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Risk of Hospital Encounters With Kidney Stones in Autosomal Dominant Polycystic Kidney Disease: A Cohort Study

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Abstract

Background: There is a perception that patients with autosomal dominant polycystic kidney disease (ADPKD) are more likely to develop kidney stones than the general population.
Objective: To compare the rate of hospital encounter with kidney stones and the rate of stone interventions between patients with and without ADPKD.
Design: Retrospective cohort study.
Setting: Ontario, Canada.
Patients: Patients with and without ADPKD who had a prior hospital encounter between 2002 and 2016.
Measurements: Rate of hospital encounter with kidney stones and rate of stone intervention.
Methods: We used inverse probability exposure weighting based on propensity scores to balance baseline indicators of health between patients with and without ADPKD. We followed each patient until death, emigration, outcomes, or March 31, 2017. We used a Cox proportional hazards model to compare event rates between the two groups.
Results: Patients with ADPKD were at higher risk of hospital encounter with stones compared with patients without ADPKD (81 patients of 2094 with ADPKD [3.8%] vs 60 patients of 1902 without ADPKD [3.2%]; 8.9 vs 5.1 events per 1000 person-years; hazard ratio 1.6 [95% CI, 1.3-2.1]). ADPKD was not associated with a higher risk of stone intervention (49 of 2094 [2.3%] vs 47 of 1902 [2.4%]; 5.3 vs 3.9 events per 1000 person-years; hazard ratio 1.2 [95% CI = 0.9-1.3]).
Limitations: We did not have information on kidney stone events outside of the hospital. There is a possibility of residual confounding.
Conclusion: ADPKD was a significant risk factor for hospital encounters with kidney stones.

Abrégé

Contexte: Il existe une perception selon laquelle les patients atteints de polykystose rénale autosomique dominante (ADPKD) seraient plus susceptibles de développer des calculs rénaux que la population générale.
Objectif: Comparer les taux d'hospitalisations et d'interventions pour calculs rénaux entre des patients atteints ou non d'ADPKD.
Type d'étude: Étude de cohorte rétrospective.
Cadre: Ontario, Canada.
Sujets: Des patients atteints ou non d'ADPKD qui avaient déjà été hospitalisés entre 2002 et 2016.
Mesures: Les taux d'hospitalisations et d'interventions pour calculs rénaux.
Méthodologie: Nous avons utilisé une pondération d'exposition à probabilité inverse fondée sur les scores de propension afin d'équilibrer les indicateurs de santé de base entre les patients atteints ou non d'ADPKD. Nous avons suivi chaque patient jusqu'à son décès, jusqu'à son émigration, jusqu'au résultat ou jusqu'au 31 mars 2017. Nous avons utilisé un modèle de risques proportionnels de Cox pour comparer les taux d'événements entre les deux groupes.
Résultats: Les patients atteints d'ADPKD présentaient un risque plus élevé d'être hospitalisés pour calculs rénaux que les patients non atteints d'ADPKD (81 patients sur 2094 atteints d'ADPKD [3,8 %] contre 60 patients sur 1902 sans ADPKD [3,2 %]; 8,9 contre 5,1 événements pour 1 000 années-personnes; risque relatif: 1,6 [IC 95 %: 1,3 à 2,1]). L'ADPKD n'a pas été associée à un risque plus élevé d'interventions pour retirer des calculs rénaux (49 patients sur 2094 atteints d'ADPKD

[2,3 %] contre 47 patients sur 1902 sans ADPKD [2,4 %]; 5,3 contre 3,9 événements pour 1 000 années-personnes; risque relatif: 1,2 [IC 95 %: 0,9 à 1,3]).
Limites: Nous n'avions pas d'information sur les événements liés aux calculs rénaux à l'extérieur de l'hôpital. Il existe une possibilité de facteurs de confusion résiduels.
Conclusion: L'ADPKD s'est avéré un facteur de risque important d'être hospitalisé pour des calculs rénaux.

Keywords
administrative data, autosomal dominant polycystic kidney disease, epidemiology, kidney stones, population health research

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What was known before

The prevalence of kidney stones and stone interventions in patients with ADPKD remains unclear.

What this adds

ADPKD is associated with an increased rate of hospital encounter with kidney stone, and urologist are not more or less aggressively managing stones in patients with ADPKD than in patients without ADPKD with otherwise similar baseline health.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most commonly inherited kidney disease and is characterized by focal cyst development.[1] In ADPKD, cysts develop in the kidney that increase in size and number over time.[2] This causes structural deformation of the kidney, which, along with metabolic abnormalities, is believed to predispose patients with ADPKD to kidney stones.[3] Specifically, the structural damage to the kidney results in more urinary stasis, which favors urinary crystals to form and stagnate.[4,5] Prior cross-sectional studies suggest kidney stones are more prevalent in patients with ADPKD compared with unaffected family members. However, none of the between-group comparisons in prior studies were statistically different.[6-11] Additionally, no prior study adjusted for important covariates, or longitudinally compared the risk of stones in patients with ADPKD to patients without ADPKD.[6-11] Finally, most inferences about the difference in stone risk in patients with ADPKD were indirect comparisons with the general population.

Kidney stones in patients with ADPKD are associated with significant pain and morbidity.[12] In the chronic kidney disease population, patients with stones are at higher risk of end-stage kidney disease compared with patients without stones, with the suggestion that this is also true in patients with ADPKD.[13,14] For these reasons, stones should be optimally managed in patients with ADPKD. However, the structural kidney deformation in ADPKD may make optimal stone management challenging. There is limited evidence on how stones are currently managed in patients with ADPKD, and we are unsure how frequently patients with ADPKD receive stone interventions such as shockwave lithotripsy (SWL), ureteroscopy, and percutaneous nephrolithotomy (PCNL).

In this study, we used large health care databases to describe the rate of hospital encounters (emergency department visits or hospital admissions) with kidney stones in patients with ADPKD, and the rate and type of kidney stone interventions. To put these rates into context, we studied a group of patients without ADPKD. We also assessed whether risk factors for hospital encounters with kidney stones and kidney stone interventions were similar in patients with and without ADPKD.

Subjects/Patients and Methods

Design and Setting

We conducted a retrospective cohort study using Ontario's health care administrative databases held at ICES (a not-for-profit research institute). Health care services in Ontario are funded through the Ontario Health Insurance Plan (OHIP) program; with the exception of outpatient medications, which are only funded for segments of the population including

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those 65 years and older. These health care encounters are recorded in administrative databases, which are linked using unique encoded identifiers and held at ICES. We reported this study following guidelines for observational studies conducted using routinely collected data (Supplementary Table S1).[15,16]

Data Sources

We linked 7 databases to create the study cohort, describe baseline characteristics, and ascertain outcomes. The Canadian Institute for Health Information Discharge Abstract Database, Same Day Surgery, and the National Ambulatory Care Reporting System (NACRS) databases contain diagnostic and clinical information on hospital admissions, same day surgery, and all emergency department visits in Ontario, respectively. The OHIP database captures physician-billing claims for all hospital and outpatient services for patients covered in Ontario. The Registered Persons Database (RPDB) includes reliable demographic information and vital statistics. The ICES Physician Database contains physician demographic and practice information. The Canadian Organ Replacement Register (CORR) contains information on all patients receiving chronic dialysis and kidney transplants. All variables were complete in this study except for average neighborhood income and urban or rural residency.

Population and Timeline

Our study cohort included Ontarians with ADPKD who were identified using diagnosis codes from emergency department visits and hospitalizations between April 1, 2002 and March 1, 2016. The set of codes used to identify ADPKD were validated elsewhere.[17] We excluded the following patients: 1) patients aged 18 years and below to exclude those with autosomal recessive polycystic kidney disease who may have been misclassified as ADPKD; 2) patients with missing demographic or linkage data, or those who died on or before the cohort entry date for data cleaning reasons; 3) non-Ontario residents who received care from a health care facility in Ontario; 4) patients with a history of end-stage kidney disease, as many have no urine output making the presence of kidney stones less relevant. Patients with prior kidney stones and treatments for kidney stones were eligible for study participation; this was treated as an important baseline characteristic that was included in the propensity score model and was also considered in subgroup analysis. We selected the first hospital encounter during the accrual period for patients with more than one hospital encounter.

Our non-ADPKD control population included patients with at least one hospital admission or emergency department visit for any reason between April 1, 2002, and March 1, 2016, who were not in the ADPKD cohort. For all patients with more than one hospital encounter, we selected the first encounter. We applied the same exclusion criteria as we did for the ADPKD cohort. In addition, we excluded patients with administrative codes for other cystic diseases and congenital anomalies of the urinary system, as these codes can occasionally capture patients with ADPKD. We then randomly selected 50,000 controls (vs the entire Ontario population with hospital encounter) for computational efficiency.

The date of discharge for patients identified with hospital admission records and the date of registration for patients identified from the emergency department records served as the date of cohort entry. We followed each patient until March 31, 2017, and censored the observational period at time of death or emigration from the province (defined as no evidence of any health care encounter in the province over a 3-year period).

Outcome

The two outcomes were (a) time to first hospital encounter with kidney stone; and (b) time to first stone intervention, which was a composite outcome of SWL, ureteroscopy, and PCNL. The administrative codes used to identify outcomes are detailed in Supplementary Table S2. In a validation study, codes similar to the ones we used to identify stones had a positive predictive value of 96% compared with chart review.[18,19] We identified stone intervention events using physician billing codes. We expect these codes to have excellent validity similar to other fee for service codes.[20] Any stone-related database codes that appeared within 90 days of each other were considered the same event. For stone intervention, we did not restrict to individuals with a hospital encounter with kidney stone, because we wanted to capture stone interventions in both the inpatient and outpatient settings.

Analysis

We used inverse probability exposure weighting based on propensity scores to ensure similar distribution of indicators for baseline health between patients with and without ADPKD.[21] We calculated propensity scores using logistic regression with ADPKD as the dependent variable, and 20 covariates detailed in Supplementary Table S3 as independent variables. Upon review, we truncated the extreme weights to ensure that the weights were stable and the extreme weights were not driving the results. We assigned every control with weights greater than 99th percentile as the 99th percentile weight, and every control with weights less than the first percentile as the first percentile weight. The results of truncated weights are presented in this article while the non-truncated weights results are presented as Supplementary Tables S4 to S7 and Figure S1.

We described baseline characteristics for patients with and without ADPKD as mean and standard deviation for continuous variables, and frequencies and percentages for binary or categorical variables before and after weighting.

We assessed whether there was imbalance in the baseline characteristics between the two groups using standardized differences. Standardized difference is the difference in mean divided by the pooled standard deviation, and a value greater than 10% suggests significant imbalance.[22]

We plotted the cumulative incidence function for stones censoring the observational time for death, or emigration from the province. In our primary analysis, we compared the rate of outcomes between the groups with and without ADPKD using a Cox proportional hazards regression model censoring on death, dialysis, kidney transplant, emigration from the province, or end of follow-up. In an additional analysis, we treated death, dialysis, and kidney transplant as a competing event and calculated the subdistribution hazards ratio using Fine and Gray's model.[23] The 95% confidence intervals for the hazard and subdistribution hazards ratios were calculated using bootstrapping methods.[24] We estimated the absolute between-group difference in the rate of our outcomes using the PROC NLMIXED procedure in SAS.

In exploratory subgroup analyses, we tested whether the associations between ADPKD (yes/no) and our outcomes were modified by baseline age (18-40 years, 41-60 years, and >60 years), sex, and prior stone history using interaction terms in Cox proportional hazards models. We also assessed the association between age, sex, income quintile, and date of cohort entry with both outcomes separately in patients with and without ADPKD using multivariable Cox proportional hazards models. We assessed for multi-collinearity among the potential risk factors by determining the variance inflation factors; all variance inflation factors were less than two indicating this was of minimal concern.

Patients with ADPKD generally receive more abdominal imaging than patients without ADPKD, which could explain why kidney stones may be detected more frequently in patients with ADPKD. To gain insight into this potential surveillance bias, we compared the rate of abdominal imaging during follow-up in patients with ADPKD with controls using Cox proportional hazards regression.

Prior to using each Cox proportional hazards model, we assessed the proportional hazards assumption using time-dependent covariate test. When proportional hazard assumption was violated, we reported average hazard ratio (HR) over a period of 15 years. We performed all analyses using SAS 9.4 (SAS Institute, Inc., Cary, North Carolina) with a statistical significance of $P < .05$.

Results

Cohort Selection and Baseline Characteristics

From 4361 potentially eligible patients with ADPKD, the final cohort included 2094 patients with ADPKD identified in Ontario (Supplementary Figure S1). From 7 153 842 potentially eligible non-ADPKD controls, 4 547 371 met the eligibility criteria. From the eligible controls, we randomly sampled 50 000 controls which corresponded to 1902 patients in the weighted cohort after truncating weights (Supplementary Table S2). Table 1 and Supplementary Table S4 summarize the baseline characteristics of the two groups. After weighting, the mean (standard deviation, SD) age was 57 (18) years for patients with ADPKD, and 57 (4) years for patients without ADPKD, and 49% of patients with ADPKD and 52% of patients without ADPKD were women. The two groups were similar in the mean number of visits to their primary care physician, emergency department, and urologist in the prior year, and were similar in baseline comorbidities.

Follow-Up Period

The median length of follow-up for a kidney stone event was 5.4 years (5.0 years in patients with ADPKD, 5.8 years in controls, maximum 15.5 years). A total of 270 patients with ADPKD and 436 controls in the weighted cohort were followed for a period of 10 years or more. The median (IQR) age at the time of last follow-up for the entire cohort was 62 years (49-77). Of the 3996 total individuals, 2153 (54%) were alive and event-free at the end of study follow-up (March 31, 2017), 70 (2%) were censored at time of emigration from the province, 965 (24%) died, and 141 (4%) had the event of interest during follow-up. The total person-years of follow-up was 21 021 (9144 for patients with ADPKD, 11 877 for non-ADPKD controls). The follow-up period for a stone intervention event was similar to a stone event, with details presented in Supplementary Table S5. Less than 2% of the ADPKD and control groups experienced 2 or more stone events or stone intervention events in follow-up (and we only considered the time to the first event).

Outcomes

Figure 1 and Table 2 present the main outcomes. The proportional hazard assumption was met for the outcome of hospital encounter with kidney stones both for the main analysis and when death was treated as a competing event (ADPKD status and time interaction term, $P = .7$ and $P = .4$, respectively). The same was also true for the outcome of stone intervention (ADPKD status and time interaction term, $P = .4$ and $P = .4$, respectively).

The rate of a hospital encounter with kidney stones was significantly higher in the ADPKD group than the control group (81 of 2094 patients with ADPKD [3.9%] vs 60 of 1902 patients without ADPKD [3.2%]; 8.9 vs 5.1 events per 1000 person-years; HR = 1.6, 95% confidence interval [CI] = 1.3-2.1). Contrarily, the results showed that there was no difference in the rate of hospital encounter with kidney stones in patients with ADPKD group and control group when accounting for death and dialysis as a competing event (average subdistribution HR over 15 years 1.2, 95% CI = [0.9-6.1]).

Table 1. Characteristics of the ADPKD Cohort and Controls at the Time of Cohort Entry After Inverse Probability Exposure Weighting Based on Propensity Scores.

	ADPKD (n = 2,094)	Non-ADPKD (n = 1,902)	Standardized difference, %[a]
Mean (SD) age, years	57 (18)	57 (4)	1
Women, n (%)	1069 (51)	984 (52)	1
Income fifth, n (%)[b]			
Quintile 1 (lowest)	436 (21)	399 (21)	0
Quintile	420 (20)	381 (20)	0
Quintile 3	425 (20)	386 (20)	0
Quintile 4	368 (18)	336 (18)	0
Quintile 5 (highest)	445 (21)	400 (21)	0
Rural Town, n (%)[c]	238 (11)	222 (12)	1
No. of visits to primary care physician in prior year (%)			
None	95 (5)	84 (4)	1
1-2	258 (12)	229 (12)	1
3-4	246 (12)	228 (12)	1
5-6	265 (13)	243 (13)	0
7-8	251 (12)	231 (12)	0
9-10	180 (9)	169 (9)	1
>10	799 (38)	719 (38)	1
No. of visits to emergency department in the prior year (%)			
None	350 (17)	340 (18)	3
1-3	1427 (68)	1308 (69)	1
4-6	252 (12)	201 (11)	5
7-9	44 (2)	35 (2)	2
10-12	13 (1)	12 (1)	0
>12	8 (0)	6 (0)	1
No. of visits to urologist in the prior year (%)			
None	1495 (71)	1406 (74)	6
1-2	344 (16)	282 (15)	4
3-4	122 (6)	105 (6)	1
5-6	71 (3)	59 (3)	2
7-8	34 (2)	29 (2)	1
9-10	13 (1)	10 (1)	1
>10	15 (1)	11 (1)	2
Abdominal imaging in the prior 5 years, n (%)	1885 (90)	1693 (89)	3
Comorbidities in the past 5 years			
Acute kidney injury, n (%)	17 (1)	10 (1)	4
Urinary tract obstruction, n (%)	111 (5)	85 (4)	4
Urinary tract infection, n (%)	594 (28)	465 (24)	9
Primary hyperparathyroidism, n (%)	43 (2)	27 (1)	5
Gout, n (%)	290 (14)	208 (11)	9
Obesity, n (%)	155 (7)	144 (8)	1
Diabetes mellitus, n (%)	509 (24)	460 (24)	0
Hypertension, n (%)	1662 (79)	1471 (77)	5
Osteoporosis, n (%)	209 (10)	178 (9)	2
Prior hospital encounter or intervention for stone	281 (13)	209 (11)	7
Prior hospital encounter for stone, n (%)	278 (13)	208 (11)	7
Prior intervention for stone, n (%)	58 (3)	49 (3)	1
Inflammatory bowel disease, n (%)	72 (3)	62 (3)	1

Note. Discharge date was date of entry into cohort for those identified with hospital admission records and was registration date for those identified with emergency department records. ADPKD = Autosomal dominant polycystic kidney disease.

[a]Standardized difference is the difference in means or proportions divided by the pooled standard deviation. Unlike hypothesis testing, standardized difference is not influenced by sample size. A standardized difference of <10% indicates negligible difference.

[b]Income was categorized by fifths of average neighborhood income. Income quintile was missing for <1% of the cohort. For these individuals we assumed that their household income was part of the third quintile.

[c]Rural/Urban residency status was missing for <1% of the cohort. For these individuals, we assumed they resided in an urban area.

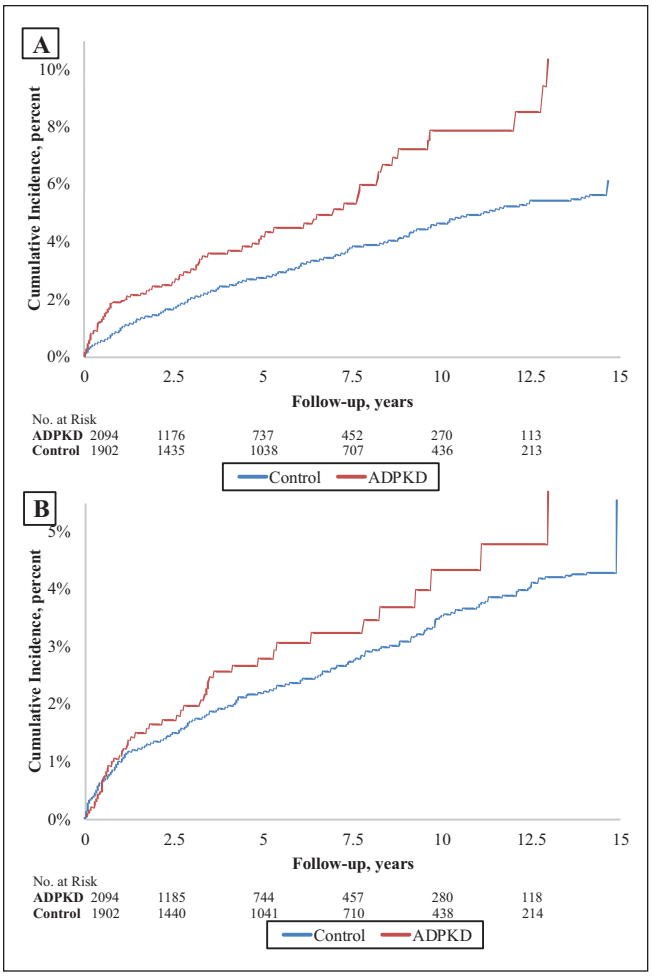

Figure 1. Cumulative incidence function of (A) time to first hospital encounter with kidney stone; and (B) time to first stone intervention.
Note. ADPKD = autosomal dominant polycystic kidney disease.

There was no statistically significant difference, on average, in the rate of stone intervention in patients with ADPKD compared with controls (49 of 2094 [2.3%] vs 47 of 1902 [2.5%]; 5.3 vs 3.9 events per 1000 person-years; HR 1.2; 95% CI = [0.9-1.2]). The results were similar when treating death as a competing event (average subdistribution HR over 15 years 1.4, 95% CI = [0.7-1.3]). Ureteroscopy was the most common type of intervention in both groups. Sex, age, and stone event in the prior 5 years did not significantly modify the effects of ADPKD on the rate of stones, or stone intervention (Table 3).

The rate of abdominal imaging was significantly higher in patients with ADPKD compared with controls (1826 of 2094 [87.2%] vs 1310 of 1902 [68.9%]; 169.5 vs 121.7 events per 1000 person-years; HR = 1.3, 95% CI = [1.2-1.3]).

Multivariable Risk Factor Analysis

The adjusted HRs for each of the studied risk factors are summarized in Table 4. Older age was significantly associated with a lower rate of a hospital encounter with stones in patients with ADPKD only, and a higher rate of stone interventions in patients without ADPKD only. Patients without ADPKD aged between 41 and 60 experienced a higher rate of hospital encounter with kidney stones compared with patients aged 18 to 40 years. Male sex was associated with a higher risk of hospital encounter with kidney stone and stone intervention in both the ADPKD and non-ADPKD group.

Hazards ratio was obtained by censoring for death, dialysis initiation, end of follow-up, and emigration from Ontario. The estimate was weighted using inverse probability exposure weighting based on propensity score.

Discussion

It is uncertain whether the incidence of hospital encounters with kidney stones and stone interventions in patients with ADPKD differs from patients with similar baseline health status without ADPKD. It is also not clear whether some factors associated with these events are similar between the two groups. Our study addresses these knowledge gaps. We found the rate of first hospital encounter with kidney stones was significantly higher in patients with ADPKD compared with similar patients without ADPKD, while the rate of stone interventions did not significantly different between the two groups. Ureteroscopy was also the most prevalent intervention type for both patients with and without ADPKD.

There are several possible explanations for the increased rate of hospital encounters with stones in patients with ADPKD. Cysts may lead to more urinary stasis, which favors urinary crystals to form, cause stones to stagnate, and promote stone growth leading to more kidney stones. Given their ongoing renal concerns, patients with ADPKD may also be more likely to present to hospital when they develop a stone compared with patients without ADPKD. We found no statistical difference in the rate of stone intervention between patients with ADPKD and similar patients without ADPKD. It is possible urologists were less inclined to perform interventions in patients with ADPKD with complex anatomy, choosing to favor medical treatments. Uric acid stones are the most prevalent stone in patients with ADPKD, and urologists may use dissolution treatment to treat these stones first, even in situations where the stones are large.[25,26]

Studies examining the burden of kidney stones in patients with ADPKD relative to a non-ADPKD population are scarce. To date, only six cross-sectional studies report the prevalence of kidney stones in both patients with ADPKD and their unaffected family members.[6-11] Two of six studies that performed statistical comparisons found that the prevalence of stones was not different between the two groups.[7,8] The prior studies also did not adjust for any covariates in their analyses. To the best of our knowledge, our study is the first longitudinal study that adjusted for covariates and compared the rate of hospital encounter with kidney stones and stone intervention between patients with ADPKD and controls with similar baseline health. It is also the largest study

Table 2. Comparison of the Hazards of (a) Time to First Hospital Encounter With Stone, and (b) Time to First Stone Intervention Between Patients With ADPKD Cohort and Patients Without ADPKD With Similar Baseline Health.

	Hospital encounter for stone		Stone intervention	
	ADPKD	Non-ADPKD	ADPKD	Non-ADPKD
Median (interquartile range) follow-up, years	5.0 (2.2-9.1)	5.8 (2.7-9.7)	5.2 (2.3-9.2)	5.8 (2.7-9.7)
Total follow-up, person-years	9144	11 876	9245	11 913
No. who died, (%)	483 (23)	482 (25)	491 (23)	486 (26)
No. who emigrated, (%)	32 (2)	38 (2)	32 (2)	39 (2)
No. who went on dialysis during follow-up	642 (31)	25 (1)	650 (31)	25 (1)
No. of unique patients with event, (%)	81 (4)	60 (3)	49 (2)	47 (2)
Type of Intervention				
Shockwave lithotripsy *or* percutaneous nephrolithotomy or combination of 2 or more intervention performed on the same day or within the same hospital admission	N/A	N/A	17 (1)	19 (1)
Ureteroscopy	N/A	N/A	35 (1)	28 (1)
No. of events per 1000 person-years	8.9	5.1	5.3	3.9
Hazards ratio (95% CI)[a]	1.6 (1.3-2.1)	1.0 (Reference)	1.2 (0.9-1.7)	1.0 (Reference)
Subhazards ratio (95% CI)[b]	1.2 (0.9-1.6)	1.0 (Reference)	0.9 (0.7-1.3)	1.0 (Reference)
Risk difference per 1000 person-years (95% CI)	3.8 (1.5-6.1)	0.0 (Reference)	1.4 (−0.0 to 3.2)	0.0 (Reference)

Note. ADPKD = autosomal dominant polycystic kidney disease; N/A = not applicable; CI = confidence interval.
[a]Hazards ratio was obtained by censoring for death, dialysis initiation, end of follow-up, and emigration from Ontario. The estimates were weighted using inverse probability exposure weighting based on propensity scores. The proportional hazard assumption was met for both the hospital encounter with stone outcome (ADPKD status and time interaction term, $P = .7$) and stone intervention outcome (ADPKD status and time interaction term, $P = .4$).
[b]Hazards ratio was obtained by censoring for emigration and end of follow-up from Ontario, and accounting for death and dialysis initiation as a competing event. The estimates were weighted using inverse probability exposure weighting based on propensity scores. The proportional hazard assumption was met for both the hospital encounter with stone outcome (ADPKD status and time interaction term, $P = .4$) and stone intervention outcome (ADPKD status and time interaction term, $P = .4$).

to date on this topic, and loss to follow-up was minimal with only about 2% of persons in the cohort emigrating from Ontario. We expect patients identified with ADPKD with the administrative coding algorithm truly had ADPKD given the high positive predictive value of International Statistical Classification of Diseases and Related Health Problems, tenth edition (ICD-10) codes that we used to identify patients with ADPKD.[17] Additionally, we used inverse probability exposure weighting based on propensity scores to ensure our two groups had similar baseline indicators of health status; this allowed us to adjust for a large number of covariates prior to conducting statistical analyses.[21]

Our study is not without limitations. A small number of events meant some estimates were imprecise. Other conditions, such as cyst rupture, may have been misclassified as kidney stone events and kidney stone events may have been misclassified as cyst rupture. We did not have information on kidney stone events outside of the hospital, which represents a large proportion of stone events not captured in this study. This deficiency should be addressed in future studies. Some relevant information such as the amount of daily water consumed was also not available in our health care data sources, and some measures in our data sources could be miscoded. We also did not have information on the type of stone. These factors along with the observational design of our study raise the possibility of residual confounding. The control group may include patients with ADPKD who never underwent abdominal imaging. However, the prevalence of ADPKD ranges between 1 in 1000 to 1 in 400 and we would expect less than 125 patients with undiagnosed ADPKD among the 50 000 controls. We do not anticipate the few undiagnosed patients with ADPKD to meaningfully change the result. With our data sources, we could only enter ADPKD patients with a history of at least one hospital encounter into the cohort, so the results may generalize less well to healthier segments of the ADPKD population; future studies should consider repeating this study in a more representative sample of patients with ADPKD. We could not ascertain which type of procedure was performed first in a small subset of our patients in both groups, because two or more different types of interventions were performed on the same day or within the same hospitalization. The applicability of the Fine and Gray model when using inverse probability exposure weighting remains unclear. Furthermore, censoring on competing event usually underestimates the HR as observed in our study. Therefore, the subdistribution HR should be interpreted with caution. We only conducted the competing risk analysis to explore the potential impact of death and dialysis as a competing event and primarily interpreted the primary analysis. Although HR is statistically significant and subdistribution HR is nonsignificant for hospital encounter with stone among patients with ADPKD compared with patients

Table 3. Hazard Ratio of Hospital Encounter With Kidney Stone and Stone Intervention Among Patients With ADPKD Versus Patients Without ADPKD With Similar Indicators for Baseline Health in Various Subgroups.

	No. of events/ No. at risk		No. of events per 1000 person-years		Hazards ratio[a] (95% confidence interval)
	ADPKD	Non-ADPKD	ADPKD	Non-ADPKD	
Hospital encounter with kidney stone					
Overall	81/2094	60/1,902	8.9	5.1	1.6 (1.3-2.1)
Sex					
Male	49/1025	36/918	13.0	6.6	1.8 (1.3-2.5)
Female	32/1069	24/984	5.9	3.8	1.5 (1.0-2.3)
Age, years					
18-40	34/440	16/422	11.9	5.2	2.3 (1.5-3.4)
41-60	29/748	23/571	8.9	5.9	1.4 (0.9-2.1)
>60	18/906	21/909	6.0	4.3	1.2 (0.7-2.1)
Stone intervention or hospital encounter with stone in the prior 5 years					
Yes	48/281	32/209	43.6	25.0	1.4 (1.0-1.9)
No	33/1813	28/1693	4.1	2.6	1.4 (1.0-2.0)
Stone intervention					
Overall	52/2094	47/1902	5.3	3.9	1.2 (0.9-1.7)
Sex					
Male	33/1025	27/918	8.1	5.0	1.5 (1.0-2.2)
Female	19/1069	20/984	3.3	3.0	1.0 (0.6-1.7)
Age, years					
18-40	18/440	8/422	5.8	2.5	2.3 (1.3-4.1)
41-60	21/748	18/571	5.7	4.3	1.1 (0.6-1.9)
>60	13/906	21/909	4.3	4.3	0.9 (0.5-1.6)
Stone intervention or hospital encounter with stone in the prior 5 years					
Yes	34/281	32/209	28.2	24.7	0.9 (0.5-1.7)
No	18/1813	15/1693	2.0	1.4	1.4 (0.9-2.4)

Note. ADPKD = autosomal dominant polycystic kidney disease.
[a]Hazards ratio was obtained by censoring for death, dialysis initiation end of follow-up, and emigration from Ontario. The estimate was weighted using inverse probability exposure weighting based on propensity scores. The proportional hazard assumption was assessed using time-dependent covariate test, and was met for all subgroup analyses.

Table 4. Risk Factors for Hospital Encounter With Kidney Stones and Stone Interventions in Patients With ADPKD and Patients Without ADPKD With Similar Indicators for Baseline Health When Each Group Was Analyzed Separately.

	Hospital encounter with stone		Stone intervention	
Risk factors	ADPKD	Non-ADPKD	ADPKD	Non-ADPKD
Age				
41-60 (vs 18-40)	0.5 (0.3-0.9)	1.5 (1.0-2.1)	0.7 (0.3-1.5)	1.7 (1.1-2.5)
60+ (vs 18-40)	0.3 (0.2-0.6)	1.2 (0.9-1.7)	0.5 (0.2-1.2)	1.4 (1.0-2.2)
Male (vs female)	2.6 (1.6-4.2)	2.0 (1.6-2.6)	2.6 (1.3-5.1)	1.5 (1.1-2.0)
Income quintiles				
Quintile 2 (vs Quintile 1)	1.2 (0.6-2.3)	1.1 (0.7-1.7)	1.7 (0.6-4.3)	1.2 (0.8-2.0)
Quintile 3 (vs Quintile 1)	1.1 (0.6-2.0)	1.2 (0.8-1.7)	1.1 (0.4-3.3)	1.4 (0.9-2.4)
Quintile 4 (vs Quintile 1)	0.9 (0.4-2.1)	1.1 (0.7-1.7)	1.0 (0.3-3.2)	1.6 (1.0-2.7)
Quintile 5 (vs Quintile 1)	1.1 (0.5-2.2)	1.1 (0.7-1.7)	1.5 (0.5-3.9)	1.2 (0.7-2.1)
Date of Entry into Cohort				
April 1, 2007, to March 31, 2012 (vs before April 1, 2007)	1.2 (0.7-2.1)	1.0 (0.8-1.4)	1.5 (0.7-3.5)	0.9 (0.6-1.3)
After March 31, 2012 (vs before April 1, 2007)	0.9 (0.4-1.8)	1.4 (0.9-2.1)	1.2 (0.4-3.4)	1.2 (0.8-1.9)

Note. Separate multivariable Cox proportional hazards regression models created for ADPKD group and non-ADPKD group with similar indicator for baseline health. The date of entry into cohort was discharge date for those identified using hospital admission records and registration date for those identified with emergency department records. ADPKD = autosomal dominant polycystic kidney disease.

without ADPKD, both estimates do show that patients with ADPKD experience a higher rate of hospital encounter with kidney stones compared with patients without ADPKD.

Overall, our results suggest that ADPKD increases the rate of hospital encounters with kidney stones, and that urologists are not more or less aggressively managing stones in patients with ADPKD than in patients without ADPKD with otherwise similar baseline health. Future studies should focus on further quantifying the burden of kidney stones in patients with ADPKD in all settings, and strategies to prevent their development and minimize their impact on patient health. Additionally, future studies should explore whether additional, important subgroups, such as patients with larger total kidney volume, have a higher chance of developing stones.

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Ethics Approval and Consent to Participate

The use of ICES data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, and did not require review by a Research Ethics Board. No informed consent from patients was required.

Consent for Publication

Consent for publication was obtained from all authors.

Availability of Data and Materials

Not applicable.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Y.P. served as an expert consultant on drug development (Otsuka, Pfizer, and Genzyme/Sanofi) related to autosomal dominant polycystic kidney disease. All other authors declare no competing interests.

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Supplemental Material

Supplemental material for this article is available online.

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