study to date on this topic has been able to account for change in diabetes status during follow-up. Third, the findings of our study only apply to patients undergoing nephrectomy and further studies are needed to determine whether diabetes influences progression on surveillance for small renal masses. We also did not have information of recurrence-free survival, an outcome which may help determine different surveillance strategies following nephrectomy. Fourth, we balanced groups on the individual comorbidities as we did not have sufficient information to use a validated indicator for comorbidity, such as the Charlson Comorbidity Index [5]. Finally, there was limited follow-up in our study and additional studies may help determine the potential long-term influence of diabetes on kidney cancer survival.

Despite these limitations, our large multi-center study found that diabetics undergoing nephrectomy have similar survival outcomes compared to nondiabetics. This information can be used to counsel patients and avoid undertreatment in diabetics.

5. Conclusion

This large multi-center cohort found that diabetes and nondiabetics have similar survival following nephrectomy for kidney cancer.

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