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Epidemiology of upper urinary tract stones and stone management in autosomal dominant polycystic kidney disease

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Abstract

Upper urinary tract stones are a major determinant of pain and is suggested to accelerate disease progression in patients with autosomal dominant polycystic kidney disease (ADPKD). For these reasons, stones should be optimally managed in patients with ADPKD. However, the kidney distortions may make managing stones challenging in patients with ADPKD. Understanding of the epidemiology of upper urinary tract stones and stone intervention and the outcomes of stone interventions is limited. The aim of this thesis is to understand the epidemiology of upper urinary tract stones and stone interventions and consequences of stone management in patients with ADPKD.

To address this knowledge gap, we conducted two systematic reviews to understand the current knowledge on the prevalence and incidence of upper urinary tract stones, and the success and complication rate of the three common stone interventions (shockwave lithotripsy [SWL], ureteroscopy, and percutaneous nephrolithotomy [PCNL]) in patients with ADPKD. We conducted a chart review to validate International Classification of Diseases, 10th revision (ICD-10) codes related to ADPKD. We then conducted two cohort studies using ICES data to determine and compare the rate of stones and rate of stone intervention, and the complication rate of the most common stone intervention (ureteroscopy) in patients with ADPKD to patients without ADPKD with similar baseline health.

Chapter 2 showed that that there is poor consensus on how often patients with ADPKD develop or undergo intervention for upper urinary tract stones.

Chapter 3 showed that the efficacy and safety of stone interventions in patients with ADPKD remains uncertain.

Chapter 4 summarized the limitations of the existing literature based on the findings of the two systematic reviews.

Chapter 5 showed that majority of the patients with ICD-10 codes related to ADPKD truly have ADPKD according to strict clinical criteria.

Chapter 6 showed that patients with ADPKD presented to the hospital with upper urinary tract stones more, and that urologist were not managing stones in patients with ADPKD in a similar manner to comparable patients without ADPKD. It also showed that ureteroscopy is the most commonly performed stone intervention.

Chapter 7 showed ADPKD is associated with a statistically significant increase emergency department visits in selected patients with ADPKD who received ureteroscopy for upper urinary tract stones compared to patients without ADPKD.

Results can inform the use of ICD-10 codes to build ADPKD cohorts, inform clinical practice guidelines, and guide prognostication.

Keywords

Epidemiology, ADPKD, polycystic kidney disease, upper urinary tract stones, population health research, healthcare administrative data

Summary for Lay Audience

Autosomal dominant polycystic kidney disease is a condition where the kidneys are filled with many cysts. Over time, the cysts grow in size and number and cause the kidneys to fail. Upper urinary tract stones are a major reason for pain and may cause kidneys to fail faster in these patients. For these reasons, stones should be managed well in patients with ADPKD. However, the kidney cysts in these patients may make this challenging. A thorough review of the literature shows that little is known about the rate of upper urinary tract stones and stone interventions, and the outcomes of ureteroscopy (a common procedure to treat upper urinary tract stones). The aim of this thesis was to fill this knowledge gap.

We did this by conducting large, follow-up studies using administrative databases. Our validation studies show that we can confidently use administrative codes to identify patients with ADPKD. This thesis confirms that hospital encounters with upper urinary tract stones are a manifestation of ADPKD. From the administrative data, urologists approach stones in ADPKD in a similar manner compared to patients without ADPKD, despite the distorted kidney anatomy potentially making stone interventions more challenging. Of all three commonly used interventions (SWL, ureteroscopy, and PCNL), ureteroscopy is the most common intervention used to manage stones in both patients with and without ADPKD. Our final thesis study shows that patients with ADPKD do not experience more ureteroscopic complications and hospital admission for any reason. However, they did experience more hospital presentation and emergency department visit for any reason compared to patients without ADPKD. This may be a consideration for patient counselling.

The knowledge gained from this thesis identifies knowledge gaps, and lays the foundation for future studies on ADPKD using healthcare administrative databases. It also clarifies the rate of hospital encounters with upper urinary tract stones and the rate of stone interventions, and provides the best evidence we have to date to inform clinical practice.

Co-Authorship Statement

All studies included in this thesis was primarily conceived, designed, and executed by Vinusha Kalatharan. Vinusha Kalatharan also wrote the initial draft of all manuscripts included in this thesis, and integrated feedbacks from co-authors and reviewers. The data for chapters 5, 6, and 7 were provided by ICES. The supervisory committee, Drs. Amit Garg, York Pei, Blayne Welk, and Sisira Sarma, and other research team members provided feedback, data cuts according to ICES regulations, and/or methodological or content expertise on an as needed basis and were listed as co-authors accordingly. All co-authors contributed and approved the manuscripts. The contributions of Vinusha Kalatharan and each of the co-authors is detailed below, and recognized as footnotes in the beginning of each chapter.

Chapter 2: Vinusha Kalatharan and Amit X Garg conceived and actively participated in the design and coordination of the study. Vinusha Kalatharan developed the comprehensive search strategy with the help of the librarian, John Costello. Vinusha Kalatharan and Gary Grewal screened all relevant citations, abstracted information using a standardized data abstraction form developed by Vinusha Kalatharan, and assessed the risk of bias of each included study. Danielle M Nash resolved any disagreement between the two reviewers. Vinusha Kalatharan wrote the first draft of the manuscript, and integrated all co-authors' and reviewers' comments. All authors read and approved the final article.

Chapter 3: Vinusha Kalatharan and Amit X Garg conceived and actively participated in the design and coordination of the study. Vinusha Kalatharan developed the comprehensive search strategy with the help of the librarian, John Costello. Vinusha Kalatharan and Racquel Jandoc screened all relevant citations and abstracted information using a standardized data abstraction form developed by Vinusha Kalatharan. Vinusha Kalatharan and Gary Grewal assessed the risk of bias of each included study. Danielle M Nash resolved any disagreement between the two reviewers. Vinusha Kalatharan conducted the analysis, wrote the first draft of the manuscript, and integrated all co-authors' and reviewers' comments. All authors read and approved the final article.

Chapter 5: Vinusha Kalatharan, York Pei, and Amit X Garg conceived and actively participated in the design and coordination of the study. Vinusha Kalatharan was the main reviewer, conducted the main analysis, wrote the first draft of the manuscript, and integrated the comments of all co-authors and reviewers. Kristin Clemens assisted with the data collection, and Rebecca K McTavish was the second reviewer. Matthew Rochon reviewed images of patients that required additional information. Stephanie Dixon conducted analysis and provided analytical support for the ICES proportion of the data. All authors read and approved the final article.

Chapter 6: Vinusha, Amit, Blayne, Danielle, and Stephanie actively participated in the design of the study. Vinusha executed the study, conducted the analyses, and wrote the first draft of the manuscript as first-author. Stephanie and Justin provided analytical support. All authors read, critically revised, and approved the final article. Vinusha integrated the feedbacks of all authors and reviewers.

Chapter 7: Vinusha, Amit, Blayne, Danielle, and Eric actively participated in the design of the study. Vinusha executed the study, conducted the analyses, and wrote the first draft of the manuscript as first-author. Eric and Justin provided analytical support. All authors read, critically revised, and approved the final article. Vinusha integrated the feedbacks of all authors and reviewers.

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Abbreviations

ACEi	angiotensin converting enzyme inhibitors
AKI	acute kidney injury
AMOSO	Academic Medical Organization of Southwestern Ontario
ARBs	angiotensin II receptor blockers
CCI	Canadian Classification of Health Intervention
CCI	Canadian Classification of Health Intervention
CI	confidence interval
CIHI	Canadian Institute for Health Information
CIHI-DAD	Canadian Institute for Health Information Discharge Abstract Database
CKD	chronic kidney disease
CT	computed tomography scan
ESKD	end-stage kidney disease
Fam Hx	family history
HR	hazards ratio
ICD-10	International Classification of Diseases, 10th revision
ICD-9	International Classification of Diseases, 9th revision
ID	identification number
IPDB	ICES Physician Database
IPTW	inverse probability treatment weighting
IQR	interquartile range
IV	intravenous
KUB	kidney, ureter, bladder
kV	kilovolts
LHIN	Local Health Integration Network

LHRI	Lawson Health Research Institute
MOHLTC	Ministry of Health and Long-Term Care
N/A	not applicable
NACRS	National Ambulatory Care Reporting System
NR	not reported
NSAIDs	nonsteroidal anti-inflammatory drugs
OHIP	Ontario Health Insurance Plan
PCNL	percutaneous nephrolithotomy
PHIPA	Personal Health Information Protection Act
PKD	polycystic kidney disease
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
RD	risk difference
RPDB	Registered Persons Database
RR	relative risk
SDS	same day surgery
SSMD	Schulich School of Medicine and Dentistry
SWL	shockwave lithotripsy
U/S	ultrasound
UTI	urinary tract infection
WHO	World Health Organization

Chapter 1 - Introduction

1.1 BURDEN OF UPPER URINARY TRACT STONES IN THE GENERAL POPULATION

Upper urinary tract stones are a common occurrence in the general population (prevalence ranging between 0.1% and 14.8% and the incidence ranging between 24.2 and 81.0 individuals per 100,000 person-years) with its prevalence increasing globally.[1] The prevalence of upper urinary tract stones is higher in men than in women, with the difference in stone prevalence between men and women decreasing overtime.[2] Approximately half of the patients experience a recurrent upper urinary tract stone event within seven years of the first stone occurrence, if left untreated.[3]

Upper urinary tract stone events impose a significant burden on the healthcare system.[4] In the United States in 2009, there were 1.3 million emergency department visits for upper urinary tract stones, of which 20% resulted in a hospitalization.[4] The number of emergency department visits increased 20%, and the rate of hospitalization increased 14% between 2005 and 2009.[4] This clinical demand translates to a significant economic burden on the healthcare system, with annual estimates greater than $5 billion.[4] Upper urinary tract stones impose both a direct cost and an indirect cost via lost work productivity.[4]

1.2 AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic kidney disorder with no cure.[5,6] It has an estimated prevalence of 1 in 1000 to 1 in 400 worldwide, and is characterized by focal cyst development in both kidneys.[7–11] It is primarily diagnosed using ultrasound according to the Ravine criteria (Table 1-1) prior to 2009, and according to the Pei criteria (Table 1-2) after 2009.[12,13] In early stages of ADPKD, the cysts cause structural deformation to the kidney and damage adjacent nephrons, but overall kidney function is maintained by compensatory hyperfiltration of functioning nephrons.[14,15] As

the number and size of cysts increase progressively, more nephrons become damaged, and overall kidney function starts to decline.[16] The level of kidney function is indicated by chronic kidney disease (CKD) stages in patients with ADPKD (Table 1-1).[17] The earlier stages of CKD are defined by kidney damage (determined by albuminuria (albumin type proteins in the urine)), and mild-to-moderate reductions in how well the kidney clears the blood of waste products, which is indicated by the estimated glomerular filtration rate (eGFR).[17,18] Further decrements in eGFR defines more advanced stages of CKD.[17,18] By the age of 55, about half of the patients with ADPKD reach end-stage kidney disease (ESKD) and require kidney transplantation or dialysis to sustain life.[19,20] Currently, tolvaptan is the only drug approved to delay progression to ESKD, and much of current research on patients with ADPKD is focused on identifying other therapeutic agents. However, kidney failure is not the only manifestation of ADPKD; patients with ADPKD are affected with other morbidities that warrant attention to prevent loss of health-related quality of life.[21] One such morbidity is upper urinary tract stones.[22]

Table 1-1. Ravine ultrasonographic criteria for diagnosing autosomal dominant polycystic kidney disease

Age	Positive Family History	Negative Family history
< 30 years	2 cysts bilaterally or unilaterally	5 cysts bilaterally
30 to 60 years	4 cysts bilaterally	5 cysts bilaterally
> 60 years	8 cysts bilaterally	8 cysts bilaterally

Table 1-2. Pei ultrasonographic criteria for diagnosing autosomal dominant polycystic kidney disease (ADPKD) among patients with a positive family history

Age (years)	Diagnostic Criteria
15 to 39	At least 3 cysts (unilateral or bilateral)
40 to 59	2 cysts/kidney
$\geq$ 60	4 or more cysts/kidney

*Note: Fewer than 2 cysts in individuals $\geq$ 40 years old and are at risk of ADPKD is sufficient to rule out the disease.

Table 1-3. Chronic kidney disease stages categorized based on the classification system established by the National Kidney Foundation outcome Quality initiative

Chronic Kidney Disease Stage	Clinical Characteristics
Stage 1	Persistent albuminuria & eGFR $\geq$ 90 mL/min/1.73m^2
Stage 2	Persistent albuminuria & 60 $\leq$ eGFR > 90 mL/min/1.73m^2
Stage 3	30 > eGFR > 60 mL/min/1.73m^2
Stage 4	15 > eGFR $\geq$ 30 mL/min/1.73m^2
Stage 5	eGFR $\leq$ 15 mL/min/1.73m^2

Abbreviations: eGFR, estimated glomerular filtration rates

1.3 UPPER URINARY TRACT STONES IN ADPKD

Many popular educational materials and clinical practice guidelines indicate patients with ADPKD are at higher risk of upper urinary tract stones.[23,24] Although the exact mechanism underlying stone formation in patients with ADPKD is unknown, this makes clinical sense based on our speculation of the pathophysiology of stone disease in patients with ADPKD. In general, supersaturation of salts causes crystals to form in the urine (crystallization).[25] There are inhibitors to prevent crystallization in our urine (e.g. citrate).[25] However, as salts become more and more supersaturated, clusters of crystals start to form (nuclei).[25] Nucleation often needs a surface or a seed (e.g. epithelial lining, other crystal, cell debris).[25] Over time, these microscopic nuclei aggregate together to form stones.[25] In patients with ADPKD, the kidney cysts lead to urinary stasis, which along with metabolic abnormalities, such as hyperoxaluria (high urinary excretion of oxalate), hyperuricosuria (high uric acid level in urine), hypocitraturia (low citrate concentration, an inhibitor of crystallization in urine), may promote stone formation.[26–28] The kidney cysts in these patients may also impede stone passage promoting stone growth. Although the idea that the cystic burden in patients with ADPKD may make them more susceptible to upper urinary tract stones makes clinical sense, a systematic review has not been conducted to summarize the burden of stones in patients with

ADPKD, and to give insight into whether patients with ADPKD have a higher risk of upper urinary tract stones compared to non-ADPKD patients of similar baseline health. Understanding the burden of upper urinary tract stones in patients with ADPKD would inform future clinical practice guidelines and guide prognostication.

Upper urinary tract stones in patients with ADPKD are associated with significant pain and morbidity.[29] In the general CKD population, patients with stones are at higher risk of ESKD compared to patients without stones, with the suggestion that this is also true in patients with ADPKD.[30,31] For these reasons, stones should be optimally managed in patients with ADPKD. A clinical practice guideline on recommended upper urinary tract stone management in patients with ADPKD states that similar approaches are being taken to manage stones as the general population. The interventions appear safe and efficacious based on limited evidence.[24]

1.4 UPPER URINARY TRACT STONE MANAGEMENT IN THE GENERAL POPULATION

Most stones usually do not require a urological intervention, and will often pass within four weeks upon presenting symptoms.[32] Pain may be managed with narcotics or Nonsteroidal Anti-Inflammatory Drugs (NSAIDs).[32] However, urgent intervention is often required in the presence of infection/urosepsis, intractable pain, vomiting, impending acute renal failure, and/or obstruction.[25] Prior to the 1980s, open stone surgery or nephrectomy (i.e. partial or full removal of a kidney) was performed to remove stones in anatomically abnormal kidneys.[33,34] However, recently less invasive procedures are used.[35] These procedures are shock wave lithotripsy (SWL), ureteroscopy, and percutaneous nephrolithotomy (PCNL).[35]

1.4.1 Shockwave lithotripsy (SWL) in the general population

SWL is the least invasive treatment option and is one of the recommended first-line treatments for proximal ureteral or renal stones less than 1 cm.[36,37] SWL emits shockwaves from an external device, which propagates through the body and causes the

stones to fragment by either exerting mechanical stress or by causing the cavitation bubbles within the stones to collapse.[32,38] SWL is non-invasive and associated with few short-term or long-term complications; the rate of major (0.4%) and minor (5.8%) complications for SWL is low in the general population.[36] Some SWL related complications include transient hematuria, pain, perirenal hematoma, and acute kidney injury.[39] SWL is contraindicated for pregnant women and for patients with uncontrolled hypertension, uncontrolled coagulopathy, or a distal urinary obstruction to where the stone is located.[36]

1.4.2 Ureteroscopy in the general population

Ureteroscopy is an alternative first-line therapy for stones in the ureter or kidney (generally < 2cm). It is performed by inserting a rigid, semi-rigid, or flexible ureteroscope through the urethra, and by positioning it close to the stone.[40,41] Various instruments, such as a laser or a pneumatic intracorporeal lithotripter, are then used to fragment the stones.[42] Other instruments, such as stone baskets, can be used to remove the stone fragments.[43] Ureteral stents are often used with ureteroscopy to prevent obstruction from ureteral oedema or residual stone fragments (especially in the presence of ureteric injury, stricture, solitary kidney, CKD, or a large stone).[43] Ureteral stents are associated with patient discomfort.[36] In the general population, the percentage of patients that are stone free after ureteroscopy is approximately 90%.[36]

1.4.3 Percutaneous nephrolithotomy (PCNL) in the general population

PCNL is recommended for large stones (>2cm), or in cases where retrograde access to the ureter or kidney is not possible. During PCNL, a renal calyx is punctured with the guidance of fluoroscopy and/or ultrasound to gain access to the stone.[42] Various instruments, such as lasers, can then be introduced to fragment the stone, and instruments such as suction, graspers, or baskets are introduced to remove the stones.[23] Although this procedure is relatively more invasive than the other procedures for stone removal, it is still considered safe and efficacious to treat large, multiple, or complex stones in the general population.[23]

1.5 UPPER URINARY TRACT STONE MANAGEMENT IN ADPKD

Optimal stone management requires proper access to upper urinary tract stones. The structural kidney deformation in patients with ADPKD may make gaining optimal access challenging leading to potentially lower stone free rates following SWL, ureteroscopy, and PCNL. The kidney distortion may also increase complication rates in patients with ADPKD. For example, the kidney distortion may impede passage of residual stones, and may lead to urinary tract obstruction; this may cause an acute kidney injury (AKI) event. Additionally, patients with ADPKD are more likely to develop a urinary tract infection (UTI).[45,46] During a UTI event, a coexisting stone may passively trap bacteria and provide an environment that protects the bacteria from the host immune system and antibiotics allowing it to grow easily.[47,48] The passively trapped bacteria may be released upon fragmentation resulting in a UTI event post-discharge.[47] Preoperative obstruction may limit drainage of the urine infected by the released bacteria and sepsis may also result.[48] Therefore, patients with ADPKD may also be at higher risk for sepsis post-intervention. Overall, stone interventions may be associated with lower success rate (i.e. lower stone free rate), and higher post-operative complication rate. However, a systematic review on the outcomes of SWL, ureteroscopy, and PCNL to understand the current state of knowledge and to identify knowledge gaps on this topic is lacking.

1.6 OVERALL AIMS

Understanding of the epidemiology of upper urinary tract stones and stone intervention and the outcomes of stone interventions is limited. The **overarching aim** of this thesis is to understand the epidemiology of upper urinary tract stones and stone interventions, and consequences of upper urinary tract stone management, in patients with ADPKD. We will address current knowledge gaps with the following five studies and their respective objectives.

1.7 STUDY OBJECTIVES

My thesis consists of five manuscripts, and the first two manuscripts are systematic reviews of the literature. My five thesis manuscripts and their respective objectives are outlined below:

<u>STUDY 1</u> - Stone prevalence in patients with ADPKD: a systematic review and meta-analysis

> **Objective 1:** To review English-language studies reporting the incidence and prevalence of stones and stone interventions in adults with ADPKD.

<u>STUDY 2</u> – Efficacy and safety of surgical upper urinary tract stone interventions in patients with ADPKD: a systematic review.

> **Objective 2:** To systematically review studies describing being stone free after the intervention and post-operative complications as reported by each study of the three main stone interventions in adults with ADPKD: shockwave lithotripsy (SWL), ureteroscopy, and percutaneous nephrolithotomy.

<u>STUDY 3</u> – Positive predictive values of International Classification of Diseases, 10th Revisions coding algorithms to identify patients with ADPKD

> **Objective 3:** To determine whether different International Classification of Diseases, 10th, revision coding algorithms in large healthcare databases identify adult patients who meet strict clinical criteria for ADPKD as assessed through medical chart review.
>
> ***Secondary objective:*** To assess the number of patients identified with different ADPKD coding algorithms in Ontario.

<u>STUDY 4</u> – Risk of hospital encounters with upper urinary tract stones in patients with ADPKD: a cohort study

Objective 4: To describe the rate of hospital encounters (emergency department visits or hospital admissions) with upper urinary tract stones, and the rate and type of stone intervention in patients with ADPKD.

Secondary objectives:

a) To compare the rate of hospital encounters (emergency department visits or hospital admission) with stones in patients with and without ADPKD with otherwise similar indicators for baseline health.

b) To determine whether the association between ADPKD (yes, no) and the outcomes are modified by age, sex, and hospital encounters with stones or stone interventions in the prior five years.

c) To identify risk factors for hospital encounters with stones and stone interventions in patients with ADPKD. To also do the same in patients without ADPKD with otherwise similar baseline health as those with ADPKD.

STUDY 5 – Complications in patients with ADPKD undergoing ureteroscopy

Objective 5: To describe the 30-day cumulative incidence of ureteroscopic complications, (composite of urinary tract infection, acute kidney injury, and sepsis), all-cause hospital presentation (either an emergency room visit or hospital admission), all-cause hospital admission, and all-cause emergency department visit following ureteroscopy in patients with ADPKD compared to patients without ADPKD.

1.8 STRUCTURE OF THESIS

An integrated manuscript-based format will be used to present the work of this thesis in a series of five manuscripts, each of which is presented as a chapter.

Chapter 2 addresses objective 1 of the thesis, and it identifies knowledge gaps and summarizes the prevalence and incidence of upper urinary tract stone and stone intervention reported in the literature. This chapter contains a part of the literature review, and a version of this chapter has been published the *Canadian Journal of Kidney Health and Diseases* as the first manuscript: "Stone prevalence in autosomal dominant polycystic kidney disease: a systematic review and meta-analysis."

Chapter 3 addresses objective 2 of the thesis, and it summarizes the outcomes of the three commonly used stone interventions (SWL, ureteroscopy, and PCNL) in patients with ADPKD. This chapter contains the second part of the literature review and a version of this chapter has been published the *Canadian Journal of Kidney Health and Diseases* as the second manuscript: "Efficacy and safety of surgical upper urinary tract stone interventions in autosomal dominant polycystic kidney disease: a systematic review."

Chapter 4 discusses the limitations of the existing literature based on results from Chapters 2 and 3.

Chapter 5 addresses objective 3 of the thesis, and provides insight into whether patients with hospital encounter codes related to ADPKD truly have ADPKD. A version of this chapter has been published in the Canadian Journal of Kidney Health and Diseases: "Positive predictive values of International Classification of Diseases, 10^{th} Revision coding algorithms to identify patients with autosomal dominant polycystic kidney disease."

Chapter 6 addresses objective 4 of the thesis, and it describes the rate of upper urinary tract stones and rate of stone interventions compared to non-ADPKD patients with similar indicators for baseline health. A version of this chapter has been submitted for publication as the fourth manuscript: "Risk of hospital encounters with upper urinary tract stones in autosomal dominant polycystic kidney disease: a cohort study".

Chapter 7 addresses objective 5 of the thesis, and it provides an interim perspective on whether ADPKD is associated with an increased risk of post-operative outcomes following ureteroscopy. A version of this chapter has been submitted for publication as

the fifth manuscript: “Ureteroscopic complications in patients with autosomal dominant polycystic kidney disease”

The last chapter (Chapter 8) of this thesis is the discussion. This chapter summarizes the major findings of this thesis, links all the chapters of the thesis together, states strengths and limitations of the thesis, and discusses future directions.

Additional details on the healthcare administrative databases used for my thesis are provided in Appendix A. Appendix B provides copyright information.

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Chapter 2 - Stone prevalence in autosomal dominant polycystic kidney disease: a systematic review and meta-analysis[a]

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2.1 INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most commonly inherited kidney disease and is characterized by focal cyst development in both kidneys.[1] In early stages of ADPKD, the cysts cause structural deformation to the kidney and damage adjacent nephrons, but overall kidney function is maintained by compensatory hyperfiltration of functioning nephrons.[2,3] As the number and size of cysts increase progressively, more nephrons become damaged, and overall kidney function starts to decline.[4] By the age of 55, about half of the patients reach end-stage kidney disease (ESKD) and require kidney transplantation or dialysis to sustain life.[5,6]

ESKD is not the only kidney manifestation of ADPKD. Previous studies suggest that upper urinary tract stones are more prevalent in patients with ADPKD compared to the general population; however, there remains uncertainty about the incidence and prevalence of upper urinary tract stone in patients with ADPKD.[7–12] Upper urinary tract stones in patients with ADPKD are associated with significant morbidity. For example, stones are a significant determinant of pain, and may accelerate disease progression to ESKD in patients with ADPKD.[13,14]

We conducted this systematic review to critically appraise and summarize studies which reported the incidence and prevalence of upper urinary tract stones and stone interventions in patients with ADPKD. This encompassed studies which also included patients without ADPKD as a comparator.

2.2 METHODS

2.2.1 Design and study selection

We conducted this systematic review using a pre-specified protocol not previously published but detailed below, and report this review according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.[15]

The following studies met our eligibility criteria for review: a) published English full-text articles and conference proceedings; b) any study design (for example, cross-sectional, or cohort study); c) mean age of studies population 18 years or older; d) study populations not solely restricted to patients with ESKD; e) reported prevalence or incidence of stones; and f) studies published any time after 1970 (the resolution of imaging modalities in older studies would be different from current ones). In some studies, patients without ADPKD were included as a comparator to patients with ADPKD, and in such cases we abstracted information on both groups of patients.

2.2.2 Identifying relevant articles

We performed a comprehensive search of bibliographic databases from 1970 to February 2019 (MEDLINE, EMBASE, Web of Science, BIOSIS Preview, and CINAHL) to identify all relevant journal articles and conference proceedings (detailed in Table 2-1). To identify further relevant articles, we also used the 'cited by' function on Web of Science and Google Scholar, and 'related article' function on Google Scholar and 'similar article' function on PubMed to identify other relevant articles. We also reviewed the reference lists of all relevant articles.

Two reviewers (VK and GG) independently removed duplicates and rated the title and abstract of each citation as "relevant", "possibly relevant" or "not relevant". We then retrieved the full-text of "relevant" and "possibly relevant" articles to assess study eligibility. The two reviewers resolved any disagreement through discussion and consensus.

Table 2-1. Search strategy used to identify relevant articles.

Database	Search Strategy
MEDLINE	1. Polycystic Kidney Diseases/ or Polycystic Kidney, Autosomal Dominant/ 2. (((polycystic or "type 2" or "type II" or "type 1" or "type I" or "autosomal dominant" or pkd) adj3 (kidney* or renal)) or adpkd).mp. 3. 1 or 2 4. exp Urolithiasis/

	5. (nephrolith* or urolith* or ureterolith* or lithias* or urolyt or urolyts or ((kidney* or renal or urin* or ureter*) adj3 (calculus or calculi or stone*))).mp. 6. 4 or 5 7. 3 and 6
EMBASE	1. kidney polycystic disease/ 2. (((polycystic or "type 2" or "type II" or "type 1" or "type I" or "autosomal dominant" or pkd) adj3 (kidney* or renal)) or adpkd).mp. 3. 1 or 2 4. urolithiasis/ or calcium oxalate stone/ or calcium stone/ or nephrolithiasis/ or staghorn stone/ or uric acid stone/ or ureter stone/ 5. (nephrolith* or urolith* or ureterolith* or lithias* or urolyt or urolyts or ((kidney* or renal or urin* or ureter*) adj3 (calculus or calculi or stone*))).mp. 6. 4 or 5 **7.** 3 and 6
CINAHL	1. (MH "Kidney, Cystic") OR (MH "Polycystic Kidney, Autosomal Dominant") 2. (((polycystic or "type 2" or "type II" or "type 1" or "type I" or "autosomal dominant" or pkd) N3 (kidney* or renal)) or adpkd) 3. S1 OR S2 4. (MH "Urolithiasis+") 5. (nephrolith* or urolith* or ureterolith* or lithias* or urolyt or urolyts or ((kidney* or renal or urin* or ureter*) N3 (calculus or calculi or stone*))) 6. S4 OR S5 7. S3 AND S6
Web of Science **&** **BIOSIS Preview**	(((((((((polycystic OR "type 2") OR "type II") OR "type 1") OR "type I") OR "autosomal dominant") OR pkd) NEAR (kidney* OR renal)) OR adpkd) AND (((((((((nephrolith* OR urolith*) OR ureterolith*) OR lithias*) OR uralyt) OR uroliths) OR ((((kidney* OR renal) OR urin*) OR ureter*) NEAR ((calculus OR calculi) OR stone*))) OR ((((ESWL OR eswls) OR SWL) OR lithotrips*) OR litholapax*)) OR ((((ureteroscop* OR ureterorenoscop*) OR RIRS) OR retrograde intrarenal surgery) OR FURS)) OR ((PCNL OR mpnl) OR (percutaneous NEAR (nephrostom* OR nephrolithotom*)))))

2.2.3 Data abstraction

Two reviewers (VK and GG) independently abstracted data from all included articles, recorded the data on the standardized abstraction form (Table 2-2), and resolved any disagreements through discussion, or with the help of a third reviewer (DMN). We collected data on study characteristics, patient characteristics, incidence or prevalence of stones, and stone characteristics. We abstracted the prevalence of stone intervention from the included studies that reported it.

We assessed the methodological quality of included studies using a modified Downs and Black checklist (Table 2-3). We assigned all included studies a score between 0 and 22 based on our modified checklist with a higher score indicating a greater quality.[16]

Table 2-2. Data abstraction form

Study Characteristics

ID	Author (Year) *Country*	Study design	No. of centers	Inclusion criteria	Recruitment period	Mean (standard deviation) follow-up	ADPKD sample size	ADPKD case definition
1								

Imaging modality used for ADPKD diagnosis	Control population	Control sample size	Quality score	Stone type	Setting

Patient Characteristics

ID	Author (Year) *Country*	Mean age (standard deviation) (years)	No. of males (%)	No. of patients on dialysis (%)	No. of transplant recipients (%)	No. of patients who had ESKD (%)	No. of hypertensive patients (%)	No. of patients with UTI (%)	Serum creatinine (µmol/L)
1									

Prevalence and Characteristics of Stones

ID	Author (Year) *Country*	No. of unique patients with stones	Prevalence of stone (%)	Stone definition	Modality used to diagnosis stone	Symptoms	Location
1							

Composition	No. of patients that underwent stone intervention	% of patients with stone that underwent intervention	% of ADPKD patients who underwent intervention

Abbreviations: autosomal dominant polycystic kidney disease, ADPKD; end-stage kidney disease, ESKD; urinary tract infection, UTI

Table 2-3. Modified Downs and Black Checklist for observational studies

	Description of Criteria	Probable Answers
1	**Is the hypothesis/aim/objective of the study clearly described?**	1-Yes; 0-No
2	**Are the main outcomes to be measured clearly described in the Introduction or Methods section?**	1-Yes; 0-No
3	**Are the inclusion and exclusion criteria of the populations clearly described?**	1-Yes; 0-No
4	**Is the case definition for ADPKD clearly described?**	1-Yes; 0-No
5	**Is the ADPKD case definition valid or reliable?** *After 2009, Pei criteria; between 1994 and 2009 Ravine criteria; before 1994 other definitions that sounds reasonable*	1-Yes; 0-No
6	**Is the distribution of age, sex, and baseline kidney function in each group of subjects to be compared clearly described?**	1-Yes; 0-No
7	**Are the main findings of the study clearly described?** *Simple data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions.*	1-Yes; 0-No
8	**Does the study provide estimate of the random variability in the data for the main outcome?** *In non-normally distributed data, the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation, or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimate used were appropriate and the question should be answered yes.*	1-Yes; 0-No
9	**Have the characteristics of patients lost to follow-up been described?** *This should be answered YES where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered nowhere a study does not report the number of patients lost to follow-up. If LOF <15% then NO.*	1-Yes; 0-No; 0-N/A
10	**Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?**	1-Yes; 0-No; 0-N/A

11	**Were the subjects asked to participate in the study representative of the entire population from which they were recruited?**	1-Yes; 0-No; 0-UTD
12	**Were those subjects who were prepared to participate representative of the entire population from which they were recruited?** *The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.*	1-Yes; 0-No; 0-UTD
13	**Was the prevalence of stone estimated at a place or facility that is representative of where most of the source population would attend?** *If recruited from tertiary care center, then NO. If recruited from outpatient clinic, then YES.*	1-Yes; 0-No; 0-UTD
14	**There are no unplanned retrospective analyses performed (i.e. data dredging)?** *Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes. If authors report any outcomes/clinical characteristics that were not explicitly referenced in the intro/method section, then my answer to this question is NO; If methods section too brief/not detailed enough, then UTD)*	1-Yes; 0-No; 0-UTD
15	**In cohort studies, do the analyses adjust for different length of follow-up of patients, or in case-control studies is the time period between the intervention and outcome the same for cases and controls?** *Where follow-up was the same for all study patients, the answer should be yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.*	1-Yes; 0-No; 0-UTD; 0-N/A
16	**Were the statistical tests used to assess the main outcome appropriate?** *The statistical techniques used must be appropriate to the data. For example, non-parametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.*	1-Yes; 0-No; 0-UTD; 0-N/A
17	**Reported a case definition for stone?**	1-Yes; 0-No; 0-UTD

18	**Was the case definition for stones accurate and reliable**? *For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrate the outcome measure are accurate, the question should be answered as yes. If authors reference a validation study for their stone definition, or comment on the sensitivity/specificity of the method they used to identify stone, then answer yes*	1-Yes; 0-No; 0-UTD
19	**Were the ADPKD population and controls recruited from the same population?**	1-Yes; 0-No; 0-UTD; 0-N/A
20	**Were the ADPKD population and the controls recruited from the same time period?** *For a study which does not specify the time period over which patient were recruited, the question should be answered as unable to determine.*	1-Yes; 0-No; 0-UTD; 0-N/A
21	**Was there adequate adjustment for confounding in the analyses from which the main finding was drawn?** *Should be answered no if: 1) the distribution of known confounders in the different treatment group was not described;or 2) the distribution of known confounders differed between the two groups but was not taken into account in the analysis.*	1-Yes; 0-No; 0-UTD; 0-N/A
22	**Were losses of patients to follow-up taken into account?** *If the number of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.*	1-Yes; 0-No; 0-UTD; 0-N/A

Abbreviations: not applicable, N/A; unable to determine, UTD

2.2.4 Data analysis

We used a Fischer Exact test for studies with controls that did not statistically compare the prevalence of stones between patients with ADPKD and controls. We also calculated the prevalence ratio of upper urinary tract stones for each of the studies with controls using Cochrane Review Manager 5.3. We assessed for heterogeneity across all studies using the I^2 test. I^2 values of 25%, 50%, and 75% corresponds to low, moderate and high levels of heterogeneity, respectively.[17] We conducted a meta-analysis to combine the results if I^2 was less than 75%. We calculated the meta-analyzed prevalence ratio estimates for upper urinary tract stones using a random effects model and Cochrane Review Manager 5.3.

2.3 RESULTS

2.3.1 Study selection

A schematic diagram of the study selection process is presented in Figure 2-1. Our search yielded 1812 citations, and we identified 29 eligible articles that met our eligibility criteria. We identified an additional 20 eligible articles through our further search strategy described above, which resulted in a total of 49 eligible articles (a total of 9,396 patients with ADPKD) [7–12,14,18–59]. The chance corrected agreement between two independent reviewers for full-text eligibility was excellent ($\kappa = 0.86$).

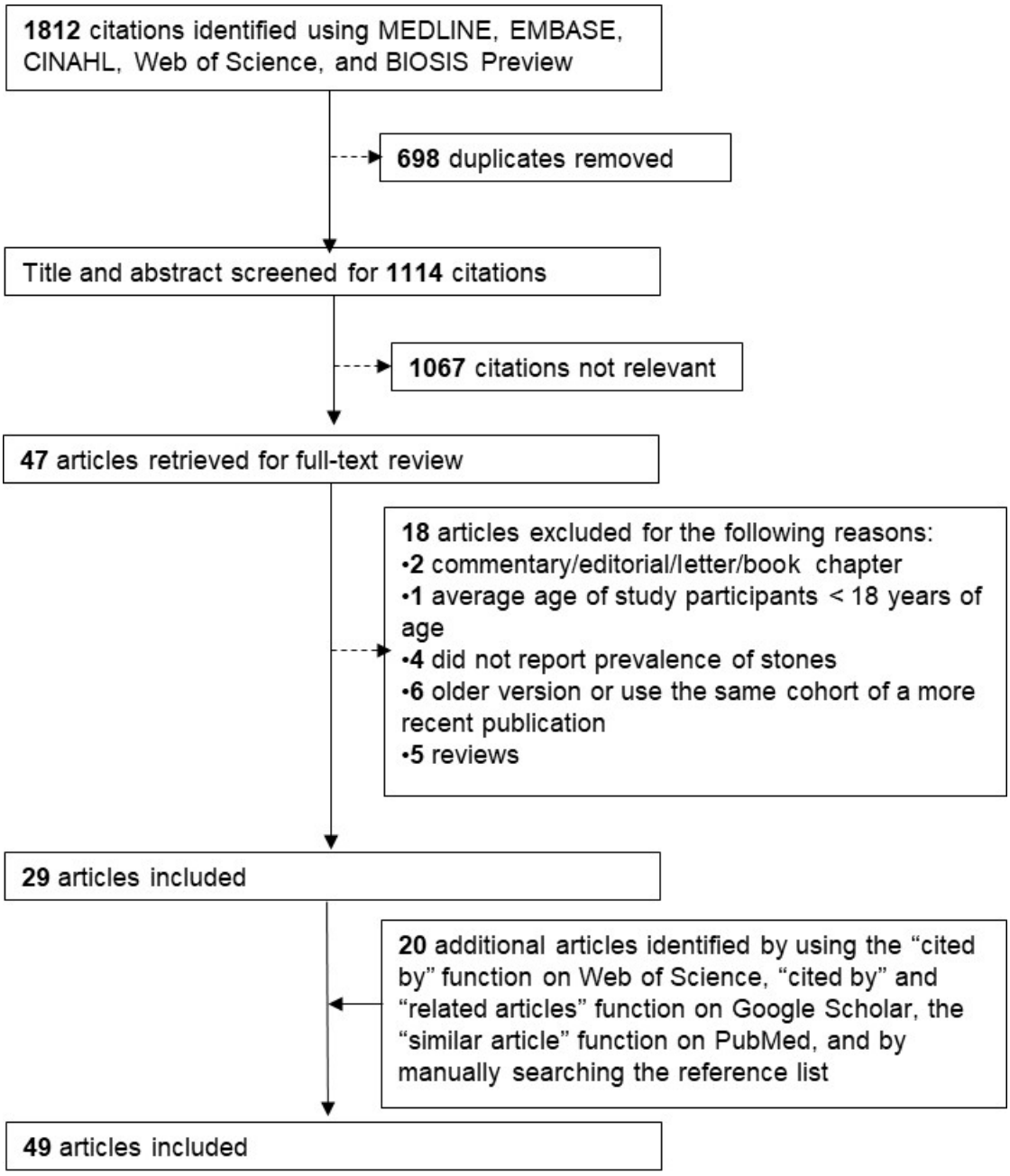

Figure 2-1. Study selection

2.3.2 Description of included studies

The characteristics of included studies are summarized in Table 2-1. The 49 eligible studies were published between 1977 and 2019, and the studies were conducted in Turkey (7 studies) followed by the United States (6 studies), Albania (5 studies), Brazil

(3 studies), India (3 studies), Spain (3 studies), Canada (2 studies), Italy (2 studies), and Japan (2 studies). A single study was conducted in Bulgaria, China, Cyprus, Greece, Ireland, Korea, Pakistan, Philippines, Republic of Macedonia, Saudi Arabia, Senegal, Taiwan, Tunisia, and the United Kingdom, and one was a multi-national study. The country where the study was conducted was unknown for one study. The number of centres participating in a study was unclear in 19 of 49 studies; of the remainder, 21 studies were single center, and 9 were multi-center. Among the 49 included studies, 12 were cohort studies, 33 were cross-sectional studies, and the study design was unclear for 4 studies.

Table 2-4. Study Characteristics

Author (Year) *Country*	**No. of Centers**	**Eligibility Criteria**	**Recruitment Period**	**Mean (SD) Follow-up**	**ADPKD sample size**	**ADPKD Case Definition** *(imaging modality)*	**Control population** *(sample size)*	**Quality Score**[œ]
Cross-sectional Studies								
Al-Muhanna (1995) *Saudi*	1	ADPKD	NR	N/A	30	1. 5+ renal cysts distributed between both kidneys *(U/S, intravenous pyelogram, or CT)*	None	**4**
Baishya (2012) *India*	Unclear	ADPKD	Since 1992	N/A	452	NR *(NR)*	None	**6**
Bajrami (2016) *Albania*	Unclear	ADPKD	2011 to 2014	N/A	100	Ravine criteria *(x-ray or U/S)*	None	**9**
Chang (2013) *Taiwan*	1	ADPKD	October 2008 to May 2011	N/A	46	1. Ravine criteria; <u>*OR*</u> 2. No fam hx + bilateral kidney enlargement + at least 10 cysts in each kidney *(U/S)*	None	**9**
Corradi (2009) *Italy*	Multi-center (unclear)	ADPKD	Since April 2007	N/A	100	Ravine criteria *(U/S)*	None	**12**

Author (Year) *Country*	**No. of Centers**	**Eligibility Criteria**	**Recruitment Period**	**Mean (SD) Follow-up**	**ADPKD sample size**	**ADPKD Case Definition** *(imaging modality)*	**Control population** *(sample size)*	**Quality Score**[Œ]
Demitriou (2000) *Cyprus*	1	1. Alive 2. Has an affected family member with a *PKD2* mutation	up to August 1998	N/A	106	1. 1+ cyst in one kidney for patients aged 5 to 14 years; 2. 2+ unilateral cysts or one in each kidney for patients aged 15 to 19; 3. 3+ cysts in both kidneys combined for patients aged 20 to 29; 4. 2+ cysts in each kidney for patients aged 30 to 59; *AND* 5. 4+ cysts in each kidney for patients aged 60 or over *(U/S)*	unaffected family members *(105)*	**11**
Duli (2013) *Albania*	Unclear	ADPKD	NR	N/A	180	Unclear *(NR)*	None	**7**
Ekin (2014) *Turkey*	1	ADPKD	1995 to 2014	N/A	144	1. 5+ renal cysts in both kidneys *(NR)*	None	**9**
Gall (2017) *France*	22	1. Genkyst study participants 2. 18+ years old 3. Mutation in *PKD2* gene	January 2010 to March 2016	N/A	293	1. Pei criteria; *OR* 2. 10+ cysts in both kidneys combined + no fam hx *(NR)*	None	**10**

Author (Year) *Country*	**No. of Centers**	**Eligibility Criteria**	**Recruitment Period**	**Mean (SD) Follow-up**	**ADPKD sample size**	**ADPKD Case Definition** *(imaging modality)*	**Control population** *(sample size)*	**Quality Score**[Œ]
Galliani (2015) *Italy*	28	ADPKD	February 2013 to April 2014	N/A	462	NR *(NR)*	None	**2**
Gonzalo (1995) *Spain*	Unclear	1. At-risk of ADPKD 2. Asymptomatic 3. 13+ years old	June 1993 to December 1994	N/A	65	1. 1+ cysts in each kidney; *OR* 2. 2+ cysts in one kidney *(U/S)*	unaffected family members *(60)*	**13**
Grampsas (2000) *United States*	1	1. ADPKD 2. Part of The University of Colorado Health Sciences Center's Research Study Group database	NR	N/A	48	NR *(NR)*	None	**7**
Ishibashi (1981) *Japan*	1	ADPKD	May 1972 to September 1980	N/A	118	NR *(U/S or CT)*	None	**3**
Ka (2010) *Senegal*	1	1. ADPKD 2. Black 3. 16+ years 4. Without acquired simple cyst, angiomyolipoma, tuberous sclerosis, cyst calcification, any alterations	January 1, 1995 to December 31, 2005	N/A	53	Ravine criteria *(U/S)*	None	**5**

Author (Year) *Country*	**No. of Centers**	**Eligibility Criteria**	**Recruitment Period**	**Mean (SD) Follow-up**	**ADPKD sample size**	**ADPKD Case Definition** *(imaging modality)*	**Control population** *(sample size)*	**Quality Score**[Œ]
		suggestive of malignancy						
Kaygis (2018) *Turkey*	1	1. Referred and diagnosed with ADPKD at a tertiary care center 2. Not on dialysis 3. eGFR >30 mL/min	2010 to 2016	N/A	118	Pei criteria *(U/S)*	None	**11**
Kazancioglu (2011) *Turkey*	12	ADPKD	January 2003 to December 2009	N/A	1139	5+ cysts distributed between both kidneys *(NR)*	None	**11**
Kim (NR) *Korea*	9	1. Korean 2. ADPKD and CKD 3. Pre-dialysis 4. Part of KNOW-CKD cohort 5. Provided written consent 6. Not a transplant recipient 7. Without heart failure, liver cirrhosis, or current or past history of cancer 8. Not pregnant 9. No single kidney due to trauma or kidney donation	April 2011 to February 2016	N/A	364	Pei criteria *(U/S)*	None	**11**

Author (Year) *Country*	**No. of Centers**	**Eligibility Criteria**	**Recruitment Period**	**Mean (SD) Follow-up**	**ADPKD sample size**	**ADPKD Case Definition** *(imaging modality)*	**Control population** *(sample size)*	**Quality Score**[Œ]
Kumar (2012) *India*	1	ADPKD	November 2011 to October 2012	N/A	41	Unclear *(U/S, intravenous pyelogram, CT)*	None	**7**
Memili (2007) *Turkey*	1	1. ADPKD 2. Referred to nephrology outpatient clinic	January 2003 to December 2006	N/A	136	NR *(NR)*	None	**8**
Meng (2018) *China*	1	1. ADPKD 2. Inpatient 3. Complete medical records	January 2012 to December 2016	N/A	167	Japanese criteria for patients with unknown genotype (*NR*)	None	**10**
Milutinovic (1984) *United States*	Unclear	At-risk of ADPKD	NR	N/A	140	1. Fam hx + multiple bilateral cysts *(Unclear)*	unaffected family members *(119)*	**12**
Milutinovic (1990) *United States*	Unclear	1. Fam hx of ADPKD 2. 50+ years old	NR	N/A	32	1. Bilateral renal cysts + fam hx (Unclear)	unaffected family members *(25)*	**12**
Nikolov (2012) *Unclear*	1	ADPKD referred to center	1998 to 2008	N/A	208	NR *(NR)*	None	**4**
Nishiura (2009) *Brazil*	1	1. Referred to PKD unit due to presence of affected progenitor/sibling with ADPKD 2. ADPKD confirmed using U/S	NR	N/A	125	Ravine criteria *(U/S or CT)*	None	**14**
Parfrey (1990) *Canada*	NR	Family members of index ADPKD cases	NR	N/A	Unclear	1. Reported on autopsy report, surgical report or of a death due to CKD with an ADPKD diagnosis;	Unaffected family members *(Unclear)*	**12**

Author (Year) *Country*	**No. of Centers**	**Eligibility Criteria**	**Recruitment Period**	**Mean (SD) Follow-up**	**ADPKD sample size**	**ADPKD Case Definition** *(imaging modality)*	**Control population** *(sample size)*	**Quality Score**[Œ]
						2. 1+ in each kidney; <u>*OR*</u> 3. 1+ in one kidney *(excretory urography, CT, U/S)*		
Romao (2006) *Brazil*	1	ADPKD	January 1985 to December 2003	N/A	92	1. Ravine criteria; <u>*OR*</u> 2. Fam hx + hepatic cyst *(U/S)*	None	**9**
Roscoe (1993)[‡] *Canada*	Unclear	ADPKD	NR	N/A	80	NR *(NR)*	None	**9**
Segal (1977) *United States*	2	ADPKD	NR	N/A	100	NR *(NR)*	None	**3**
Strakosha (2006) *Albania*	NR	ADPKD	NR	N/A	180	NR *(NR)*	None	**5**
Torra (1996) *Spain*	Unclear	ADPKD or at-risk of ADPKD	NR	N/A	PKD1: 146 PKD2: 20 All: 166	Ravine criteria *(U/S)*	Unaffected Family members *(150)*	**13**

Author (Year) *Country*	**No. of Centers**	**Eligibility Criteria**	**Recruitment Period**	**Mean (SD) Follow-up**	**ADPKD sample size**	**ADPKD Case Definition** *(imaging modality)*	**Control population** *(sample size)*	**Quality Score**[Œ]
Torres (1988) *United States*	1	1. ADPKD 2. Without any cyst wall calcification, or with poorly localized parenchymal calcification	1976 to 1986	N/A	751	1. Bilateral polycystic kidneys + fam hx; *OR* 2. No fam hx + bilaterally enlarged and polycystic kidneys + exclusion of other disorders associated with renal cysts *(NR)*	None	**10**
Vikrant (2017) *India*	1	1. ADPKD 2. Attending renal clinic	April 2009 to March 2015	N/A	208	1. Pei criteria; *OR* 2. Fam hx + hepatic cyst *(U/S)*	None	**13**
Yildz (2016) *Turkey*	Unclear	1. ADPKD 2. Not on renal replacement therapy 3. eGFR > 30mL/min 4. in the Turkish Nephrology Society Cystic Kidney Disease Working Group online database	NR	N/A	93	NR *(NR)*	None	**3**
Cohort Study								
Gonzalo (1990) *Spain*	1	ADPKD	June 1977 to June 1988	6 years 3 months (NR)	107	1. 3+ cysts in each kidney + fam hx *(excretory urography or U/S)*	None	

Author (Year) *Country*	**No. of Centers**	**Eligibility Criteria**	**Recruitment Period**	**Mean (SD) Follow-up**	**ADPKD sample size**	**ADPKD Case Definition** *(imaging modality)*	**Control population** *(sample size)*	**Quality Score**[Œ]
Hajji (2019) *Tunisia*	Multi-center (Unclear)	ADPKD	1969 to 2016	NR	569	NR *(NR)*	None	**10**
Hateboer (1999) *The Netherlands, Spain, Bulgaria, and the United Kingdom*	7	ADPKD	NR	NR	624	1. Ravine criteria; 2. DNA linkage test; *OR* 3. Report of ADPKD on medical records *(U/S)*	None	**14**
Idrizi (2009) *Albania*	Unclear	ADPKD	NR	NR	180	NR *(NR)*	None	**10**
Ozkok (2013) *Turkey*	1	ADPKD	January 2000 to January 2012	100 (38) months	323	Pei criteria *(U/S)*	None	**13**
Papadopoulou (1999) *Greece*	Unclear	At-risk of ADPKD	NR	NR	85	1. 2+ cysts in one kidney and one cyst in the other kidney+ fam hx (U/S)	None	**10**
Rabbani (2008) *Pakistan*	1	ADPKD	January 1997 to December 2003	7.6 (4.2) years	56	1. Fam hx + 2+ cysts in either kidney + hypertension or renal insufficiency; 2. Bilateral cysts + no fam hx; *OR* 3. Unilateral polycystic kidney + liver cyst, berry aneurysm, arterio-venous malformation or evidence of prior cerebrovascular accident on MRI/MRA *(U/S)*	None	**9**

Author (Year) *Country*	**No. of Centers**	**Eligibility Criteria**	**Recruitment Period**	**Mean (SD) Follow-up**	**ADPKD sample size**	**ADPKD Case Definition** *(imaging modality)*	**Control population** *(sample size)*	**Quality Score**[Œ]
Ritovska (2014) *Republic of Macedonia*	Unclear	ADPKD	NR	3 (NR) years	60	Unclear *(echosonography or CT)*	None	**5**
Senal (2016) *Turkey*	Unclear	ADPKD	January 1990 to January 2015	NR	300	NR *(NR)*	None	**6**
Tantoco (1986) *Philippines*	1	ADPKD	May 1973 to January 1986	3 (NR) years	60	1. Signs and symptoms + fam hx + imaging *(intravenous pyelogram, infusion intravenous pyelogram with tomogram, U/S or CT)*	None	**3**
Thong (2013)[‡] *United Kingdom*	Unclear	1. ADPKD 2. In research database 3. Have at least five years of renal function tests at the time of analysis	1978 to 2012	11.3 (5.5) years	210	NR *(NR)*	None	**8**
Wright (1993) *Ireland*	Unclear	Belonging to *PKD1* family	NR	NR	PKD1: 49 Non-PKD1: 17 All: 66	ADPKD documented the following ways: 1) by post-mortem examination; 2) by report of a death due to chronic renal failure with a clinical diagnosis of ADPKD;	None	**10**

Author (Year) *Country*	**No. of Centers**	**Eligibility Criteria**	**Recruitment Period**	**Mean (SD) Follow-up**	**ADPKD sample size**	**ADPKD Case Definition** *(imaging modality)*	**Control population** *(sample size)*	**Quality Score**[Œ]
						3) by operative report during abdominal surgery; 4) by excretory urography or CT scan; 5) by unequivocal findings on ultrasonography; *OR* 6) 1+ cyst in in at least one kidney *(diagnostic data files or ultrasound)*		
Study Design Unclear								
Delaney (1985) *United States*	1	symptomatic ADPKD	1947 to 1980	12 (NR) years	53	1. History and physical examination; *OR* 2. Diagnosis confirmed with imaging or autopsy *(intravenous pyelogram with tomograms, sonography, CT with contrast, arteriography, laparotomy)*	None	**4**
Dimitrakov (1994) *Bulgaria*	Unclear	ADPKD	NR	N/A	82	Unclear *(echography, venous urography, or CT)*	None	**5**

Author (Year) *Country*	**No. of Centers**	**Eligibility Criteria**	**Recruitment Period**	**Mean (SD) Follow-up**	**ADPKD sample size**	**ADPKD Case Definition** *(imaging modality)*	**Control population** *(sample size)*	**Quality Score**[Œ]
Higashira (1992) *Japan*	38	ADPKD	January 1988 to December 1988	N/A	316	NR *(U/S or CT)*	None	**11**
Idrizi (2011) *Albania*	Unclear	ADPKD	2002 to 2009	N/A	200	Ravine criteria *(U/S)*	None	**7**

Abbreviations: autosomal dominant polycystic kidney disease, ADPKD; computed tomography, CT; family history, Fam Hx; intravenous, IV; not applicable, N/A; not reported, NR; standard deviation, SD; ultrasound, U/S

[‡]Data was abstracted and methodological quality was assessed for the portion of the multi-component study that reported the prevalence of stones

[Œ] A modified Downs and Black checklist was used to assess the methodological quality of each included study. The methods quality score ranged between 0 and 22 with higher scores indicating higher quality.

2.3.3 Patient population

The sample size of patients with ADPKD ranged from 30 to 1139 (Table 2-4). The mean age of patients with ADPKD ranged from 26 to 61 years, 35% to 71% of the patients with ADPKD were male, up to 51% developed ESKD, 5% to 88% were hypertensive, and 1% to 73% experienced at least one prior urinary tract infection (UTI) (Table 2-5).

Six studies compared the prevalence of stones in patients with ADPKD to unaffected family members as controls.[7–12] The mean age of controls ranged from 35 to 60 years, 36% to 48% of the controls were male, 4% to 36% were hypertensive, and 2% to 36% experienced a prior UTI (Table 2-5).

Table 2-5. Patient characteristics

Author (Year) *Country*	**Mean Age (standard deviation) (years)**	**No. of Male (%)**	**No. of Patients on Dialysis (%)**	**No. of Transplant Recipient (%)**	**No. of patients who had ESRD (%)**	**No. of Hypertensive Patients (%)**	**No. of Patients with UTI (%)**	**Serum Creatinine (µmol/L)**
Al-Muhanna (1995) *Saudi*	45 (10)	13 (43)	2 (7)	2 (7)	4 (13)	17 (57)	22 (73)	NR
Baishya (2012) *India*	NR	NR	NR	NR	NR	NR	NR	NR
Bajrami (2016) *Albania*	NR	42 (42)	NR	NR	NR	NR	NR	NR
Chang (2013) *Taiwan*	48 (13)	24 (52)	NR	NR	NR	31 (67)	17 (37)	NR
Corradi (2009) *Italy*	48 (NR)	58 (58)	NR	6 (6)	29 (29)	75 (75)	NR	NR
Demitriou (2000) *Cyprus*	ADPKD: 38 (NR) CONTROL: NR (NR)	NR	ADPKD: 0 (0) CONTROL: NR (NR)	ADPKD: 1 (1) CONTROL: NR (NR)	NR	ADPKD: 24 (23) CONTROL: 4 (4)	ADPKD: 24 (23) CONTROL: 12 (11)	NR
Duli (2013) *Albania*	NR	NR	NR	NR	NR	NR	NR	NR
Ekin (2014) *Turkey*	45 (NR)	61 (42)	NR (11)	NR	NR (11)	117 (82)	14 (2)*	168 (186)
Gall (2017) *France*	61 (NR)	123 (42)	NR	NR	Unclear	221 (75)	NR	NR
Galliani (2015) *Italy*	NR	194 (42)	NR	NR	NR	NR (60)	NR (28)	NR
Gonzalo (1995) *Spain*	ADPKD: 33 (NR) CONTROL: NR (NR)	ADPKD: 26 (40) CONTROL: 28 (47)	NR	NR	NR	ADPKD: 19 (29) CONTROL: 3 (5)	ADPKD: 4 (6) CONTROL: 1 (2)	NR

Author (Year) *Country*	**Mean Age (standard deviation) (years)**	**No. of Male (%)**	**No. of Patients on Dialysis (%)**	**No. of Transplant Recipient (%)**	**No. of patients who had ESRD (%)**	**No. of Hypertensive Patients (%)**	**No. of Patients with UTI (%)**	**Serum Creatinine (µmol/L)**
Grampsas (2000) *United States*	NR	17 (35)	NR	NR	NR	23 (48)	NR	NR
Ishibashi (1981) *Japan*	44 (NR)	54 (46)	NR	NR	NR	NR	57 (54)*	NR
Ka (2010) *Senegal*	47 (5)	30 (57)	10 (19)	NR	27 (51)	36 (68)	7 (13)	NR
Kaygis (2018) *Bursa*	NR	54 (46)	0 (0)	NR	0 (0)	72 (61)	29 (25)	NR
Kazancioglu (2011) *Turkey*	NR	548 (48)	108 (11)	8 (1)	NR	828 (73)	228 (23)*	194 (194)
Kim (NR) *Korea*	47 (11)	184 (51)	0 (0)	0 (0)	NR	319 (88)	8 (2)	119 (79)
Kumar (2012) *India*	NR	29 (71)	NR	NR	13 (32)	27 (66)	6 (40)	398 (283)
Memili (2007) *Turkey*	47 (16)	65 (48)	16 (12)	1 (1)	NR	98 (72)	22 (16)	NR
Meng (2018) *China*	49 (NR)	72 (43)	NR	NR	NR	84 (50)	41 (25)	309 (290)
Milutinovic (1984) *United States*	ADPKD: 37 (14) CONTROL: 35 (16)	ADPKD: 64 (46) CONTROL: NR (NR)	ADPKD: 25 (18) CONTROLS: 0 (0)	NR	ADPKD: 28 (20) CONTROL: 0 (0)	ADPKD: 73 (52) CONTROLS: 13 (11)	ADPKD: 64 (46) CONTROLS: 33 (28)	NR
Milutinovic (1990) *United States*	ADPKD: 58 (7) CONTROL: 60 (7)	ADPKD: 15 (47) CONTROL: 9 (36)	NR	NR	ADPKD: 15 (47) CONTROL: 0 (0)	ADPKD: 22 (69) CONTROL:NR (36)	ADPKD: 13 (41) CONTROL: NR (36)	NR
Nikolov (2012) *Unclear*	NR	NR	NR	NR	NR	NR	NR	NR
Nishiura (2009) *Brazil*	NR	45 (36)	NR	NR	NR	59 (47)	4 (3)	NR

Author (Year) *Country*	**Mean Age (standard deviation) (years)**	**No. of Male (%)**	**No. of Patients on Dialysis (%)**	**No. of Transplant Recipient (%)**	**No. of patients who had ESRD (%)**	**No. of Hypertensive Patients (%)**	**No. of Patients with UTI (%)**	**Serum Creatinine (µmol/L)**
Parfrey (1990) *Canada*	NR	NR	NR	NR	NR	ADPKD: 118 (36) CONTROL: 238 (16)	ADPKD: 24 (22)* CONTROL: 35 (17)*	NR
Romao (2006) *Brazil*	35 (15)	34 (37)	NR	NR	27 (29)	61 (63)	33 (36)	212 (247)
Roscoe (1993) ‡ *Canada*	NR	NR	NR	NR	22 (28)	NR	NR	NR
Segal (1977) *United States*	NR	NR	NR	NR	NR	NR	NR	NR
Strakosha (2006) *Albania*	NR	NR	NR	NR	NR	NR	NR	NR
Torra (1996) *Spain*	NR	ADPKD: 72 (43) CONTROL: 72 (48)	NR	NR	ADPKD: 42 (25) CONTROL: NR (NR)	ADPKD: 76 (46) CONTROL: 23 (15)	ADPKD: 57 (34)* CONTROL: 26 (17)	NR
Torres (1988) *United States*	NR	393 (52)	NR	NR	NR	NR	NR	NR
Vikrant (2017) *India*	46 (15)	126 (61)	5 (2)	NR	20 (10)	145 (70)	81 (39)	292 (318)
Yildz (2016) *Turkey*	41 (13)	49 (53)	0 (0)	0 (0)	0 (0)	NR (72)	NR	NR
Gonzalo (1990) *Spain*	46 (14)	58 (54)	NR	NR	NR	73 (68)*	33 (31)*	NR
Hajji (2019) *Tunisia*	49 (14)	297 (52)	298 (52)	13 (2)	NR	321 (59)	NR (24)	459 (NR)
Hateboer (1999) *The Netherlands, Spain, Bulgaria, and*	NR	308 (49)	NR	NR	NR	227 (50)*	119 (28)*	NR

Author (Year) *Country*	Mean Age (standard deviation) (years)	No. of Male (%)	No. of Patients on Dialysis (%)	No. of Transplant Recipient (%)	No. of patients who had ESRD (%)	No. of Hypertensive Patients (%)	No. of Patients with UTI (%)	Serum Creatinine (µmol/L)
the United Kingdom								
Idrizi (2011) *Albania*	NR	97 (49)	NR	NR	NR	NR	108 (54)	NR
Ozkok (2013) *Turkey*	53 (15)	149 (46)	46 (14)	NR	48 (14)	255 (79)*	64 (21)*	NR
Papadopoulou (1999) *Greece*	26 (12)	44 (52)	NR	NR	NR	ADPKD: 4 (5)	ADPKD: 1 (1)	NR
Rabbani (2008) *Pakistan*	NR	40 (71)	NR	NR	7 (13)	38 (68)	NR	398 (282)
Ritovska (2014) *Republic of Macedonia*	43 (13)	NR	NR	NR	NR	NR	NR	NR
Senal (2016) *Turkey*	NR	143 (48)	NR	NR	NR	231 (83)*	52 (19)*	203 (221)
Tantoco (1986) *Philippines*	44 (NR)	30 (50)	NR	NR	17 (28)	40 (67)	17 (28)	NR
Thong (2013) ‡ *United Kingdom*	46 (16)	102 (49)	NR	NR	NR	147 (70)	57 (27.2)	NR
Wright (1993) *Ireland*	NR	NR	NR	NR	12 (18)	16 (24)	5 (8)	NR
Delaney (1985) *United States*	NR	21 (40)	9 (17)	NR	NR	11 (21)	10 (19)	NR
Dimitrakov (1994) *Bulgaria*	NR	34 (41)	NR	NR	NR	NR	NR	NR
Idrizi (2009) *Albania*	NR	NR	NR	NR	NR	NR	108 (60)	NR

Author (Year) *Country*	**Mean Age (standard deviation) (years)**	**No. of Male (%)**	**No. of Patients on Dialysis (%)**	**No. of Transplant Recipient (%)**	**No. of patients who had ESRD (%)**	**No. of Hypertensive Patients (%)**	**No. of Patients with UTI (%)**	**Serum Creatinine (µmol/L)**
Higashira (1992) *Japan*	51 (13)	167 (53)	72 (23)	NR	72 (23)	201 (64)*	NR	354 (380)

Abbreviations: autosomal dominant polycystic kidney disease, ADPKD; not reported, NR; standard deviation, SD; urinary tract infection, UTI

‡Data was abstracted for the portion of the multi-component study that reported the prevalence of stones.

*Denominator includes a subset of the population.

2.3.4 Quality assessment of studies

The methodological quality of the studies was limited as the methods quality score ranged from 2 to 14 out of 22 (where higher scores indicates higher methodological quality).

The internal validity of studies' results is affected by the definition of the exposure being investigated and the outcome of interest. Of the 49 studies, 29 specified the definition for ADPKD. Patients with ADPKD were identified using the Ravine's criteria in 6 studies, Ravine's criteria or another additional criterion such as family history and liver cysts in 3 studies, Pei's criteria in 3 studies, Pei's criteria and an additional criterion in 2 studies, at least 5 cysts in each kidney in 3 studies, and other criteria in the remaining 13 studies; the definition for ADPKD was unclear or not reported in the remaining 19 studies. Ravine and Pei criteria to diagnose ADPKD are summarized in Table 2-6 and Table 2-7, respectively.[61,62] Some studies used a definition different from the most accepted diagnostic criteria at the time the study was published. For example, Ekin et al. (2014) and Kazancioglu et al. (2011) defined patients with at least five cysts in each kidney as patients with ADPKD, although Pei's criteria were the most commonly used diagnostic criteria for ADPKD during the time period in which the studies were conducted.[29,46]

Table 2-6. Ravine ultrasonographic criteria for diagnosing autosomal dominant polycystic kidney disease

Age	Positive Family History	Negative Family history
< 30 years	2 cysts bilaterally or unilaterally	5 cysts bilaterally
30 to 60 years	4 cysts bilaterally	5 cysts bilaterally
> 60 years	8 cysts bilaterally	8 cysts bilaterally

Table 2-7. Pei ultrasonographic criteria for diagnosing autosomal dominant polycystic kidney disease (ADPKD)

Age (years)	Diagnostic Criteria
15 to 39	At least 3 cysts (unilateral or bilateral)
40 to 59	2 cysts/kidney
≥ 60	4 or more cysts/kidney

*Note: Fewer than 2 cysts in individuals ≥ 40 years old and are at risk of ADPKD is sufficient to rule out the disease.

Thirty of the 49 studies described how they identified patients with stones, while the remaining 19 studies did not. Among the 30 studies that specified how the stones were detected, 3 studies relied on patient self-report of a history of stones, 14 solely relied on radiological evidence of stone, and 13 studies relied on combination of radiological evidence of stone and at least one other criterion (i.e. stone passage and recovery, surgical removal of stone and self-report of stone). Among the 27 of the 30 studies that used radiological evidence of stones as one of their diagnostic criteria, 9 reviewed historic imaging, 10 reviewed recent imaging, and the nature of considered imaging was unclear in 8 studies. Eight of the 27 studies thoroughly described what they were looking for on the radiological image to identify stones. Amongst the five studies that reported asymptomatic stones, the percentage of patients ranged between 1% and 68%.[18,19,22,38,49]

The setting and source population from which the samples are recruited affects the study generalizability. For 21 of the studies, the setting or population from which the sample was recruited from was unclear or not reported. Patients were recruited from hospitals in 18 studies, outpatient clinics in 7 studies, solely from an inpatient setting in 1 study, an outpatient ADPKD specialty clinic in 1 study, and from both an inpatient and outpatient setting for 1 study. It is unclear if patients were recruited from an inpatient or outpatient setting for 20 studies and setting was not reported for one study.

Six of the 49 studies compared the prevalence of stones in patients with ADPKD to controls, which were unaffected family members. All of these studies were cross-

sectional. Only two of the six studies statistically compared the prevalence of stones in patients with ADPKD to controls. Both of these studies used univariate analyses and did not adjust for any confounders.

2.3.5 Prevalence and characteristics of stones and prevalence of stone intervention

In patients with ADPKD, the prevalence of stones ranged between 3% and 59% (Table 2-8). Of those patients with stones, 2% to 47% underwent at least one stone intervention. UTI and flank pain were the predominant precursor to diagnosis of stones in patients with ADPKD.[18,22,25,38,41,49] In most patients, stones were solely located in the renal calyces [18,19]. Most stones were composed of uric acid according to six studies[7,19,21,22,38,49], and oxalate according to two studies (Table 2-9).[23,27]

Table 2-8. Prevalence of stones and stone intervention in patients with autosomal dominant polycystic kidney disease and controls

Author (Year) *Country*	**Stone Definition (*Modality)***	**No. of unique patients with stones (%)**	**No. of unique patients who underwent stone intervention (%)**
Al-Muhanna (1995) *Saudi*	NR *(Unclear)*	5 (17)	NR
Baishya (2012) *India*	NR *(NR)*	19 (4)	9 (2)
Bajrami (2016) *Albania*	Echogenic focus with posterior acoustic shadowing within the kidney [R] *(U/S; or plain abdominal KUB film, intravenous pyelography and non-contrast helical CT in cases where stones were not observed on U/S or KUB film)*	58 (58)	NR
Chang (2013) *Taiwan*	NR *(NR)*	19 (41)	NR
Corradi (2009) *Italy*	NR *(NR)*	24 (24)	NR
Demitriou (2000) *Cyprus*	Passage of stone or presence of stone on a plain KUB film or U/S [ψ] *(Plain KUB film or U/S)*	ADPKD: 21 (20) CONTROL: 4 (4)	NR
Duli (2013) *Albania*	Image of stone within the urinary collecting system [R] *(U/S, renal radiography, CT)*	106 (59)	NR
Ekin (2014) *Turkey*	Presence and absence of stone on U/S [ψ] and/or history of passing stone *(U/S)*	24 (17)	NR
Gall (2017) *France*	NR *(NR)*	57 (20)	NR
Galliani (2015) *Italy*	NR *(NR)*	102 (22)	NR
Gonzalo (1995) *Spain*	Hyperechogenic image with posterior shadowing [R] *(U/S or plain roentgenogram with tomograms)*	ADPKD: 7 (11) CONTROL: 2 (3)	NR
Grampsas (2000) *United States*	Echogenic focus with posterior acoustic shadowing within the kidney but outside an identifiable cyst [R] + with or without a clinical history of stone *(U/S)*	15 (31)	NR

Author (Year) *Country*	**Stone Definition (*Modality)***	**No. of unique patients with stones (%)**	**No. of unique patients who underwent stone intervention (%)**
Ishibashi (1981) *Japan*	NR *(NR)*	10 (13)	NR
Ka (2010) *Senegal*	NR *(NR)*	6 (11)	NR
Kaygis (2018) *Bursa*	History of stone or positive imaging [R] *(U/S, non-contrast CT)*	28 (24)	10 (8)
Kazancioglu (2011) *Turkey*	Presence or absence of urinary tract stones on U/S [ϒ] and/or history of passing stone *(U/S)*	278 (27)*	NR
Kim (NR) *Korea*	NR *(NR)*	92 (29)*	NR
Kumar (2012) *India*	NR *(NR)*	6(15)	NR
Memili (2007) *Turkey*	Presence and absence of upper urinary tract stone [ψ] *(U/S)*	39 (29)	NR
Meng (2018) *China*	NR *(NR)*	65 (39)	NR
Milutinovic (1984) *United States*	Stones apparent on radiogram [ϒ] or passed in urine *(radiogram)*	ADPKD: 16 (11) CONTROL: 5 (4)	NR
Milutinovic (1990) *United States*	Stone apparent on radiograms [R] or were found in urine *(radiogram)*	ADPKD: 5 (17) CONTROL: 3 (12)	NR
Nikolov (2012) *Unclear*	NR *(NR)*	29 (14)	NR
Nishiura (2009) *Brazil*	Image of stone within the renal collection system[R] *(U/S and CT)*	35 (28)	NR
Parfrey (1990) *Canada*	Self-report history of upper urinary tract stones during interview *(NR)*	ADPKD: 16 (15) * CONTROL: 20 (10) *	NR
Romao (2006) *Brazil*	NR *(NR)*	15 (16)	NR
Roscoe (1993) [‡] *Canada*	Acoustic shadowing on radiologic imaging [ψ] *(NR)*	8 (10)	NR
Segal (1977) *United States*	NR *(NR)*	20 (20)	NR

Author (Year) *Country*	**Stone Definition (*Modality)***	**No. of unique patients with stones (%)**	**No. of unique patients who underwent stone intervention (%)**
Strakosha (2006) *Albania*	Presence on imaging [R] *(ultrasound or abdominal x-ray)*	81 (45)	2 (1)
Torra (1996) *Spain*	Passage of stone with recovery of stone or evidence of stone within the collecting system as reported by the radiologist [ψ] *(unclear)*	ADPKD: 29 (18) CONTROL: 15 (10)*	NR
Torres (1988) *United States*	Historical evidence of passage, recovery, surgical removal of stone, evidence of stone within the collecting system, or renal papillary tips as reported by radiologist [ψ] *(excretory urogram for a subset [79 patients]; unclear for remaining patients)*	151 (20)	31 (4)
Vikrant (2017) *India*	History of stone passage, removal of stone or calcific foci/nephrocalcinosis seen on imaging [ψ] *(unclear)*	81 (39)	NR
Yildz (2016) *Turkey*	Self-reported history of stone *(NR)*	23 (25)	NR
Gonzalo (1990) *Spain*	Passage or surgical removal of stones or presence of radio-opaque deposits on x-ray [Ɏ] *(x-ray)*	32 (30) [ʌ]	NR
Hajji (2019) *Tunisia*	NR *(NR)*	28 (5) [ʌ]	NR
Hateboer (1999) *The Netherlands, Spain, Bulgaria, and the United Kingdom*	Radiological evidence of upper urinary tract stone [Ɏ] *(U/S, plain radiographs, intravenous pyelograms, CT)*	42 (10)* [ĸ]	NR
Idrizi (2009) *Albania*	An echogenic focus with posterior acoustic shadowing within the kidney but outside an identifiable cyst and with or without clinical history of stone [R] *(U/S and X-ray)*	76 (42) [Œ]	2 (1)
Ozkok (2013) *Turkey*	Self-reported hx of passing stone or presence or absence of upper urinary tract stone on ultrasound [ψ] *(U/S)*	101 (33) [Œ]	NR
Papadopoulou (1999) *Greece*	Self-reported history of stone during interview *(NR)*	3 (4) [Œ]	NR
Rabbani (2008) *Pakistan*	Presentation on imaging [ψ] *(NR)*	6 (11) [Œ]	NR

Author (Year) *Country*	**Stone Definition (*Modality)***	**No. of unique patients with stones (%)**	**No. of unique patients who underwent stone intervention (%)**
Ritovska (2014) *Republic of Macedonia*	Evidence on imaging [R] *(echosonography and CT scan)*	22 (37) [Œ]	NR
Senal (2016) *Turkey*	NR *(NR)*	68 (28)* [Œ]	NR
Tantoco (1986) *Philippines*	Presence of radiopaque stone on radiographic ultrasound [Ɏ] *(radiograph or U/S)*	18 (30) [^]	NR
Thong (2013) [‡] *United Kingdom*	NR *(NR)*	16 (8) [Œ]	NR
Wright (1993) *Ireland*	NR *(NR)*	2 (3) [Œ]	NR
Delaney (1985) *United States*	Passage of stone or surgical removal of stones from urinary tract or presence of radio-opaque deposits on x-ray [Ɏ] *(x-ray)*	18 (34)	1 (2)
Dimitrakov (1994) *Bulgaria*	Presence or absence of upper urinary tract stone on imaging [Ɏ] *(echography, venous urography, CT)*	23 (28)	NR
Higashira (1992) *Japan*	NR *(NR)*	53 (18)*	NR
Idrizi (2011) *Albania*	Echogenic focus with posterior acoustic shadowing within the kidney [Ɏ] *(U/S; or plain abdominal KUB film, intravenous pyelography and non-contrast helical CT in cases where stones were not observed on U/S or KUB film)*	116 (58)	4 (2)

Abbreviations: computed tomography scan, CT; kidney, ureter, bladder, KUB; not reported, NR; ultrasound, U/S

* The denominator only includes a subset of the study population

[‡] Data was abstracted for the portion of the multi-component study that reported the prevalence of stones

[R] Patients underwent prospective abdominal imaging.

[ψ] Authors reviewed historic images to ascertain stone event.

[Ɏ] Unclear whether investigators prospectively imaged abdomen or reviewed past abdominal images or imaging report to identify stone event.

[Œ] Stone event was ascertained at baseline; therefore, the percentage is a prevalence estimate.

[κ] Stone was ascertained at baseline and during follow-up; therefore, the percentage is a prevalence estimate.

[^] Unclear whether stone event was ascertained at baseline or during follow-up; therefore, unknown whether the reported percentage was a prevalence or incidence estimate.

Table 2-9. Symptoms and characteristics of stones

Author (Year) *Country*	Symptoms	Location	Composition
Baishya (2012) *India*	• Anorexia: 3 (16%) • Fever: 1 (5%) • Fluid Overload: 2 (11%) • Hematuria: 5 (26%) • Pain: 6 (32%) • Vomiting: 3 (16%) • Weakness: 2 (11%)	Location of stones in the 23 kidneys with stones among 19 patients (denominator is 23): • Renal calyces: 10 (28%) • Renal pelvis: 2 (9%) • Both renal pelvis and calyces: 5 (22%) • Ureter: 5 (22%) • Staghorn: 1 (4%)	NR
Bajrami (2016) *Albania*	NR	NR	• Calcium oxalate: NR (39%) • Urate: NR (47%) • Other compounds: NR (14%)
Demitriou (2000) *Cyprus*	NR	NR	Majority were uric acid
Kaygis (2018) *Bursa*	Lower back pain: 10 (36%)	NR	NR
Nishiura (2009) *Brazil*	Low back pain	NR	NR
Strakosha (2006) *Albania*	• 40% of patients with stone associated with a history of UTI and flank pain	NR	• Calcium oxalate: NR (39%) • Urate: NR (47%) • Other Compounds: NR (14%)
Torres (1988) *United States*	NR	Among the 71 patients where details about stone location is available: • Only renal calyces: 63 (89%) • Renal pelvis/Staghorn: 4 (6%) • Ureter: 4 (6%)	Composition examined in 30 patients: • Calcium carbonate: 3 (10%) • Calcium oxalate: 14 (47%) • Calcium phosphate: 6 (20%) • Struvite: 3 (10%) • Uric Acid: 17 (57%)
Idrizi (2009) *Albania*	History of UTI and flank pain: NR (40%)	NR	• Calcium oxalate: NR (39%) • Urate: NR (47%) • Other compounds: NR (14%)
Idrizi (2011) *Albania*	• UTI and Flank pain: 70 (60%) • Gross Hematuria: 65 (56%)	NR	Among the 63 patients with information on stone composition: • Calcium oxalate: 25 (39%) • Uric acid: 30 (47%) • Other compounds: 8 (14%)

Author (Year) *Country*	**Symptoms**	**Location**	**Composition**
Delaney (1985) *United States*	NR	NR	• Calcium oxalate: 3 (50%) • Uric Acid stones: 1 (17%) • Calcium oxalate stones in one occasion and uric acid or calcium phosphate stones on the other occasion: 2 (33%)
Dimitrakov (1994) *Bulgaria*	NR	NR	• Oxalate: 12 (52%) • Urate: 6 (26%) • Mixed composition: 5 (22%)

Abbreviation: not reported, NR; urinary tract infection, UTI
* The denominator only includes a subset of the study pop8ulation

The prevalence of stones ranged from 3% to 12% in family members confirmed not to be affected with ADPKD (Table 2-3). None of the studies described the characteristics of stones in unaffected family members. All six studies that compared the prevalence of stones in patients with and without ADPKD reported stones were more prevalent in patients with ADPKD; however, four studies did not statistically analyze the prevalence of stones between the two groups, and the remaining two studies found no statistical difference. When we statistically compared the prevalence of stones in patients with ADPKD to unaffected family members in the four studies that did not conduct any statistical analyses, we found that only one out of the four studies found a significant difference. Meta-analysis of the calculated prevalence ratios across six cross-sectional studies show that patients with ADPKD had a higher prevalence of upper urinary tract stones compared to unaffected family members (unadjusted prevalence ratio: 1.8, 95% confidence interval: 1.3 to 2.6, p=0.0007; test for heterogeneity: I^2 = 0%, p=0.8) (Figure 2-2).

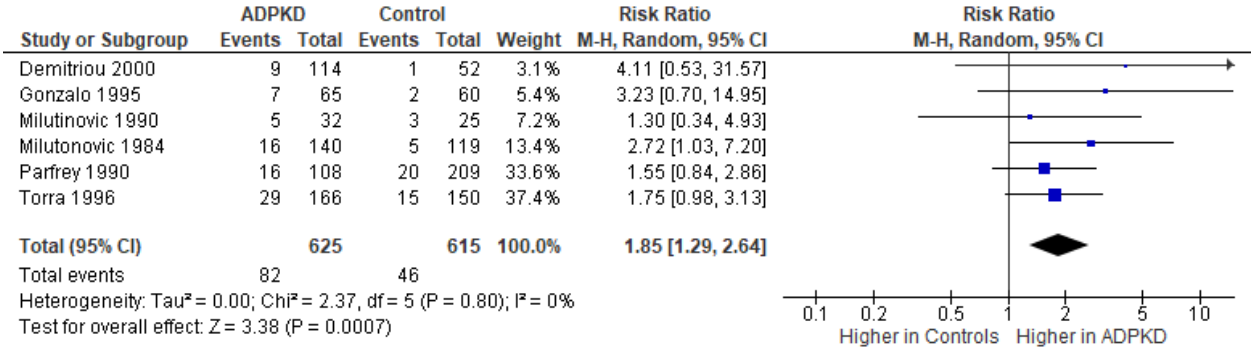

Figure 2-2. Calculated unadjusted prevalence ratio of stones in patients with autosomal dominant polycystic kidney disease compared to unaffected family members

Note: The prevalence ratios were calculated using prevalence estimates obtained from studies and Cochrane Review Manager 5.3.

Six studies reported the prevalence of stone intervention in patients with ADPKD, which ranged between 1% and 8% (Table 2-8). None of the studies with controls reported the prevalence of stone intervention in unaffected family members.

2.3.6 Stone incidence

No study clearly reported the incidence of upper urinary tract stones and the incidence of stone intervention in patients with ADPKD. Most cohort studies included in this review assessed upper urinary tract stones at cohort entry and not during follow-up. Whether the reported percentage was a prevalence or incidence estimate was unclear for three of the included cohort studies.

2.4 DISCUSSION

Many popular educational materials and clinical practice guidelines state that upper urinary tract stones are common in patients with ADPKD, and its prevalence may be five to ten times higher than the general population.[63,64] This makes clinical sense based on our knowledge of the pathophysiology of ADPKD; the kidney cysts in patients with ADPKD leads to urinary stasis which promotes stone formation.[24] Our review of the literature, however, indicates that the evidence to support these assertions is weak, and illuminates several knowledge gaps about the clinical epidemiology of stones in ADPKD. No study has clearly reported the incidence of stones in ADPKD. Prevalence estimates in ADPKD varied widely ranging from 3% to 59% for upper urinary tract stones, and from 1% to 8% for stone interventions. UTI and flank pain were the predominant precursors to diagnosis of stones; however, UTI and flank pain are not specific to stones and are also manifestations of ADPKD independent of stones. It is likely that UTI and flank pain was associated with ADPKD itself rather than stones because most of the stones in ADPKD were located in the renal calyces where they would be less likely to be symptomatic. Uric acid stones are the most prevalent stone composition in patients with ADPKD. The wide-ranging prevalence estimates along with the discovery that no published studies clearly

reported stone incidence, confirms that how often patients with ADPKD develop upper urinary tract stones remains uncertain.

There are several reasons why prevalence estimates of stones varied drastically across studies. These include inconsistent stone definitions, different distributions of stone risk factors, potential recall bias in studies that relied on patient self-report to identify stone events, and relying on past imaging reports done for reasons other than stone identification. Self-report is particularly problematic because the symptoms of flank pain and hematuria are common with ADPKD in the absence of stone disease. Patients with ADPKD may be more likely to undergo renal imaging, which would lead to over-detection of potentially clinically insignificant stones which may also exist undetected in the general population. The variability in imaging modalities used across studies and even between patients in the same study may also explain the variable prevalence estimates across studies. For example, computed tomography (CT) is a more sensitive method of stone detection than ultrasound and would provide a more accurate estimate of stone prevalence.[65,66] Most of the studies published to date on stones in ADPKD were conducted in a single-center, and are of poor methodological quality. Additionally, only six studies compared the prevalence of stones in patients with ADPKD to controls.[7–12] Among these six studies, only two statistically compared the prevalence of stones between the two groups,[9,10] and none of these studies adjusted for confounders.[7–12] Additionally, not all patients with ADPKD were hospitalized; as a result, prevalence estimates obtained from patients recruited from an inpatient setting must be generalized to the broader ADPKD population with caution. Similarly, the prevalence estimates obtained from patients recruited from an outpatient specialty clinic must also be generalize to the broader ADPKD population with caution due to increased surveillance. Also, only 8 of 49 of the included studies described the composition of stones in patients with ADPKD; none of the eight studies compared the composition of stones in patients with ADPKD to patients without ADPKD.

This review serves as a call to action for better research in this field. We recommend conducting large, multi-center studies that compare the risk of stones and risk of stone intervention between a representative population of ADPKD and controls to better

characterize the magnitude of upper urinary tract stone and stone intervention risk in patients with ADPKD. We also recommend such studies adjust for important confounders, such as hypertension, to better characterize the true association between ADPKD and upper urinary tract stones and stone intervention. Imaging tests are much more advanced, widespread, and frequent over time; this may lead to the possibility of detecting stones in ADPKD that may not be clinically relevant. Examining risk of upper urinary tract stone diagnosis and upper urinary tract stones that require intervention separately would provide insight into whether there is a potentially higher burden of asymptomatic stone that were detected incidentally on imaging. More reliable estimates of the magnitude of risk of stones and stone intervention would provide insight into clinical management practices and help patients with ADPKD and their physicians better prognosticate. If patients with ADPKD are truly at higher risk for upper urinary tract stones, then nephrologists may want to consider preventative measures for upper urinary tract stones. For example, if patients with ADPKD are at higher risk of upper urinary tract stones and hypocitraturia, then nephrologists may want to screen for hypocitraturia and treat patients with potassium citrate. Nephrologists may also want to consider treating large cysts that obstruct the urinary system and cause urinary stasis. Preventing stone formation would alleviate pain due to upper urinary tract stones and potentially slow down disease progression in patients with ADPKD. We also recommend comparing the composition of stones observed in patients with ADPKD compared to patients without ADPKD. New medications used in ADPKD, such as vasopressin receptor 2 antagonists, may alter the urine composition and change the types of renal stones that these patients get. Future ADPKD-specific risk factors, such as mutation type, of upper urinary tract stone studies may help identify patients at high-risk for stones and provide further insight into the pathophysiology of upper urinary tract stones in patients with ADPKD.

Our study is the first to systematically review and summarize the prevalence of stones in patients with ADPKD. Unlike past narrative reviews, we used a comprehensive search strategy across five different databases, and two reviewers independently screened all citations retrieved from the search strategy to identify all relevant articles. We also conducted this review in accordance with an *a priori* protocol and published guidelines

for systematic reviews. Two independent reviewers abstracted the data to minimize human error and bias.

There are some limitations inherent in our systematic review. First, we only included original journal articles and conference proceedings published in English. However, studies show that language-restricted meta-analysis does not lead to biased estimates.[67] Second, the definitions for ADPKD and stones varied across studies; therefore, the pooled estimate must be interpreted with caution.

2.5 CONCLUSION

Our systematic review highlights that there is poor consensus on the prevalence of stones in patients with ADPKD. A more methodologically robust study is needed to better characterize the magnitude of risk of stones and stone intervention in patients with ADPKD. This information can help patients with ADPKD and physicians with their prognostication, and might inform the use of interventions to reduce the risk of stones.

2.6 ADDENDUM

There has been quite some time between when we initially searched for relevant studies (February 2019) and when we completed the thesis (July 2020). Since the time from the last search (February 2019), an additional conference proceeding of 241 patients with ADPKD was published which described disease progression and renal and extrarenal manifestations.[68] 135 of the 241 (56%) of the patients with ADPKD experienced a upper urinary tract stone over a span of 18 years, and the methods quality score for this conference proceeding was 8.[68] Findings from this study does not change the conclusion of this chapter review that there is poor consensus on the prevalence of stones in patients with ADPKD.

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Chapter 3 - Efficacy and safety of surgical upper urinary tract stone interventions in autosomal dominant polycystic kidney disease: a systematic review[b]

[b] We thank our librarian, John Costello, for reviewing the search strategy. The ICES Kidney, Dialysis, and Transplantation Program provided funding for this study. Vinusha Kalatharan's training was supported by the Canadian Institutes of Health Research Doctoral Scholarship and the Doctoral Scholarship from the KRESCENT Program (a national kidney research training partnership of the Kidney Foundation of Canada, the Canadian Society of Nephrology, and the Canadian Institutes of Health Research). Dr. Amit Garg was supported by the Dr. Adam Linton Chair in Kidney Health Analytics and a Clinician Investigator Award from the Canadian Institutes of Health Research. The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or public of this article: Dr. York Pei 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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3.1 INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic kidney disorder with no cure.[1,2] It is characterized by focal cyst development leading to a progressive enlargement of both kidneys and kidney failure.[3,4] The prevalence of stones in patients with ADPKD ranges from 3 to 59%. The wide range of upper urinary tract stone prevalence reported in the literature can be explained by several factors including inconsistent stone definitions, different distributions of stone risk factors, potential recall bias in studies that relied on patient self-reported data to identify stone events, and relying on past imaging reports for reasons other than stone identification.[5] Upper urinary tract stones in patients with ADPKD are associated with significant morbidity. For example, stones are a major determinant of pain and may accelerate chronic kidney disease progression.[6,7] For these reasons, effective stone management is important in patients with ADPKD. However, the distorted kidneys and the reduced kidney function in patients with ADPKD may make active stone removal more challenging. For example, the cysts in patients with ADPKD may hinder optimal stone access and hence the success rate of stone interventions.

A published clinical practice guideline states that stone management in patients with ADPKD should not differ from the general population, and recommends that if necessary that stone interventions be considered.[8] The guideline authors also indicated that their recommendation was based on limited evidence.

Irrespective of whether a patient has ADPKD or not, urgent intervention is often required in the presence of infection/urosepsis, intractable pain, vomiting, impending acute renal failure, and/or obstruction.[9] Currently, shock wave lithotripsy (SWL), ureteroscopy, and percutaneous nephrolithotomy (PCNL) are commonly used procedures to remove stones.[8] The choice of stone intervention to treat stone is primarily dependent on stone characteristics such as, stone location and size, and availability of equipment. In some instances, a combination of interventions may be required to remove stones. SWL emits shockwaves from an external device, which then propagate through the body and cause the stones to fragment.[10,11] The fragmented stones then pass on their own in the

subsequent weeks. SWL is least invasive stone intervention, and is not recommended for pregnant women, and for patients with uncontrolled hypertension, uncontrolled coagulopathy, or a distal urinary obstruction to where stone is located.[12] Ureteroscopy is performed by inserting a rigid, semi-rigid, or flexible ureteroscope through the urethra and into the ureter, and positioning it close to the stone.[13,14] Instruments, such as laser, are used to fragment the stones, and these stone fragments can be left to pass or can be removed using instruments such as stone baskets or graspers.[15] During PCNL, a renal calyx is punctured percutaneously with fluoroscopy and/or ultrasound guidance to gain a access to the stone.[16] Stones are then fragmented using instruments, such as lasers or pneumatic lithotripters, and removed using tools such as graspers or suction devices.[9] PCNL is relatively the most invasive stone intervention.[9]

We undertook this systematic review to critically appraise and summarize the results of studies which described the efficacy and safety outcomes of the three main stone interventions (SWL, ureteroscopy, and PCNL) in adults with ADPKD. The outcomes of interest were the proportion of patients who were stone-free after the intervention, and the proportion who experienced at least one post-operative complication.

3.2 METHODS

3.2.1 Design and study selection

We conducted this systematic review using an internal pre-specified protocol and reported this review according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.[17]

We included studies that met the following eligibility criteria: (1) published English language full-text articles and conference proceedings; (2) any study design; (3) at least two patients with ADPKD included in the study; (4) with and without a comparator group; and (5) described any efficacy or safety outcome following at least any one of SWL, ureteroscopy, and/or PCNL in adults with ADPKD and upper urinary tract stones. If multiple publications reported outcomes on similar groups of patients, then we

abstracted data on the study published more recently. We only included studies with comparators if outcomes of a stone intervention were compared between ADPKD and non-ADPKD populations who underwent the same stone intervention; we did not include studies if outcomes of two different interventions were compared in patients with ADPKD.

3.2.2 Identifying relevant articles

With an experienced librarian, we developed a comprehensive search strategy (Table 3-1) to identify eligible published, original journal articles and conference proceedings on upper urinary tract stone interventions performed in adults with ADPKD. We retrieved all citations using MEDLINE (1947 to February 2019), EMBASE (1947 to February 2019), Web of Science, BIOSIS Preview (1955 to February 2019), and CINAHL.

Two reviewers (VK and RJ) removed duplicates and rated the remaining title and abstracts obtained from the search syntax. We retrieved the full text of all "relevant" and "potentially relevant" articles to further assess study eligibility. To identify additional eligible articles, we also manually searched the reference list of all included articles, used the "cited by" function in Google Scholar and Web of Science, and the "similar article" feature of PubMed. The two reviewers resolved any disagreement by consensus.

3.2.3 Data abstraction

One author (VK) developed a standardized form to abstract data from each study including information on study, patient and stone characteristics, interventions, and outcomes. Two authors (VK and RJ) pilot-tested and improved the form by independently extracting data from five eligible articles. Using the final data abstraction form (see Table 3-2), two abstractors independently extracted data from remaining studies, recorded the data, and resolved any disagreement by consensus.

Two authors (VK and GG) assessed the methodological quality of each of the included studies using a modified Down's and Black checklist (Table 3-3). We assigned a score between 0 and 22 for all included studies, with a higher score indicating better methodological quality.

3.2.4 Data analysis

Results were described qualitatively. The heterogeneity of included studies precluded a formal meta-analysis.

Table 3-1. Search strategy used to identify relevant articles related to thesis

DATABASE	SEARCH STRATEGY
MEDLINE	1. Polycystic Kidney Diseases/ or Polycystic Kidney, Autosomal Dominant/ 2. (((polycystic or "type 2" or "type II" or "type 1" or "type I" or "autosomal dominant" or pkd) adj3 (kidney* or renal)) or adpkd) 3. 1 or 2 4. lithotripsy/ or lithotripsy, laser/ 5. (ESWL or ESWLs or SWL or lithotrips* or litholapax*) 6. 4 or 5 7. 3 and 6 8. Ureteroscopy/ 9. (ureteroscop* or ureterorenoscop* or RIRS or retrograde intrarenal surgery or FURS) 10. 8 or 9 11. 3 and 10 12. Nephrostomy, Percutaneous/ 13. (PCNL or mPCNL or (percutaneous adj3 (nephrostom* or nephrolithotom*))) 14. 12 or 13 15. 3 and 14 16. 7 or 11 or 15
EMBASE	1. kidney polycystic disease/ 2. (((polycystic or "type 2" or "type II" or "type 1" or "type I" or "autosomal dominant" or pkd) adj3 (kidney* or renal)) or adpkd) 3. 1 or 2 4. extracorporeal lithotripsy/ 5. (ESWL or ESWLs or SWLs or lithotrips* or litholapax*) 6. 8 and 9 7. 3 and 6 8. ureteroscopy/ 9. (ureteroscop* or ureterorenoscop* or RIRS or retrograde intrarenal surgery or FURS) 10. 8 or 9 11. 3 and 10 12. percutaneous nephrolithotomy/ 13. (PCNL or mPCNL or (percutaneous adj3 (nephrostom* or nephrolithotom*)))

	14. 12 or 13 15. 3 and 14 16. 7 or 11 or 15
Web of Science & BIOSIS Preview	1. (((((polycystic or "type 2" or "type II" or "type 1" or "type I" or "autosomal dominant" or pkd) NEAR/3 (kidney* or renal)) or adpkd))) 2. (ESWL or ESWLs or SWL or lithotrips* or litholapax*)) 3. ((ureteroscop* or ureterorenoscop* or RIRS or retrograde intrarenal surgery or FURS)) 4. ((PCNL or mPCNL or (percutaneous NEAR/3 (nephrostom* or nephrolithotom*)))) 5. #4 OR #3 OR #2 6. #5 AND #1
CINAHL	7. (MH "Kidney, Cystic") OR (MH "Polycystic Kidney, Autosomal Dominant") 8. (((polycystic or "type 2" or "type II" or "type 1" or "type I" or "autosomal dominant" or pkd) N3 (kidney* or renal)) or adpkd) 9. S1 OR S2 10. (MH "Lithotripsy+") 11. (ESWL or ESWLs or SWL or lithotrips* or litholapax*) 12. S4 OR S5 13. S3 AND S6 14. (MH "Ureteroscopy") 15. (ureteroscop* or ureterorenoscop* or RIRS or retrograde intrarenal surgery or FURS) 16. S8 OR S9 17. S3 AND S10 18. (MH "Nephrostomy, Percutaneous") 19. (PCNL or mPCNL or (percutaneous adj3 (nephrostom* or nephrolithotom*))) 20. S12 OR S13 21. S3 AND S14 22. S7 OR S11 OR S15

Table 3-2. Data abstraction form

UID	Author	Title	Study No.	Type of Stone Intervention	Country	Study Design	Centre

Sample size	No. of affected kidneys	Recruitment Period	Mean (SD) Length of Follow-up	% of patients lost to follow-up	No. of Male (%)	Mean (SD) Age

ADPKD Population	Stone Free Status (SFS) Definition	Modality Used to Assess SFS	Time since treatment to assess SFS	No. (%) of patients stone free after one session

No. (%) of patient stone free after all sessions	No. (%) of kidney units stone free after one session	No. (%) of kidney unit stone free after all session	No. (%) of patients that underwent ancillary procedures

Ancillary Procedure Details	No. (%) of patients undergoing a follow-up procedure	Follow-up procedure Details	Time since first treatment	Intraoperative Complications	Post-Operative Complications

Pre-operative Serum Creatinine	Post-operative Serum Creatinine	Operative Time	No. (%) of patients who had stent placed after procedure

PCNL					
Modality used to guide PCNL	Dilator	Type of Nephroscope	Instrument Used to Fragment Stone	Instrument Used to Remove Stone	No. (%) of patients with multiple access tract

Type of Lithotripter	No. of Shockwaves [Mean (SD; range)]	Voltage of Shockwaves (kV)	Type of Ureteroscopy	Instrument Used to Fragment Stone

Abbreviation: kilovolts, kV; percutaneous nephrolithotomy, PCNL; standard deviation, SD; stone free status, SFS; unique identification number, UID

Table 3-3. Modified Downs and Black checklist

	Description of Criteria	Probable Answers
1	**Is the hypothesis/aim/objective of the study clearly described?**	1-Yes; 0-No
2	**Are the main outcomes to be measured clearly described in the Introduction or Methods section?** *If assessing being stone-free or any complication are first mentioned in the Results section, the question should be answered NO.*	1-Yes; 0-No
3	**Are the inclusion and exclusion criteria of the populations clearly described?**	1-Yes; 0-No
4	**Is the case definition for ADPKD clearly described?**	1-Yes; 0-No
5	**Is the ADPKD case definition valid or reliable?** *If the case definition of ADPKD was not reported, then UTD. After 2009, Pei criteria; between 1994 and 2009 Ravine criteria; before 1994 other definitions that sounds reasonable*	1-Yes; 0-No; 0-UTD
6	**Is the distribution of age, sex, and baseline kidney function in each group of subjects to be compared clearly described?**	1-Yes; 0-No
7	**Are the main findings of the study clearly described?** *Simple data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions.*	1-Yes; 0-No
8	**Does the study provide estimate of the random variability in the data?** *In non-normally distributed data, the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation, or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimate used were appropriate and the question should be answered yes.*	1-Yes; 0-No
9	**Have any post-operative adverse events of the intervention been reported?** *If study reports no patient experience of any complications, or list any post-operative adverse events, then YES; if the results do not mention anything about complications, then answer NO.*	1-Yes; 0-No
10	**Have the characteristics of patients lost to follow-up been described?** *If no loss to follow-up, then YES. If authors describe any characteristics of those loss to follow-up then answer YES. If authors do not describe any characteristics and just state number of follow-up, then NO. If author does not mention number of patients lost to follow-up but reported the main*	1-Yes; 0-No; 0-N/A

	outcome for all patients, then YES. If the author does not report number of patients' loss to follow-up, but only report outcome in a subset of the patients, then NO.	
11	**Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?** *If statistical analysis was not conducted, then N/A.*	1-Yes; 0-No; 0-UTD; 0-N/A
12	**Were the subjects asked to participate in the study representative of the entire population from which they were recruited?** *(i.e. did they recruit all or a consecutive patient or a random sample?)*	1-Yes; 0-No; 0-UTD
13	**Were those subjects who were prepared to participate representative of the entire population from which they were recruited?** *The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.*	1-Yes; 0-No; 0-UTD
14	**Were the staff, places, and facilities where the patient was treated, representative of the treatment most patients receive?**	1-Yes; 0-No; 0-UTD
15	**There are no unplanned retrospective analyses performed (i.e. data dredging)?** *Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes. If authors report any outcomes/clinical characteristics that were not explicitly referenced in the intro/method section, then my answer to this question is NO; If methods section too brief/not detailed enough, then UTD)*	1-Yes; 0-No; 0-UTD; 0-N/A
16	**In cohort studies, do the analyses adjust for different length of follow-up of patients, or in case-control studies is the time period between the intervention and outcome the same for cases and controls**? *If length of follow-up was the same for all study patients, the answer should be YES. If different lengths of follow-up were account for by, survival analysis for example, the answer should be yes. Studies where differences in follow-up are ignored should be answered NO.*	1-Yes; 0-No; 0-UTD; 0-N/A
17	**Reported case definition of stone free status?**	1-Yes; 0-No; 0-UTD; 0-N/A

18	**Were the ADPKD population and controls recruited from the same population?** *N/A for all case series*	1-Yes; 0-No; 0-UTD; 0-N/A
19	**Were the ADPKD population and the controls recruited from the same time period?** *For a study which does not specify the time period over which patient were recruited, the question should be answered as unable to determine. N/A for all case series*	1-Yes; 0-No; 0-UTD; 0-N/A
20	**Was there adequate adjustment for confounding in the analyses from which the main finding was drawn?** *If the distribution of known confounders in the different treatment group was not described or the distribution of known confounders differed between the two groups but was not considered in the analysis, then NO. If effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the questions should be answered as NO.* ***N/A for case series.***	1-Yes; 0-No; 0-UTD; 0-N/A
21	**Were losses of patients to follow-up considered?** *If the number of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered YES.*	1-Yes; 0-No; 0-UTD; 0-N/A

Abbreviations: autosomal dominant polycystic kidney disease, ADPKD; not applicable, N/A; unable to determine, UTD

3.3 RESULTS

Figure 3-1 summarizes the study selection process. Our search strategy yielded 221 citations that we reviewed and identified 24 eligible articles. We identified an additional article when manually searching the reference lists of the study conducted by Delakas et al. (1997).[18] This yielded a total of 25 relevant articles (311 patients with ADPKD) published between 1993 and 2019. Studies were conducted in India (n=7), United States (n=6), China (n=3), Greece (n=2), and Kuwait (n=2). One study was conducted in each of the following countries: Azerbaijan, Denmark, Iran, Romania, and Taiwan. Of the 25 included articles, 24 studies were case series (96%), and one (4%) was a cohort study. Sixteen (64%) of these were full-text journal articles, and nine (36%) were conference proceedings.

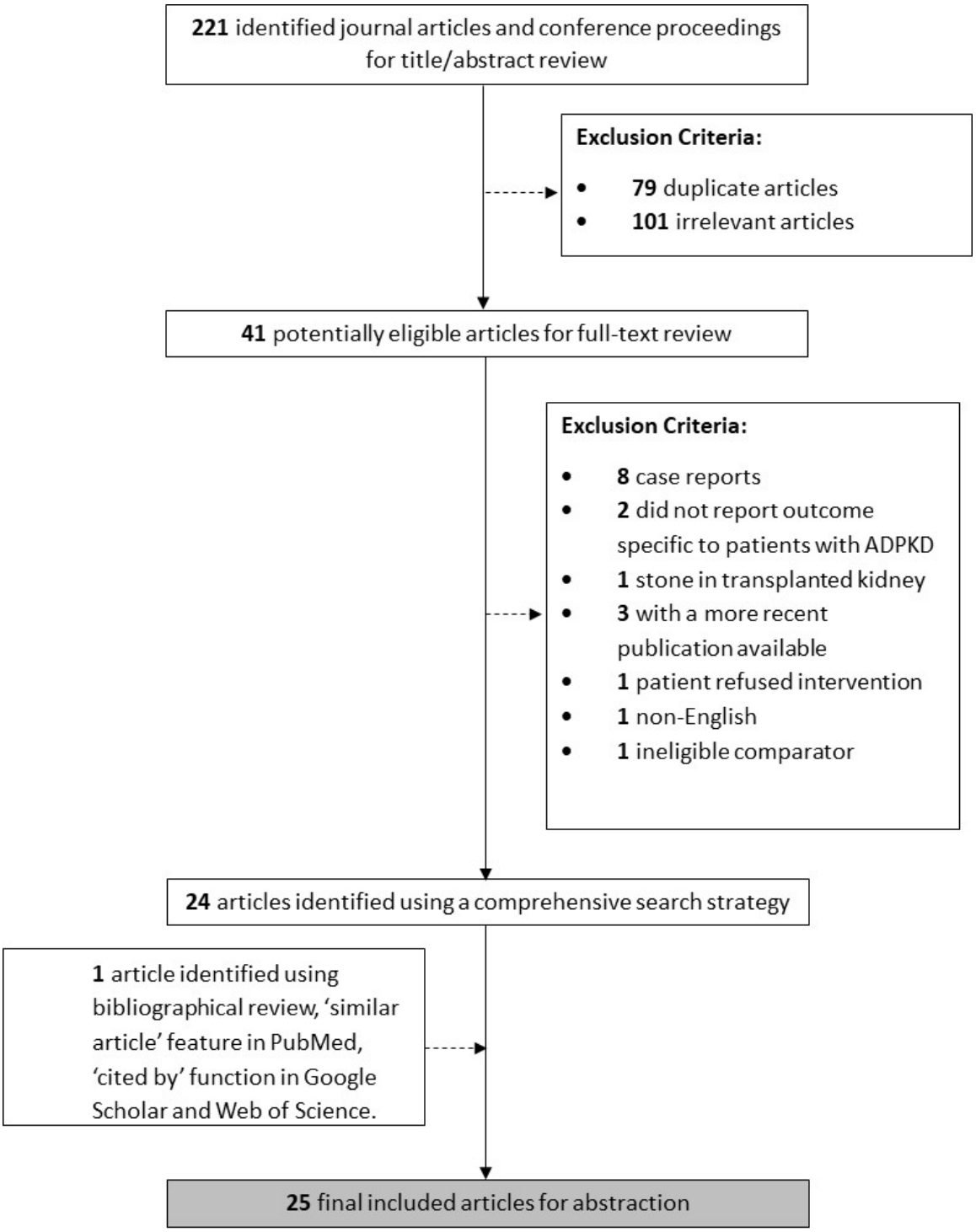

Figure 3-1. Study selection.

The number of patients in each study ranged from 2 to 29 cases (2 to 30 kidneys), and the mean age of the patients ranged from 32 to 61 years. The stone interventions were

performed between October 1981 and January 2017. It was unclear whether the interventions were emergent or elective in all included studies. The study and patient characteristics of each included study are summarized in Table 3-4, and overall outcomes of stone interventions are listed in Table 3-5.

Table 3-4. Study and patient characteristics of included studies.

Author (Year) *Country* (Citation)	**No. of Cases (No. of Kidneys)**	**No. of Centres**	**Recruitment Period**	**Length of Follow-up, Mean (SD)**	**Mean Age (SD), years**	**No. of Male (%)**	**Quality Score**[±]
Shockwave Lithotripsy *- Case Series*							
Baishya (2012) * *India* [14]	3 (3)	Unclear	Since 1992	1.5 (1.3) years	NR	NR	9
Cass (1995) * *United States* [30]	4 (NR)	1	NR	3 months[‡]	61 (12)	2 (50)	7
Chen (1993) * *Taiwan* [31]	2 (2)	1	June 1986 to December 1989	NR	NR	NR	9
Delakas (1997) *Greece* [18]	13 (16)	1	April 1990 to October 1994	5.6 (NR) months	55 (NR)	7 (54)	9
Deliveliotis (2002) * *Greece* [26]	4 (Unclear)	Unclear	NR	1 month[‡]	49 (NR)	3 (75)	8
Ng (2000) * *United States* [32]	3 (3)	1	Since 1993	NR	NR	NR	9
Singh (2019) * *India* [24]	3 (3)	1	January 1990 to July 2014	NR	NR	NR	12
Ureteroscopy *- Case Series*							
Baishya (2012) * *India* [14]	2 (3)	Unclear	Since 1992	7.3 (1.2) months	NR	NR	9
Franke (2010) * *Denmark* [33]	9 (NR)	1	NR	NR	NR	NR	7
Geavlete (2017) * *Romania* [28]	11 (Unclear)	1	January 2007 to January 2017	NR	61 (NR)	NR	8
Ng (2000) * *United States* [32]	2 (3)	1	Since 1993	NR	NR	NR	9
Singh (2019) * *India* [24]	5 (6)	1	January 1990 to July 2014	NR	NR	NR	12
Yili (2012) *China* [13]	13 (15)	1	2005 to 2010	3 (NR)	35 (NR)	9 (69)	11
Percutaneous Nephrolithotomy *- Cohort*							

Author (Year) *Country* (Citation)	**No. of Cases (No. of Kidneys)**	**No. of Centres**	**Recruitment Period**	**Length of Follow-up, Mean (SD)**	**Mean Age (SD), years**	**No. of Male (%)**	**Quality Score**[±]
Khorrami (2012) *Iran* [29]	• ADPKD: 8 (NR) • CONTROL: 100 (NR)	1	2003 to 2011	NR	• ADPKD: 45 (5) • CONTROL: 47 (4)	• ADPKD: 7 (88) • CONTROL: NR	4
Percutaneous Nephrolithotomy *- Case Series*							
Al-Kandari (2009) *Kuwait* [23]	19 (20)	2	1995 to 2007	NR	42 (9)	12 (63)	11
Al-Kandari (2008) *United States* [34]	29 (30)	2	NR	NR	NR	21 (72)	4
Baishya (2012) * *India* [14]	3 (3)	Unclear	Since 1992	2.2 (0.8) years	NR	NR	9
Bendigeri (2016) *India* [35]	13 (17)	NR	NR	NR	NR	10 (77)	8
Boaz (2016) *India* [36]	19 (23)	Unclear	January 2003 to July 2015	NR	NR	NR	6
Enganti (2017) *India* [37]	22 (Unclear)	Unclear	January 2014 to April 2016	NR	42 (NR)	NR	4
Ismayil (2014) * *Azerbaijan* [38]	3 (NR)	NR	2004 to 2014	NR	NR	NR	6
Khadgi (2016) *Kuwait* [25]	7 (NR)	NR	March 2010 to September 2012	NR	42 (8)	3 (43)	12
Lei (2014) *China* [19]	23 (23)	Unclear	January 2007 to December 2012	NR	43 (11)	17 (74)	12
Sabnis (2016) *United States* [22]	10 (NR)	NR	NR	NR	NR	8 (80)	7
Singh (2013) *India* [39]	22 (26)	1	2002 to 2011	35 (NR) months	38 (NR)	NR	8
Singh (2019) * *India* [24]	6 (6)	1	January 1990 to July 2014	NR	NR	NR	12
Srivastava (2012) *India* [40]	22 (25)	1	January 2000 to January 2010	NR	40 (14)	18 (82)	10

Author (Year) *Country* (Citation)	**No. of Cases (No. of Kidneys)**	**No. of Centres**	**Recruitment Period**	**Length of Follow-up, Mean (SD)**	**Mean Age (SD), years**	**No. of Male (%)**	**Quality Score**[±]
Umbreit (2010) *United States* [21]	9 (11)	1	October 1981 to February 2009	2.7 (NR) years	32 (NR)	7 (78)	9
Wang (2017) *United States* [41]	11 (13)	Unclear	Since 2010	NR	50 (13)	8 (73)	7
Zhang (2014) *China* [27]	11 (12)	1	January 2002 to December 2012	36 months[‡]	42 (11)	7 (64)	11

Abbreviations: not reported, NR; standard deviations, SD

*The described cases are a subset of a larger case series.

[‡]The reported length of follow-up is not the average but rather constant for all included patients.

[±] A modified Downs and Black checklist was used to assess the methodological quality of each included study. The methods quality score ranged between 0 and 22 with higher scores indicating higher quality.

Table 3-5. Outcomes of stone interventions.

Author (Year) *Country*	**No. of Patients Stone Free after One Session (%)**	**No. of Patients who Underwent Follow-up Procedures (%)**	**Intraoperative Complications, No. of Patients (%)**	**Post-operative Complications, No. of Patient (%)**	**Pre-operative Serum Creatinine [mean (SD; range)] (µmol/L)**	**Post-operative Serum Creatinine [mean (SD; range)] (µmol/L)**
Shockwave Lithotripsy *- Case Series*						
Baishya (2012) *India*	0 (0)	2 (67)	NR	NR	NR	NR
Cass (1995) *United States*	2 (50)	Unclear	NR	None	NR	NR
Chen (1993) *Taiwan*	0 (0)	NR	NR	None	NR	NR
Delakas (1997) *Greece*	9 (69)	2 (15)	None	• At least one complication: Unclear • Colic pain that improved with oral analgesics: 3 (23) • Transient Gross Hematuria: 8 (62)	NR	NR
Deliveliotis (2002) *Greece*	1 (25)	NR	NR	None	NR	NR
Ng (2000) *United States*	NR	1 (33)	NR	None	76.6 (10.2; 70.7 to 88.4)	79.6 (25.0; 61.9 to 97.2)
Singh (2019) *India*	NR	1 (33)	NR	• At least one complication: 2 (33) • Fever: 2 (33)	NR	NR
Ureteroscopy - Case Series						
Baishya (2012) *India*	2 (100)	0 (0)	NR	None	NR	NR
Franke (2010) *Denmark*	9 (100)	0 (0)	NR	None	NR	NR

Author (Year) *Country*	No. of Patients Stone Free after One Session (%)	No. of Patients who Underwent Follow-up Procedures (%)	Intraoperative Complications, No. of Patients (%)	Post-operative Complications, No. of Patient (%)	Pre-operative Serum Creatinine [mean (SD; range)] (µmol/L)	Post-operative Serum Creatinine [mean (SD; range)] (µmol/L)
Geavlete (2017) *Romania*	8 (73)	Unclear	NR	• At least one complication: 3 (27) • Fever: 1 (9) • Hematuria: 1 (9) • Renal colic: 1 (9)	NR	NR
Ng (2000) *United States*	NR	0 (0)	NR	None	556.9 (399.6; 274.0 to 839.8)	300.6 (75.0; 247.5 to 353.6)
Singh (2019) *India*	NR	0 (0)	NR	• At least one complication: 1 (20) • Fever: 1 (20)	NR	NR
Yili (2012) *China*	11 (85)	2 (15)	None	• At least one complication: 3 (23) • Low-grade fever: 1 (8) • Flank pain: 1 (8) • Moderate stent pain: 1 (8)	NR (NR; 70.7 to 291.7)	NR
Percutaneous Nephrolithotomy *- Cohort*						
Khorrami (2012) *Iran*	• ADPKD: 7 (88) • CONTROL: 91 (91)	NR	• ADPKD: None • CONTROL: None	• Urinary leakage from nephrostomy tube was longer in patients with ADPKD (31 ± 4 hours) vs. controls (6 ± 1.5 hours)	NR	NR
Percutaneous Nephrolithotomy *- Case Series*						

Author (Year) *Country*	No. of Patients Stone Free after One Session (%)	No. of Patients who Underwent Follow-up Procedures (%)	Intraoperative Complications, No. of Patients (%)	Post-operative Complications, No. of Patient (%)	Pre-operative Serum Creatinine [mean (SD; range)] (µmol/L)	Post-operative Serum Creatinine [mean (SD; range)] (µmol/L)
Al-Kandari (2009) *Kuwait*	16 (84)	3 (16)	Unclear	• At least one complication: 3 (15) • Mild hematuria with low-grade fever: 1 (5) • Bleeding through nephrostomy tube after declamping: 1 (5) • Low grade fever: 1 (5)	150.3 (70.7; NR)	132.6 (70.7; NR)
Al-Kandari (2008) *United States*	NR	2 (7)	•At least one complication: 3 (10) • Renal Pelvic Tear: 2 (7) • Intraoperative bleeding: 1 (3)	None	NR	NR
Baishya (2012) *India*	2 (67)	1 (33)	NR	• At least one complication: 2 (67) • Post-operative fever: 1 (33) • Pain in operating site: 1 (33)	NR	NR
Bendigeri (2016) *India*	NR	3 (23)	NR	• At least one complication: Unclear • Fever: 3 (23) • Blood transfusion: 1 (8)	NR	NR
Boaz (2016) *India*	NR	4 (21)	• At least one complication: 1 (5) • Blood transfusion: 1 (5)	• At least one complication: 4 (21) • Fever: 4 (21) • Sepsis: 1 (5)	179.5 (84.2; 97.2 to 389.0)	175.9 (71.6; 97.2 to 309.4)

Author (Year) *Country*	**No. of Patients Stone Free after One Session (%)**	**No. of Patients who Underwent Follow-up Procedures (%)**	**Intraoperative Complications, No. of Patients (%)**	**Post-operative Complications, No. of Patient (%)**	**Pre-operative Serum Creatinine [mean (SD; range)] (µmol/L)**	**Post-operative Serum Creatinine [mean (SD; range)] (µmol/L)**
Enganti (2017) *India*	NR	NR	NR	• At least one complication: 5 (23) • Renal pelvic perforation: 1 (5) • Hematuria requiring blood transfusion: 2 (9) • Perirenal fluid collection: 2 (9)	NR	NR
Ismayil (2014) *Azerbaijan*	2 (67)	1 (33)	NR	• At least one complication: 3 (100) • Blood transfusion: 3 (100)	NR	NR
Khadgi (2016) *Kuwait*	7 (100)	0 (0)	NR	• At least one complication: 3 (43) • Fever: 1 (14) • Urinary tract infection: 1 (14) • Bleeding: 1 (14)	NR	NR
Lei (2014) *China*	16 (70)	6 (26)	NR	• At least one complication: Unclear • Fever: 4 (17) • Urinary tract infection: 3 (13) • Blood transfusion: 2 (9) • Selective renal artery embolization: 1 (4)	148.2 (110.1; 77.0 to 568.0)	• Immediately after: 149.2 (86.2; 72.0 to 475.0) • One-month follow-up: 136.2 (86.7; 53.0 to 441.0)4545554444

Author (Year) *Country*	**No. of Patients Stone Free after One Session (%)**	**No. of Patients who Underwent Follow-up Procedures (%)**	**Intraoperative Complications, No. of Patients (%)**	**Post-operative Complications, No. of Patient (%)**	**Pre-operative Serum Creatinine [mean (SD; range)] (µmol/L)**	**Post-operative Serum Creatinine [mean (SD; range)] (µmol/L)**
Sabnis (2016) *United States*	NR	0 (0)	NR	• At least one complication: 2 (20) • Fever: 2 (20)	NR	NR
Singh (2013) *India*	12 (55)	10 (45)	• At least one complication: 4 (18) • Hypotension requiring resuscitation but did not require termination of procedure: 4 (18)	• At least one complication: Unclear • Blood transfusion: 9 (32) • Fever due to cyst infection: 4 (18) • Perirenal hematoma collection: 4 (18) • Renal failure that worsened: 3 (14) • Hydrothorax: 2 (9) • Hemothorax: 1 (5) • Pneumothorax: 1 (5) • Paralytic ileus: 3 (14)	NR	NR
Singh (2019) *India*	NR	Unclear	NR	• At least one complication: Unclear • Fever: 2 (33) • Urinary tract infection: 1 (17)	NR	NR

Author (Year) *Country*	No. of Patients Stone Free after One Session (%)	No. of Patients who Underwent Follow-up Procedures (%)	Intraoperative Complications, No. of Patients (%)	Post-operative Complications, No. of Patient (%)	Pre-operative Serum Creatinine [mean (SD; range)] (µmol/L)	Post-operative Serum Creatinine [mean (SD; range)] (µmol/L)
Srivastava (2012) *India*	Unclear	3 (14)	NR	• At least one complication: Unclear • Fever: 4 (18) • Blood transfusion: 3 (14) • More than one transfusion: 1 (5) • Positive fungal culture with antibiotic treatment for 3 months: 1 (5)	NR	NR
Umbreit (2010) *United States*	NR	2 (18)	None	None	123.8 (NR; 79.6 to 238.7)	123.8 (NR; 70.7 to 247.5)
Wang (2017) *United States*	NR	7 (64)	NR	• At least one complication: Unclear • Severe hematuria: 1 (9) • Fever: 5 (45) • Paralytic ileus: 1 (9) • Urinary tract infection: 3 (27)	89.3 (15.9; NR)	90.5 (18.6; NR)
Zhang (2014) *China*	5 (45)	4 (36)	NR	• At least one complication: Unclear • Bleeding: 3 (27) • Fever: 4 (36) • Blood transfusion: 2 (18) • Infection: 1 (9)	1337.5 (291.7; 875.2 to 1780.4)	1262.4 (198.0; 951.2 to 1527.6)

Abbreviations: not reported, NR; standard deviation, SD

3.3.1 Quality assessment of studies

The methods quality score was highly variable and ranged between 4 to 12 out of 22 (where higher scores indicates studies of higher methodological quality).

The ADPKD and outcome definitions affect the internal validity of a study. Only one study reported the case definition of ADPKD, which defined ADPKD using the validated, Ravine ultrasonographic criteria.[19,20]

The definition of stone free status post-intervention was highly variable across studies. Seven of the 25 studies specified and defined stone free status as complete clearance or residual fragments less than a prespecified size. The prespecified size for an acceptable residual fragment was less than four millimeters for five studies, less than two millimeters for one study, and less than one millimeter for one study.

The sampling strategy and the source population influenced the generalizability of the findings to the broader ADPKD population who underwent stone intervention. Seven of the 25 studies specified how cases were recruited, and all seven studies included consecutive or all patients within a specified time frame.[13,14,21–25] One study recruited patients from an outpatient setting[26], and four studies recruited patients from a hospital setting.[18,19,27,28] For the latter, it was unclear whether the cases were recruited from a same day surgery setting, emergency department, inpatient, or an outpatient hospital-based clinic.

One conference proceeding described the efficacy outcomes of PCNL performed in patients with ADPKD compared to non-ADPKD controls, without adjustment for any covariates.[29]

3.3.2 Shockwave lithotripsy

We identified seven case series describing the outcomes and experience of treating stones in patients with ADPKD with SWL (in total 32 patients).[14,18,24,26,30–32] The characteristics of SWL for each study is summarized in Table 3-6.

Table 3-6. Characteristics of shockwave lithotripsy (SWL).

Author (Year) *Country*	**Type of Lithotripter**	**# of Shockwaves [Mean (SD; range)]**	**Voltage of Shockwave (kV)**	**Modality used to assess stone free status**	**Operative Time (minutes)**
Baishya (2012) *India*	Dornier Compact Delta	<1500	<13	X-ray, U/S of the KUB region	NR
Cass (1995) *United States*	Medstone STS Lithotripter	2050 (700; 1000 to 2400)	24	Plain radiograph	NR
Chen (1993) *Taiwan*	Dornier HM-3 Lithotripter	2500 (NR; 2000 to 3000)	20	KUB x-ray and excretory urography	NR
Delakas (1997) *Greece*	Dornier HM-4 Lithotripter	1800 (NR; 1400 to 2500)	15 to 21	Plain x-ray film and U/S	NR (35 to 88)
Deliveliotis (2002) *Greece*	Dornier HM-4 Lithotripter	Unclear	23	Plain KUB x-ray film and U/S	NR
Ng (2000) *United States*	Dornier HM-3 or MFL 5000 Lithotripter	4333 (3402; 1800 to 8200)	NR	Plain x-ray film and kidney U/S or non-contrast CT	NR
Singh (2019) *India*	NR	$\leq$ 1500	$\leq$ 13	U/S or KUB x-ray	100 (80 to 120)

Abbreviations: computed tomography, CT; kidney, ureter, bladder, KUB; kilovolts, kV; standard deviation; SD; ultrasound, U/S

None to 69% of the patients were stone free after a single SWL session, and 15% to 67% of the patients received additional follow-up procedures to achieve stone-free status.[14,18,24,26,30–32] In four of the six case series that examined at least one post-operative SWL complication, no patients experienced any complications post-operatively.[26,30–32] The percentage of patients that experienced at least one complication was unclear in one study[18], and 33% of the patients described by Singh (2019) experienced fever post-operatively.[24] The reported post-operative complications of SWL in patients with ADPKD included colic pain and fever.[18,24] Delakas and colleagues specified that none of the patients experienced any post-operative complications[18], whereas the remaining six case series did not report any intraoperative complications.[14,24,26,30–32]

3.3.3 Ureteroscopy

We identified six case series reporting stone treatment in patients with ADPKD using ureteroscopy (in total 42 patients) [13,14,24,28,32,33]. The characteristics of ureteroscopy are detailed in Table 3-7.

Table 3-7. Characteristics of ureteroscopy.

Author (Year) *Country*	**Type of Ureteroscope**	**Instrument used to Fragment Stones**	**Modality used to Assess Stone Free Status**	**Operative Time (minutes) Mean (Range)**
Baishya (2012) *India*	NR	NR	X-ray, U/S of the KUB region at one month	NR
Franke (2011) *Denmark*	Flexible ureteroscope	NR	CT	NR
Geavlete (2017) *Romania*	Flexible ureteroscope	Laser lithotripsy	NR	NR
Ng (2000) *United States*	NR	Laser for 1 of 2 patients	Plain x-ray film and renal U/S or non-contrast CT	NR
Singh (2019) *India*	Semirigid and flexible ureteroscope	Holium YAG laser	Plain x-ray KUB and U/S KUB	60 (30- 90)
Yili (2012) *China*	7.2 flexible ureteroscope	Holium YAG laser lithotripsy performed via 200um (Dornier Lightguide Super 200) core-sized fiber until only very small pieces (<1mm) remained.	U/S	46 (36-60)

Abbreviations: computed tomography, CT; kidney, ureter, bladder, KUB; not reported, NR; ultrasound, U/S

After a single session, 73% to 100% of the patients were stone-free.[13,28,33] In four case series, no patients required a second procedure to facilitate complete stone removal,[14,24,32,33] whereas another case series reported 15% undergoing a second ureteroscopy one week following the first procedure.[13] The percentage of patients that underwent a second procedure was unclear or not reported in one case series.[28] Three case series reported that none of the patients experienced any post-operative complications.[14,32,33] About 20% to 27% of the patients experienced at least one post-operative complication, such as fever, hematuria, and pain in the remaining three case series.[13,24,28] One case series reported that not a single patient experienced any intraoperative outcomes during ureteroscopy[13], whereas the remaining five case series did not report about any intraoperative outcomes.[14,24,28,32,33]

3.3.4 Percutaneous nephrolithotomy (PCNL)

Sixteen case series[14,19,21–25,27,34–41] and one cohort study[29] reported the use of PCNL for stone removal in adults with ADPKD, with 3 to 29 patients per series (3 to 30 kidneys) (in total 237 patients). PCNL-specific characteristics of each study is detailed in Table 3-8.

Table 3-8. Characteristics of percutaneous nephrolithotomy (PCNL).

Author (Year) *Country*	% of Affected Kidneys with Multiple Access Tract	Modality Used to Guide Procedure	Dilator	Type of Nephroscope	Instrument Used to Fragment Stones	Instrument Used to Remove Stones	Modality Used to Assess Stone Free Status	Operative Time (Minutes) Mean (SD; Range)
Khorrami (2012) *Iran*	NR	Fluroscopy	Metal telescoping dilator	NR	NR	NR	NR	NR
Al-Kandari (2009) *Kuwait*	5	Fluoroscopy	Amplatz sequential facial dilator in 14 procedures and Nephromax balloons in remaining 6 procedures	26F rigid nephroscope	U/S and/or pneumatic disintegration were used together	NR	• **Day of procedure:** plain abdominal x-ray and intraoperative nephrostography • **At time of nephrostomy tube removal (2 to 4 days post-operatively):** plain abdominal x-ray for radiopaque stone; nephrostomy or non-spiral CT for radiolucent stones	NR
Al-Kandari (2008) *United States*	NR	NR	NR	NR	NR	NR	NR	NR
Baishya (2012) *India*	NR	• U/S (67%) • Fluroscopy (33%)	NR	NR	NR	NR	X-ray, ultrasonography of the KUB region at one month	Unclear

Author (Year) *Country*	**% of Affected Kidneys with Multiple Access Tract**	**Modality Used to Guide Procedure**	**Dilator**	**Type of Nephroscope**	**Instrument Used to Fragment Stones**	**Instrument Used to Remove Stones**	**Modality Used to Assess Stone Free Status**	**Operative Time (Minutes) Mean (SD; Range)**
Bendigeri (2016) *India*	NR	NR	NR	NR	NR	NR	NR	NR
Boaz (2016) *India*	NR	NR	NR	NR	NR	NR	NR	85
Enganti (2017) *India*	NR	NR	NR	NR	NR	NR	NR	NR
Ismayil (2014) *Azerbaijan*	NR	NR	NR	NR	NR	NR	CT	NR
Khadgi (2016) *Kuwait*	0	Fluroscopy	fascial dilator	Semi-rigid ureteroscope (8.5/11.5 Fr)	1.5 mm pneumatic lithotripsy probe	A pulsatile pressurized irrigation pump; occasionally cleared by forceps	• **1-day post-operatively:** KUB and U/S • **12-weeks post-operatively:** non-contrast CT	54.9 (6.9; 45-60)
Lei (2014) *China*	13	• Fluroscopy (91%) • U/S (9%)	fascial dilator	8/9.8F semi-rigid ureteroscope	Pneumatic lithotripsy or holmium laser	Forceps and small fragments flushed out with an endoscopic pulsed perfusion pump	Plain KUB radiography, U/S, and CT	95.2 (14.0; NR)
Sabnis (2016) *United States*	NR	U/S or Fluroscopy	NR	NR	NR	NR	NR	NR
Singh (2013) *India*	31	Fluroscopy	Alkene metallic dilator up to 26F/28F	26F (Richard Wolf) nephroscope	Pneumatic lithoclast (Swiss Lithoclast)	NR	X-ray KUB and renal U/S	90 (NR;70-120)

Author (Year) *Country*	**% of Affected Kidneys with Multiple Access Tract**	**Modality Used to Guide Procedure**	**Dilator**	**Type of Nephroscope**	**Instrument Used to Fragment Stones**	**Instrument Used to Remove Stones**	**Modality Used to Assess Stone Free Status**	**Operative Time (Minutes) Mean (SD; Range)**
Singh (2019) *India*	NR	U/S and fluoroscopy	Serial Dilator	Unclear	laser or pneumatic lithoclast	NR	Plain x-ray KUB and U/S KUB	112 (NR; 70-145)
Srivastava (2012) *India*	Unclear	NR	Amplatz sequential facial dilators	28Fr nephroscope; Flexible nephroscope in some cases	Pneumatic lithotripter; holmium laser with flexible nephroscope in 3 patients where forceps extraction was not possible	Forceps	Non-contrast CT	NR
Umbreit (2010) *United States*	45	Fluroscopy	Amplatz fascial dilators	Rigid nephroscope; two patients also required a flexible nephroscope	• Ultrasonic lithotripsy: 10 (91%) •Electrohydraulic lithotripsy: 2 (9%)	• Basket: 2 (9%)	• **Immediately after**: endoscopy nephrostogram • **One day after**: Antegrade nephrostogram	• Unilateral PCNL = 66 (NR; 47-82) • Bilateral PCNL = 127 (NR; 121-132)
Wang (2017) *United States*	18	U/S	Amplatz fascial dilators	Rigid	Pneumatic and U/S disintegration	NR	NR	NR

Author (Year) *Country*	**% of Affected Kidneys with Multiple Access Tract**	**Modality Used to Guide Procedure**	**Dilator**	**Type of Nephroscope**	**Instrument Used to Fragment Stones**	**Instrument Used to Remove Stones**	**Modality Used to Assess Stone Free Status**	**Operative Time (Minutes) Mean (SD; Range)**
Zhang (2014) *China*	NR	U/S	6F plastic dilator then metal coaxial metal dilators (second step)	Rigid nephroscope	U/S and pneumatic disintegration	Graspers	Ultrasound/ KUB film	77 (23.5; 45- 128)

Abbreviations: computed tomography, CT; kidney, ureter, and bladder, KUB; not reported, NR; ultrasound, U/S

The stone-free status of patients after a single session ranged from 45% to 100%, and 0% to 64% of the patients required a follow-up procedure for residual stones among the 12 studies that reported it.[14,19,21–23,25,27,34–36,38–41] Two studies reported no patients experiencing any post-operative complications[21,34], seven case series did not report the percentage of patients with complications[19,24,27,35,39–41], and 15% to 100% of patients experienced at least one complication among the remaining seven case series.[14,23–25,36–38] The post-operative complications of PCNL included fever, pain, hematuria, bleeding, urinary tract infection, cyst infection, perirenal hematoma collection, hydrothorax, hemothorax, pneumothorax, paralytic ileus, worsening of pre-existing renal failure, blood transfusion, renal pelvic perforation, urinary leakage from nephrostomy tube, and sepsis.[14,19,22–25,27,35–41] None of the patients described by Umbreit *et al*. experienced any intraoperative complications.[21] In three other case series, at least one patient experienced an intraoperative complication, including bleeding, renal pelvic tear and hypotension[34,36,39]; the remaining studies did not clearly report any intraoperative complications. [14,19,22–25,27,35,37,38,40,41]

Khorrami *et al.* conducted a cohort study of patients undergoing PCNL, comparing eight patients with ADPKD to 100 patients without ADPKD.[29] There were no significant between-group differences in stone-free status, the rise in the concentration of serum creatinine after the procedure, or the decline in concentration of hemoglobin after the procedure.[29] However, urinary leakage lasted significantly longer in patients with ADPKD compared to patients without ADPKD.[29]

3.4 DISCUSSION

We conducted a systematic review of 25 studies describing at least one post-operative outcome of SWL, ureteroscopy, and PCNL in patients with ADPKD to summarize the literature and to identify knowledge gaps. The estimates are limited by small sample sizes

and between study variability in patient characteristics, stone characteristics, and treatment protocol. This concern notwithstanding, based on the literature published to date, the percentage of patients who were stone free after one session ranged from none to 69% for SWL, 73% to 100% for ureteroscopy, and 45% to 100% for PCNL. The overall complication rate ranged from none to 33% for SWL, none to 27% for ureteroscopy, and none to 100% for PCNL. Post-operative complications experienced by patients with ADPKD after any intervention included residual stones, pain, and fever. Post-operative hematuria was observed after ureteroscopy and PCNL. Other PCNL complications included urinary leakage, bleeding, renal pelvic perforation, perirenal fluid collection, urinary tract infection, cyst infection, worsening renal failure, hydrothorax, hemothorax, pneumothorax, and paralytic ileus.

The post-operative complication and stone free rates of all three stone interventions were highly variable. The variability in post-operative complication and stone free rates can be explained by between-study variability in the definitions used for stone free status, sample size, treatment protocol, timing when imaging was performed post-intervention, and the type of imaging performed to assess stone free status post-intervention. For example, among all imaging modalities used to assess stone free status, computed tomography (CT) is the most sensitive modality to detect residual stones.[42,43] Ultrasound and kidney, ureter, and bladder (KUB) radiograph cannot detect radiolucent stones, such as uric acid stones, and the ultrasound performance is poor for patients who are obese and patients with residual fragments less than 5 millimeters[42,43], and would be expected to be less sensitive in the setting of ADPKD. As a result, studies that use CT post-operatively would report a lower stone free rate compared to studies that use ultrasound or KUB. Patient and stone characteristics, including ADPKD-specific characteristics such as residual renal function and cyst volume and location, influence intervention choice and subsequent success and complication rates. In general, symptomatic stones that are between one to two centimeters would be treated with either SWL or ureteroscopy, and PCNL would be reserved for stones greater than two centimeters, or in patients where retrograde access is not possible. The success rate of all three intervention is dependent on gaining optimal access to stones.[44] Therefore, variability in patient and stone

characteristics across studies also explain the variability in reported success and complication rate.

It is difficult to determine whether SWL, ureteroscopy, and PCNL are truly efficacious and safe in patients with ADPKD because the variability described above also limits indirect comparison of stone interventions success and complication rates between that reported in patients with ADPKD and the general population. Furthermore, the ADPKD cases described in the studies were likely more selected than the general population because of their complex kidney anatomy. Future randomized controlled trials or observational studies that use a representative sample of patients with ADPKD and address potential confounding factors are required to elucidate whether ADPKD is truly associated with poor outcomes following SWL, ureteroscopy, and PCNL.

Our findings must be interpreted with caution due to several limitations. First, except for one cohort study, all studies were clinical case series. Although case series give some insight into the outcomes of stone interventions, and are useful for generating new hypotheses, the observations are not necessarily generalizable to the broader ADPKD population. Based on our systematic, comprehensive search, the conference proceeding published by Khorrami *et al*. (2009) is the only cohort study in the literature.[39] Although they compared the outcomes of PCNL in patients with ADPKD to patients without ADPKD, they did not adjust for any covariates. Second, the sample size of all included studies, including the cohort study was small so the reported estimates were imprecise. Third, most of the data were retrospectively collected. As a result, the conclusions were highly dependent on the accuracy of medical records. Fourth, the inclusion and exclusion criteria were not explicitly reported in all identified studies. Lastly, all studies published to date did not describe the cystic volume in patients with ADPKD. As a result, it was difficult to elucidate whether and how cystic volume influences post-operative complication and success rates.

Aside from inherent limitations of the information in the primary studies, with respect to the quality of this review, we used a very comprehensive search strategy to identify relevant literature. Data were carefully abstracted using a robust form. Our study is the

first systematic review to summarize the outcomes of stone interventions in adults with ADKPD.

3.5 CONCLUSION

Our systematic review shows that empirical evidence on the efficacy and safety of SWL, ureteroscopy, and PCNL in ADPKD is limited. Our findings corroborate Mallett *et al's* suggestion to undertake methodologically rigorous studies to understand the consequences of these procedures in patients with ADPKD.[8]

3.6 ADDENDUM

We updated our search to identify whether additional studies were published between February 2019 (when the initial search was conducted) and July 2020. We identified one additional study that described 21 patients with ADPKD who underwent ureteroscopy, and 11 patients with ADPKD who underwent PCNL.[46] The methods quality score of the additional study was 12. The percentage of patients who were stone free after one session was 85.9% for patients who underwent ureteroscopy, and 90.9% for those who underwent PCNL. [46] The percentage of patients who experienced one complication was 28.6% for patients who underwent ureteroscopy, and 45.5% for patients who underwent PCNL. [46] The percentage of patients who experienced at least one post-operative complication following ureteroscopy now ranges from 0% to 29% instead of 0% to 27% according to all studies published in the literature; however, the findings from this study do not change the conclusion of this chapter that empirical evidence on the efficacy and safety of SWL, ureteroscopy, and PCNL in ADPKD is limited.

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Chapter 4 - Limitations of the existing literature

4.1 Limitations of the existing literature

We conducted two systematic reviews to identify knowledge gaps, and to gain a current state of knowledge on the prevalence and incidence of upper urinary tract stones and stone interventions, and on the safety and efficacy of SWL, ureteroscopy, and PCNL in patients with ADPKD.

Our first systematic review revealed that there is still poor consensus on the prevalence of upper urinary tract stones and stone interventions in patients with ADPKD. Most studies published to date on stones in ADPKD were conducted in a single center, and are of poor methodological quality. The ADPKD and stone definitions were variable across studies. Additionally, only six studies compared the prevalence of stones in patients with ADPKD to controls.[1–6] Among the six studies, two statistically compared the prevalence of stones between the two group, and none of these studies adjusted for confounders.[3,4]

Our second systematic review showed that empirical evidence of the efficacy and safety of SWL, ureteroscopy, and PCNL in ADPKD is limited. Except for one cohort study, all studies were clinical case series. Although case series give some insight into the outcomes of stone interventions, and are useful for generating new hypotheses, the observations are not necessarily generalizable to the broader ADPKD population. Based on our systematic, comprehensive search, the conference proceeding published by Khorrami *et al*. (2009) is the only cohort study in the literature.[7] Although they compared the outcomes of PCNL in patients with ADPKD to patients without ADPKD, they did not adjust for any covariates. The sample size of all included studies, including the cohort study, was small so the reported estimates were imprecise. Most of the data were retrospectively collected. As a result, the conclusions were highly dependent on the accuracy of medical records. Lastly, the inclusion and exclusion criteria were not explicitly reported in all identified studies.

Our systematic reviews show that the epidemiological data to support the assertion that patients with ADPKD are at higher risk of upper urinary tract stones is weak. Additionally, 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 lithotripsy, for their upper urinary tract stones. We also do not know if patients with ADPKD who underwent stone interventions experience a higher risk of post-operative outcomes. More methodologically robust studies are needed to better characterize the association between ADPKD and upper urinary tract stones, and between stone interventions and post-operative outcomes. This information will help patients with ADPKD and physicians guide prognostication, and might inform the use of interventions; it will also help inform future clinical practice guidelines.

Conducting a retrospective cohort study using healthcare administrative databases would allow us to conduct large studies and give us insight into rate of hospital encounters with upper urinary tract stones and stone interventions in patients with ADPKD, and into the risk of post-operative outcomes of stone intervention in patients with ADPKD. However, we must first ensure that we can reliably identify patients with ADPKD using administrative codes. Patients with ADPKD can be identified using Ontario Health Insurance Plan (OHIP) diagnosis codes, codes submitted by physicians for the services they provide, or by using the International Classification of Diseases, 9th revision (ICD-9) codes, and International Classification of Diseases, 10th, revision (ICD-10) codes (healthcare encounter codes). Healthcare encounter codes are assigned per the ICD-9 (used in Canada prior to 2002) and ICD-10 (used in Canada in 2002 onwards) classification system by highly trained coders.[9] These data are collected for administrative purposes rather than research purposes.[10] Physician misdiagnosis, incomplete documentation in medical records, or errors by personnel who assign the administrative codes to each hospital encounter can potentially lead to misclassification.[9] Thus, patients who truly have ADPKD may not be assigned the code and patients with ICD-9 or ICD-10 codes related to ADPKD may not truly have ADPKD. Based on a comprehensive literature search of bibliographic databases, there is only a single study which validated an administrative code related to ADPKD.[11] Blanchette *et al.* validated the ICD-9 code for unspecified PKD (753.12) by using medical chart review as the reference standard.[11] The positive predictive value of the ICD-9 code 753.12 was 94.7%, indicating it identified patients who truly had ADPKD.[11] No study, to date, has formally validated the more recent ICD-10 code. Additionally, coding practices differ by countries, and even by different provinces. No study, to date, validated administrative

codes related to ADPKD in Ontario. Validating administrative codes related to ADPKD will provide assurance of the robustness of our cohort and the internal validity of our studies.

I will address the limitations in the current literature by conducting one validation study, and two cohort studies using healthcare administrative databases.

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Chapter 5 - Positive predictive value of international classification of diseases, 10th revision coding algorithms to identify patients with autosomal dominant polycystic kidney disease[c]

[c]Study funding was provided by the Polycystic Kidney Disease (PKD) Foundation of United States of America and the ICES Kidney, Dialysis, and Transplantation Program. The ICES is a non-profit research corporation funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The study was conducted at the ICES Western facility, which receives financial support from the Academic Medical Organization of Southwestern Ontario (AMOSO), the Schulich School of Medicine and Dentistry (SSMD) at Western University, and the Lawson Health Research Institute (LHRI). Dr. York Pei served as an expert consultant on drug development (Otsuka, Pfizer, and Genzyme/Sanofi) related to ADPKD. The other authors declare no competing interests. The patient records department at Victoria Hospital, and University Hospital provided the charts. Parts of this material are based on data and information compiled and provided by CIHI. The Dr. Adam Linton Chair in Kidney Health Analytics supported Amit Garg. Some of this work was conducted by trainees with offices in the Lilibeth Caberto Kidney Clinical Research Unit. The study design and conduct, opinions, results and conclusions reported in this paper are those of the authors, and are independent from the funding sources or data sources. No endorsement by ICES, AMOSO, SSMD, LHRI, Polycystic Kidney Disease Foundation of USA, or the MOHLTC is intended or should be inferred.

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5.1 INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic condition characterized by focal cyst development leading to bilateral enlargement of both kidneys.[1] Approximately, half of these patients will require end-stage kidney disease care by the age of 50.[2] ADPKD has an estimated prevalence of 1 in 1000 to 1 in 400 (0.1 to 0.25%) persons worldwide.[3] Since ADPKD is a relatively uncommon disease, using large healthcare administrative databases may allow a large number of patients with ADPKD to be identified and studied in a time-efficient and cost-effective manner. [4] However, this approach requires assurances that ADPKD is coded accurately in these data sources, and an appreciation of the number of patients with ADPKD who had at least one hospital encounter can be accurately identified in this way. This is because information available from administrative databases are collected primarily to monitor healthcare use and to assess healthcare needs, without the same rigour used in clinical research studies to assess conditions of interest.[5] Physician misdiagnoses, incomplete documentation in medical records, or errors by personnel who assign codes to each hospital encounter can all potentially lead to misclassification of a condition.[6]

We conducted a comprehensive search of bibliographic databases (search last updated to December 2015), and found only a single study in the United States that described any aspect of the accuracy of healthcare administrative database codes for ADPKD. Blanchette and colleagues assessed the positive predictive value of a single International Classification of Disease, 9th revision (ICD-9) code for any kind of polycystic kidney disease (PKD) (753.12), where a medical chart review was used to ascertain whether PKD was truly present or not.[7] In this study, the clinical criterion used to define PKD in the medical chart was not defined. In addition, despite knowing that the population comprised of members of commercial health plans, it was not clear whether the charts were from an outpatient and/or hospital-based setting.[7] In 132 patients, the positive predictive value of ICD-9 code 753.12 was 95%, indicating that most patients identified with the ICD-9 code 753.12 had ADPKD according to their medical chart review.[7]

We undertook two studies. Frist, we determined if different coding algorithms containing International Classification of Disease, 10th revision (ICD-10) codes for ADPKD

assigned during hospital encounters (emergency room visits or hospital admissions) can be used to identify adult patients who meet the clinical criteria for ADPKD in the province of Ontario, Canada. This was done to estimate the positive predictive value of various coding algorithms considering the manual chart review and a rigorous definition of ADPKD as the reference standard. Second, we used Ontario-wide healthcare databases to assess the number of patients identified with different sets of ADPKD codes to determine the proportion of the general public identified with ADPKD with each of the coding algorithms (where an expected prevalence is 0.1 to 0.25%).

5.2 METHODS

5.2.1 Study design

We completed two studies to evaluate the performance of ICD-10 coding algorithms for the identification of ADPKD patients and to understand the frequency of ICD-10 coding algorithms. For our first study, we manually reviewed inpatient and outpatient medical records (including both electronic medical records and paper charts) to assess the positive predictive values of different ICD-10 coding algorithms for ADPKD. For our second study, we conducted analyses of large healthcare databases housed at ICES, to understand the frequency of ICD-10 coding algorithm use in the province of Ontario, Canada.[8]

5.2.2 Ethics approval and consent to participate

The institutional review board at Western University, London, Ontario, Canada approved the chart abstraction study, and the one at Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada approved the second study using the healthcare administrative data housed at the ICES. The institutional review boards waived the need for patient consent. The Institute for Clinical Evaluative Sciences is a designated prescribed entity under Section 45 of the Personal Health Information Protection Act (PHIPA), and as such the need for patient consent is waived (as confirmed by the institutional review board that approved this study).

5.2.3 Data sources and database algorithms

The World Health Organization (WHO) developed the ICD-10 codes collaboratively with ten international centres to promote comparability in mortality data across countries. In Canada, the National Implementation Advisory Committee (established by the Canadian Institute for Health Information, CIHI) modified and enhanced some of the ICD-10 codes developed by WHO to better accommodate Canadians' administrative, epidemiological, and public health research needs prior to implementation. ICD-10-CA is the Canadian modification of the ICD-10 codes. The ICD-10 codes related to ADPKD used in Canada were not modified and are identical to those developed by the WHO.

ICD-10 and ICD-10-CA codes are used in Canadian administrative databases such as the CIHI Discharge Abstract Database (CIHI-DAD) and the CIHI National Ambulatory Care Reporting System (CIHI-NACRS). The CIHI-DAD houses administrative, demographic and clinical information on hospital discharge and day surgery procedures, and the CIHI-NACRS database contains information on all emergency room visits.[12] Neither CIHI-DAD nor CIHI-NACRS houses information on outpatient physician office visits. Trained personnel at each hospital in Ontario review the medical charts of all patients with healthcare encounters. Based on rules and guidelines provided by CIHI, these trained personnel code all diagnoses and procedures using the ICD-10 coding system, and then enter these codes into the CIHI-DAD and CIHI-NACRS databases.[6] These trained personnel only consider physician-recorded diagnoses in a patient's medical chart when assigning the codes, and do not review or interpret diagnostic imaging reports, laboratory values, family history, or signs and symptoms of ADPKD.

In our two studies, we compiled a list of relevant ICD-10 codes for ADPKD (Table 5-1) and developed nine unique algorithms using two databases (CIHI-DAD and CIHI-NACRS) and two ICD-10 codes, Q61.2 (polycystic kidney disease, autosomal dominant) and Q61.3 (polycystic kidney disease, unspecified) (Table 5-2).

Table 5-1. International classification of diseases, 10th revision codes relevant for autosomal dominant polycystic kidney disease.

Database	Code	Description
CIHI-DAD	Q61.3	polycystic kidney disease - unspecified
CIHI-DAD	Q61.2	polycystic kidney disease - autosomal dominant
CIHI-NACRS	Q61.3	polycystic kidney disease - unspecified
CIHI-NACRS	Q61.2	polycystic kidney disease - autosomal dominant

Abbreviations: Canadian Institute of Health Information Discharge Abstract Database, CIHI-DAD; Canadian Institute of Health Information National Ambulatory Care Reporting System, CIHI-NACRS

Table 5-2. Combination of International Classification of Diseases, 10th revision of the nine administrative coding algorithms evaluated to identify patients with autosomal dominant polycystic kidney disease.

	Administrative Code Algorithms
1	Q61.2 in CIHI-DAD
2	Q61.3 in CIHI-DAD
3	Q61.2 in CIHI-NACRS
4	Q61.3 in CIHI-NACRS
5	Q6.2 or Q61.3 in CIHI-DAD
6	Q61.2 or Q61.3 in CIHI-NACRS
7	Q61.2 in either CIHI-DAD or CIHI-NACRS
8	Q61.3 in either CIHI-DAD or CIHI-NACRS
9	Q61.2 or Q61.3 in either CIHI-DAD or CIHI-NACRS

Abbreviations: Canadian Institute of Health Information Discharge Abstract Database, CIHI-DAD; Canadian Institute of Health Information National Ambulatory Care Reporting System, CIHI-NACRS

5.3 METHODS SPECIFIC TO CHART ABSTRACTION STUDY

5.3.1 Patient selection

For the chart abstraction study, we compiled a list of adult patients (age $\geq$ 18 years) with emergency department visits and/or hospital admissions (CIHI-DAD or CIHI-NACRS) and the presence of one or more ICD-10 code Q61.2, Q61.3 between April 1st, 2002 and March 31st, 2014 at two major teaching hospitals in London, Ontario (Victoria Hospital

and University Hospital). ICD-10 codes are only available after April 1st, 2002, and thus defined our accrual start date. The main purpose of this study was to determine whether we could confidently use the ICD-10 codes related to ADPKD to identify patients with ADPKD using ICES data. The data was only available until March 31st, 2014 at the time the study was conducted, and thus defined our accrual end date. We assigned a unique Subject identification number (ID) to each patient, and saved a list of all patients' medical record numbers and Subject IDs in a password protected Microsoft Excel file, which was stored on a secure hospital network, as prescribed by our REB. If a patient had more than one code or more than one hospital and/or ambulatory care encounter, we assigned the unique subject ID to the first hospital or ambulatory care encounter because that was the first time the individual was recognized as affected with ADPKD during our study period. We included all patients with an ICD-10 code Q61.2. For the observations with ICD-10 code Q61.3, we stratified all patients by database (CIHI-DAD or NACRS) and by year of hospital encounter, and randomly sampled within strata to review the medical records of a total of 201 patients from a list of 305 patient charts eligible for review.

5.3.2 Data collection

We manually reviewed the medical records of the 201 patients. We abstracted information on physician report of ADPKD, family history of ADPKD, indication of ADPKD from surgical pathology reports or autopsy reports, and information from imaging reports (reason for examination, number of cysts in each kidney, and dimensions of each kidney). Certain imaging reports did not specify the exact number of cysts. In these instances, we interpreted "multiple cysts bilaterally" as at least three cysts in each of the two kidneys, and "innumerable cysts bilaterally" as at least four cysts in each of the two kidneys after consultation with an experienced nephrologist and radiologist. Sensitivity analysis were performed to determine whether interpreting "multiple cysts bilaterally" as at least four cysts in each kidney meaningfully changed the results. If information was missing in an electronic medical record, we obtained the paper in-patient chart. If information was still missing after reviewing the paper chart, we reviewed the nephrology outpatient chart when available. Subsequently, a senior radiology resident

(M.R.) retrieved and reviewed available diagnostic images for patients with missing or ambiguous information. We recorded all abstracted information onto a detailed data abstraction form (Table 5-3).

Table 5-3. Data abstraction form to collect relevant clinical information required to elucidate whether patients have ADPKD or not according to the reference standard.

Subject ID	Type of Polycystic Kidney Disease Diagnosis	ICD-10 Code	Current Age	Weight	Height	Sex	Last Serum Creatinine Value	Date of Last Serum Creatinine Value

Death Summary Report Date	Family Physician	Renal Family Physician	Indication of PKD	Specify how it is indicated	Physician Diagnosis	Date of Physician Diagnosis	Imaging Modality	Year of Birth

Age at U/S	Date of Imaging	Type of U/S imaging (e.g. renal U/S)	Reason for Exam	U/S indicates ADPKD	Radiologist report ADPKD	Right Kidney Dimension	RK	Left Kidney Dimension

LK	Number of renal cysts	Presence of Family History	Document that indicates Fam Hx	Genetic Screening?	Mutation detected in genetic screening	Met diagnostic criteria?	Pathology/Autopsy report	Date	Indication of PKD in pathology/autopsy report

Onset Date	Notes

Abbreviations: family history, Fam Hx; International Classification of Diseases, 10th revision, ICD-10; left kidney, LK; polycystic kidney disease, PKD; right kidney, RK; ultrasound, U/S

5.3.3 Clinical definition of ADPKD

In the chart abstraction study, two reviewers (V.K. and R.M.) independently determined whether each of the 201 patients had ADPKD or not using strict criteria (described in next paragraph). These criteria were developed in consultation with two experienced nephrologists (A.G. and Y.P.). To determine final ADPKD status, any disagreements between the two reviewers were resolved by consensus. Having two reviewers helped to reduce human error and personal bias.

A reference standard is a method used to diagnose a disease with the most acceptable accuracy and provides a standard to which new screening or diagnostic test can be compared. Currently, physicians use the ultrasound diagnostic criteria developed by Pei et al. to diagnose patients with ADPKD.[13] This criteria requires the presence of a positive family history of ADPKD, and evidence of the following number of cysts on a conventional kidney ultrasound: i) at least three cysts when counting the total number of cysts in both kidneys combined for patients 15 to 39 years old; ii) at least two cysts in each kidney for patients 40 to 59 years old; and iii) at least four cysts in each kidney for patients 60 years of age or older.[13] We used this internationally accepted diagnostic criteria as our primary clinical definition for ADPKD. One of the disadvantages of retrospectively collecting data for the reference standard is that some information required to elucidate ADPKD status based on our primary definition may have been missing. To reduce the number of patients with indeterminant ADPKD status, we developed less stringent criteria to identify patients with ADPKD. First, we classified patients with a negative or indeterminate family history of ADPKD as affected if they had innumerable cysts in both kidneys with each kidney greater than 13 cm in length. Median (10^{th} and 90^{th} percentile) is 11.2 (10.1 to 12.3) cm for the left kidney and is 10.9 (9.6 to 12.2) cm for the right kidney; hence, we chose 13 cm as a cutoff point to consider a kidney as enlarged.[14] Second, we classified all patients who had a nephrectomy performed and with a diagnosis of ADPKD in a surgical pathology or autopsy report as affected irrespective of their ADPKD family history status. Finally, we classified patients with missing imaging reports as affected with ADPKD if they had a family history of ADPKD and a clear physician reported diagnosis of ADPKD. When ADPKD status was

still ambiguous, an experienced nephrologist (A.G.) reviewed all medical records to make a determination of whether ADPKD was present or not according to clinical criteria. When there was insufficient information to make a determination of whether ADPKD was present or not, patients were excluded from analysis. Sensitivity analyses were performed to determine if classifying the excluded patients as having ADPKD, or as not having ADPKD, meaningfully changed the results.

5.3.4 Data analysis

For the chart abstraction study, we expressed continuous variables as median and interquartile ranges (IQR) and binary variables as percentages. We calculated the positive predictive value for each of the nine coding algorithms and calculated their respective 95% confidence intervals using the Wilson Score method (Figure 5-1).[15] Given the way the study was designed, we only had data from patients with hospital encounter with ICD-10 codes for ADPKD. We did not have data from patients without the codes; as a result, we could only calculate positive predictive value and could not calculate other measures of validity, such as sensitivity, specificity, and negative predictive value.

		Reference Standard: ADPKD defined by the clinical definition specified in Section D.3.3		
		ADPKD	**Non-ADPKD**	**Total**
ADPKD defined by **administrative algorithm**	ADPKD Code(s) Present	TP (a)	FP (b)	**TP + FP**
	ADPKD Code(s) Absent	FN (c)	TN (d)	**FN+TN**
	Total	**TP+FN**	**FP+TN**	**N**

Figure 5-1. Definition of positive predictive value used for the first (chart review) study.

Note: Positive Predictive Value = TP/(TP+FP). Positive predictive value is defined as the percentage of patients who truly have ADPKD according to our clinical definition of ADPKD detailed in Section D.3.3 among everyone with at least one administrative code related to ADPKD. The cells highlighted in dark grey are data that was not available.

5.4 METHODS SPECIFIC TO ICES STUDY

5.4.1 Patient Selection

We linked and analyzed CIHI-DAD and CIHI-NACRS using unique encoded identifiers at ICES. We identified all patients over the age of 18 years who were assigned either an ICD-10 Q61.2 code or Q61.3 code during an emergency department visit or hospital admission between April 1st, 2002 and March 31st, 2014. As with our first study, we only considered the first encounter for patients with more than one hospital encounter.

5.4.2 Data analysis

We estimated the number of patients with ADPKD in Ontario by calculating the percentage of the adult Ontario population with the different coding algorithms in CIHI-DAD and CIHI-NACRS described in Table D-1. We conducted all statistical analyses using SAS 9.3 (SAS Institute Inc., Cary, North Carolina, USA).

5.5 RESULTS

5.5.1 Chart abstract study sample

We obtained a list of unique patients with ICD-10 codes Q61.3 and Q61.2 using the CIHI-DAD and CIHI-NACRS database. We then included all patients with the ICD-10 code Q61.2, and stratified random sampled patients with ICD-10 code Q61.3 to sample a total of 201 patients. We abstracted information using electronic medical records for all 201 patients, inpatient charts for 117 patients, and nephrology outpatient charts for 52 patients. A senior radiology resident (M.R.) reviewed the images of 65 patients with ADPKD because imaging reports did not clearly provide all the required information. After excluding 14 patients because of insufficient information to determine ADPKD status, our final cohort consisted of 187 patients.

5.5.2 Chart abstraction patient characteristics

Among the 187 patients identified in our cohort through database codes, median (interquartile) patient age was 61 (53 to 70), and 95 (50%) were men. Family history of ADPKD was positive in 116 (62%) patients, negative in 42 (22%) patients, and was missing or indeterminate in 29 (16%) patients. A total of 158 (85%) patients met the clinical criteria of ADPKD. The number and percent of patients that satisfied each ADPKD criteria is presented in Table 5-4.

Table 5-4. Number and percentage of patients that satisfied each criterion for autosomal dominant polycystic kidney disease.

Autosomal Dominant Polycystic Kidney Disease Criteria	Number of Patients (%)
Current Ultrasonographic Diagnostic Criteria: Family History and age-dependent, ultrasonographic diagnostic criteria: a) Ages 15 to 39: at least 3 cysts in one or both kidneys b) Ages 40 to 59: at least 2 cysts in each kidney c) Ages 60 and over: at least 4 cysts in each kidney	**108** (53.73)
No family history, both kidneys > 13 cm and age-dependent minimal number of cysts: a) Ages 15 to 39: at least 3 cysts in one or both kidneys b) Ages 40 to 59: at least 2 cysts in each kidney c) Ages 60 and over: at least 4 cysts in each kidney	**37** (18.41)
Indication of ADPKD in surgical pathology report or autopsy report	**7** (3.48)
Physician report of ADPKD and family history of ADPKD or patient has ADPKD based on nephrologist adjudication	**6** (2.98)
Did not meet any criteria	**29** (14.43)
Excluded from the study given a lack of information to make a determination of whether ADPKD was present or not	**14** (6.97)

*Note: These data were obtained from chart review. In accordance with privacy regulations, cell sizes less than or equal to five cannot be reported.
Abbreviations: autosomal dominant polycystic kidney disease, ADPKD

5.5.3 Coding algorithm positive predictive value and frequency

The positive predictive values, their respective 95% confidence intervals (from our chart abstraction study), and the number of Ontarians with the 9 different coding algorithms (from our ICES study) are presented in Table 5-5. The presence of either ICD-10 code Q61.2 or Q61.3 in either the CIHI-DAD or CIHI-NACRS database had a positive predictive value of 85% (95% CI 79% to 89%) and identified 2981 adults in Ontario (0.02% of the Ontario adult population). The presence of ICD-10 code Q61.2 in either the CIHI-DAD or CIHI-NACRS database had a positive predictive value of 97% (95% CI 86% to 100%) and identified 394 adults in Ontario (0.003% of the Ontario adult population). Sensitivity analyses did not meaningfully change the results.

Table 5-5. Positive predictive values and the number of Ontarians identified by each administrative database coding algorithm.

Code Algorithm	Positive Predictive Value [95%CI]	Estimated # of Ontarians *	Percentage of adult Ontario population* (%)
CIHI-DAD Q61.2	96.97% [84.68, 99.46]	342	0.0028
CIHI-DAD Q61.3	80.00% [71.35, 86.53]	1901	0.0154
CIHI-NACRS Q61.2	100.00% [43.85, 100.00]	52	0.0004
CIHI-NACRS Q61.3	84.78% [71.78, 92.43]	686	0.0056
CIHI-DAD Q61.2 or Q61.3	84.06% [77.04, 89.23]	2243	0.0182
CIHI-NACRS Q61.2 or Q61.3	85.71% [73.33, 92.90]	738	0.0060
Q61.2 in either CIHI-DAD or CIHI NACRS	97.22% [85.83, 99.51]	394	0.0032
Q61.3 in either CIHI-DAD or CIHI-NACRS	81.46% [74.51, 86.85]	2587	0.0210
Q61.2 or Q61.3 in either CIHI-DAD or CIHI-NACRS	84.49% [78.62, 88.98]	2981	0.0242

Abbreviations: Canadian Institute for Health Information Discharge Abstract Database, CIHI-DAD; National Ambulatory Care Reporting System, NACRS

5.6 DISCUSSION

Although past studies have assessed the positive predictive value of different ICD-10 codes or coding algorithms for other diseases or conditions, there is a lack of information on the positive predictive value of ICD-10 coding algorithms for ADPKD. The positive

predictive value is reported as a number from 0 to 100%, where a high value indicates that individuals who are identified with the coding algorithm truly have the condition. We manually reviewed a random sample of medical charts from two tertiary care hospitals in London, Ontario where the medical coders in routine care had assigned a code for polycystic kidney disease. Using rigorous clinical criteria, we then determined whether ADPKD was present or not. We found that the presence of the ICD-10 code Q61.2 in hospital admissions or emergency visits had an excellent positive predictive value of 97% (95% CI: 86% to 100%). The positive predictive value of the presence of either the ICD-10 code Q61.2 or Q61.3 in either hospital admissions or emergency visit was also good at 85% (95% CI: 79% to 89%). Therefore, our study shows that administrative coding algorithms for ADPKD successfully identifies patients who truly have ADPKD, which is consistent with the findings from a study conducted by Blanchette and colleagues.[7] These values in the ADPKD setting are similar or better than the positive predictive value of ICD-10 codes or ICD-10 coding algorithms for shock (86%; 95% CI: 80% to 91%), infant respiratory distress syndrome (81%; 95% CI: 73% to 80%), and heart failure (84%; 95% CI: 81% to 87%).[16–18] While our study has several strengths, results of this study must be interpreted with caution given the limitations. First, since we only reviewed the medical charts of patients with assigned ICD-10 database codes for ADPKD, we cannot estimate other measures of validity such as negative predictive value, sensitivity, and specificity. We expect the sensitivity of the ICD-10 codes for ADPKD to be low. Since the prevalence of ADPKD is estimated to be 1 in 1000 to 1 in 400, we would expect 13,000 to 32,500 Ontarians to be affected with ADPKD [1]. However, the expansive coding algorithm (any of the two ICD-10 codes in CIHI-DAD or CIHI-NACRS) only identified approximately 3000 patients. Thus, although the two ICD-10 codes appear to have a high positive predictive value, it is possible only 9% to 23% of the patients with ADPKD in the province were captured with the algorithm.

Second, by its design, we would expect the ICD-10 coding algorithm would preferentially identify a spectrum of ADPKD patients with moderate to advanced disease requiring hospital encounters, rather than ADPKD patients managed in the community that did not have hospital encounters. The code sets may also identify some mild cases,

such as patients with ADPKD admitted for uncomplicated pregnancy. Therefore, these algorithms should only be used to assemble and study cohorts of adult patients with ADPKD and hospital encounters, rather than all patients in the province with ADPKD. Unfortunately, there are no relevant codes that can be used to identify the presence of ADPKD in the Ontario outpatient billing system.

Third, we reviewed medical charts from two hospitals at the London Health Sciences Centre. While coding practices are standardized across hospitals, any differences in coding between these two hospitals and other hospitals would influence generalizability of our study results.

Fourth, there were no reports from genetic testing in any of the patient charts, which could have helped further ascertain the presence of ADPKD in cases when a family history is absent or not available.[19]

Fifth, we are not sure that all imaging or other ancillary information for a given patient was found. For example, a patient may have had an ultrasound performed in an outpatient lab, and the nephrologist may not have a record of it. Therefore, the positive predictive value may be underestimated. Additionally, this also may explain why the percentage of our cohort is lower than the estimates reported in the published literature.

Finally, our adjudicators were aware that all reviewed records had ICD-10 codes assigned for polycystic kidney disease in the healthcare database records. While this may have influenced their adjudication of the records, we minimized the risk of information bias through the use of pre-defined diagnostic criteria for ADPKD, where two reviewers independently adjudicated each case.

5.7 CONCLUSION

In conclusion, the positive predictive value of the various coding algorithms for ADPKD is moderately high. These codes can be used to assemble and study cohorts of adult

patients with ADPKD and hospital encounters, but are expected to miss the majority of the milder forms of ADPKD where patients are healthy without hospital encounters.

5.8 ADDENDUM

5.8.1 Rationale for sampling 201 patients

At the time the study was conducted, we sampled 201 patients from 305 eligible charts for review. This was done for convenience. If we were to redo the study, we would have reviewed the charts of all 305 charts. The positive predictive value (95% CI) of the algorithm Q61.2 and Q61.3 using both databases (CIHI-DAD and NACRS) was 84.49% (78.62 to 88.98). Assuming the point estimate would remain unchanged, the corresponding number would be 84.49% (79.98 to 88.13) with 305 patients charts. In other words, reviewing all 305 charts would have not have materially improved the precision of the estimate.

5.8.2 Recommended algorithm for future studies

Although the Q61.2 code and the emergency department visit database has a perfect positive predictive value, I used a combination of the Q61.2 and Q61.3 codes and both databases (CIHI-DAD and NACRS) to assemble a robust ADPKD cohort for my cohort studies (Chapter 6 and 7). The latter coding algorithm identifies the most patients compared to the other eight coding algorithms examined and still has a positive predictive value of 84%; therefore, more patients would be identified and the internal validity of the study due to the exposure definition would not be compromised.

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Chapter 6 - Risk of hospital encounters with upper urinary tract stones in autosomal dominant polycystic kidney disease: a cohort study[d]

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Dr. York Pei 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. The results presented in this paper have not been published previously in whole or part, except in abstract form, and was presented as a poster at the American Society of Nephrology Kidney Week on November 7, 2019 in Washington, DC.

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6.1 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 upper urinary tract 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 upper urinary tract stones are more prevalent in patients with ADPKD compared to 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.

Upper urinary tract 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 to 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 healthcare databases to describe the rate of hospital encounters (emergency department visits or hospital admissions) with upper urinary tract stones in patients with ADPKD, and the rate and type of upper urinary tract 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 upper urinary tract stones and stone interventions were similar in patients with and without ADPKD.

6.2 MATERIALS AND METHODS

6.2.1 Designs and setting

The prevalence of ADPKD is between 1 in 1000 and 1 in 400.[15–17] In chapter 2 of this study, we showed that the prevalence of stone ranges between 3% and 59%[8,10,11,18–61], and the prevalence of stone intervention ranges between 1% and 8%[19,30,41,43,48,54,57]. Since the prevalence of ADPKD is lower than the prevalence of upper urinary tract stones and stone intervention, a retrospective cohort study would allow us to accrue an adequate number of patients with ADPKD and allow enough events to accumulate for a well-powered study. As a result, we conducted a retrospective cohort study using Ontario's healthcare administrative databases held at ICES (a not-for-profit research institute). Healthcare 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 those 65 years and older. Healthcare encounters are recorded in administrative databases, which are linked using unique encoded identifiers and analyzed at ICES. 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. We reported this study following guidelines for observational studies conducted using routinely-collected data.[62,63]

6.2.2 Sample size calculations

The reported life time prevalence of upper urinary tract stone varies between 1% and 20%.[64] We used the cox proportional hazard model sample size formula, to determine the minimum total sample size that would be required to have a statistical power of 80% to detect a clinically significant difference between the two groups at a significance level of 5%.[65] Since the effect size is unknown, we determined the sample size by using common effect sizes (Hazard Ratio ranging from 1.5 to 5.0). We also explored a range of values for the baseline prevalence of upper urinary tract stones (1, 5, 10, 15 and 20%). Sample size is inversely proportional to prevalence of event, and to be conservative in our sample size calculation, we assumed the overall probability of event occurring during follow-up

is 1%.We would need a total sample size of 19,097 to detect even a Hazard Ratio of 1.5 at a power of 80% and α=0.05 if the prevalence of event is 1% (Figure 6-1). Since our total sample size exceeds 19,097, our study was well-powered for this and other potential values of the prevalence and effect sizes.

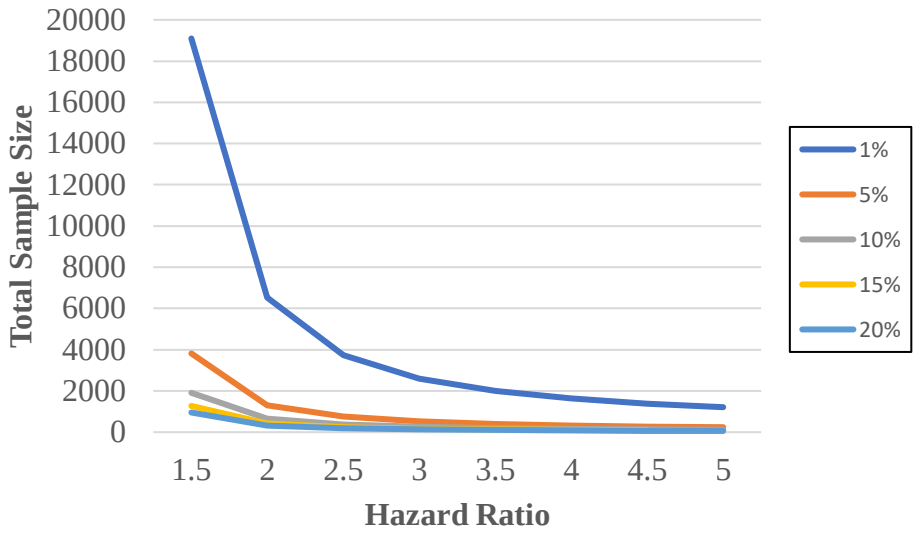


Figure 6-1. Total sample size required to detect a clinically significant difference with an effect size (Hazard Ratio) varying between 1.5 to 5.0 when the prevalence of upper urinary tract stone is 1%, 5%, 10%, 15%, and 20%.

6.2.3 Data sources

We linked seven 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. A detailed description of each of the Ontario healthcare administrative databases is described in Table A-1. All variables were complete in this study except for average neighbourhood income (<1% missing) and urban or rural residency (<1% missing). For patients with missing average neighbourhood income quintile and urban or rural residency status, we assigned an average neighbourhood income quintile value of 3 and urban residency, respectively.

6.2.4 Population and timeline

Our study cohort included Ontarians who had a hospital encounter with ADPKD (i.e. admitted to the emergency department or hospital), identified using ICD-10 codes between April 1st, 2002 and March 31st, 2016. We used the coding algorithm with the highest positive predictive value (ICD-10 codes Q612 and Q613 validated details in Chapter 3) to ensure that the internal validity of our study was not compromised.[66] The positive predictive value (95% confidence interval [CI]) of the coding algorithm that we used was 84.1% (77.0% to 89.2%). A follow-up validation study conducted by our team also showed that this coding algorithm differentiates patients with ADPKD from patients with very similar conditions (specificity=86.2%; 95% CI 75.7% to 92.5%), but it only identified a small subset of the broader ADPKD population (sensitivity=33.7%; 95% CI 30.1% to 37.7%). ICD-10 codes are only available after April 1st, 2002, and thus defined our accrual start date. An accrual end date of March 31st, 2016 ensures that each patient had the potential for at least one year of follow-up (March 31st, 2017 was the date of last available data at the time that the study was conducted). We excluded the following patients:

(1) Patients aged 18 and under. Autosomal recessive polycystic kidney disease (ARPKD) displays very similar clinical characteristics as ADPKD; both patients have multiple cysts in their kidneys. However, ARPKD primarily manifests during birth or childhood, while ADPKD, although is a congenital condition, primarily manifests during adulthood. By excluding patients under 18 years of age, we can exclude patients with ARPKD 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 healthcare facility in Ontario to limit our study population to Ontarians. We would not have follow-up data on Non-Ontario residents who received care from a healthcare facility in Ontario.
(4) Patients with a history of end-stage kidney disease, as many have no urine output making the presence of upper urinary tract stones less relevant.

Patients with prior upper urinary tract stones and treatments for upper urinary tract 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.

We compared the rate of upper urinary tract stones and rate of stone intervention in patients with ADPKD to patients without ADPKD with otherwise similar baseline health to provide context. Our study population would primarily consist of patients with more advanced ADPKD with few milder cases of ADPKD since our study included patients who were admitted to the emergency department or who were admitted to the hospital with ADPKD. To ensure our control group was as similar as possible to our study population, we included patients with at least one hospital admission or emergency department visit for any reason between April 1st, 2002 and March 31st, 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 OHIP diagnosis codes for other cystic diseases (OHIP diagnosis code 593) and congenital anomalies of the urinary system (OHIP diagnosis code 753), as these codes can occasionally capture patients with ADPKD. We then randomly selected 50,000 controls (versus the entire Ontario population with hospital encounter) for reasons of computing 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 31st, 2017 (administrative censoring), and censored the observational period at time of death or emigration from the province.

6.2.5 Outcomes

The two outcomes were (a) time to first hospital encounter with upper urinary tract stone; and (b) time to first stone intervention, which was a composite outcome of the three common stone interventions: shock wave lithotripsy (SWL), ureteroscopy, and percutaneous nephrolithotomy (PCNL). The administrative codes used to identify outcomes are detailed in Table 6-1. In a validation study, codes similar to the ones we used to identify stones had a positive predictive value of 96% compared to chart review.[67,68] We identified stone intervention events using OHIP fee codes and Canadian Classification of Health Intervention (CCI) codes. Although the OHIP fee codes for stone intervention have not been formally validated, we expect these codes to have excellent validity similar to other fee for service codes.[69] Further, the same coding algorithm used to identify stone interventions has been used in past studies. [70,71] Any stone-related database codes that appeared within 90 days of each other were considered the same event, which has been done in past ICES studies.[70] For stone intervention, we did not restrict to individuals with hospital encounters for upper urinary tract stones (outcome a), because we wanted to capture stone interventions in both the inpatient and outpatient settings.

Table 6-1. Databases and coding definitions for restriction criteria, baseline characteristics and outcome measurements.

Variable	Database & Administrative Codes
Study Population Inclusion Criteria	
ADPKD	**CIHI-DAD & NACRS ICD-10 codes:** Q612, Q613
Control Population Inclusion Criteria	

Ontarians with hospital encounter without ADPKD	**CIHI-DAD & NACRS**
Exclusion Criteria	
Chronic dialysis	**CIHI-DAD CCP codes:** 5195, 6698 **CIHI-DAD CCI codes:** 1PZ21 **OHIP Fee:** R849, G323, G325, G326, G860, G862, G865, G863, G866, G330, G331, G333, G861, G082, G083, G085, G090, G091, G092, G093, G094, G095, G096, G294, G295, G864, H540, H740 **CORR** RECIPIENT_TREATMENT dataset: select all chronic dialysis patients using [Treatment_Code not equal to 171, 181] in the prior one year.
Kidney transplantation	**CIHI-DAD CCP codes**: 6759 **CIHI –DAD CCI codes**: 1PC85 **OHIP fee codes**: S435, S434 **CORR** RECIPIENT_TREATMENT dataset: select all renal transplant patients using [Treatment_Code equal to 171] and [Transplanted_Organ_Type_Code (1-3) equal to 10, 11, 12, 18, 19] in the prior five year
Other cystic diseases and congenital anomalies of the urinary system (only for control group	**CIHI-DAD & NACRS ICD-9 codes:** 7531 **CIHI-DAD & NACRS ICD-10 codes:** Q611, Q612, Q613 **OHIP Dx codes:** 753, 593
Outcomes	

Urological Intervention	**CIHI-DAD, NACRS, & OHIP:** composite of shockwave lithotripsy, ureteroscopy, and percutaneous nephrolithotomy (refer to codes below)
Shockwave lithotripsy	**CIHI-DAD & NACRS CCI**: 1PE59KQAP, 1PE59KQAQ, 1PE59KQAR, 1PG59KQAP, 1PG59KQAQ, 1PG59KQAR **OHIP Fee Codes**: Z630
Ureteroscopy	**CIHI-DAD & NACRS CCI**: 1PE57BAAM, 1PE57BAGX, 1PE59BAAG, 1PE59BAAS, 1PE59BAAT, 1PE59BAAZ, 1PG57BAAM, 1PG57BAGX, 1PG59BAAG, 1PG59BAAS, 1PG59BAAT, 1PG59BAAZ, 1PG59BAGX, 1PE59BAAS, 1PE59BAAT, 1PE59BAAZ **OHIP Fee Codes:** Z628 AND (E760 or E761 or Z627)
Percutaneous Nephrolithotomy	**CIHI-DAD & NACRS CCI**: 1PE57DTAG, 1PE57DTAM, 1PE57DTAS, 1PE57DTAZ, 1PE57DTBD, 1PE57DTGX **OHIP Fee Codes:** Z624 AND Z627
Upper urinary tract stones	**CIHI-DAD & NACRS:** N20, N132
Baseline Characteristics	
Age	**RPDB**
Sex	**RPDB**
Rural location	**RPDB**
Neighbourhood Income	**RPDB**
Primary care physician visits in the previous one year	**IPDB:** Mainspeciality= GP/FP **OHIP**

Emergency department visit in the previous one year	**NACRS**
Urology clinic visit in the previous one year	**IPDB:** Mainspeciality= Urology **OHIP**
Abdominal imaging	**OHIP Fee codes**: J135, J128, X100, X101, X197, X409, X410, X126, X451, X455
Urinary tract obstruction	**CIHI-DAD & NACRS ICD-9 codes**: 591, 5934, 5996 **CIHI-DAD & NACRS ICD-10 codes**: N130, N131, N132, N133, N138 **OHIP Dx codes**: 591
Urinary tract infection	**CIHI-DAD & NACRS ICD-9 codes:** 5901, '5900, 5908', 5902, 5909, 5950, 5958, '5959, 5970, 5990, 6016, 6011, 6012, 6013, 6040, '6049 **CIHI-DAD & NACRS ICD-10 codes:** N10, 'N11, 'N12, N136, 'N151, N159, N160, N300, N308, N309, N340, N390, N410, N411, N412, N413, N431, N45, T835
Primary hyperparathyroidism	**CIHI-DAD & NACRS ICD-9 codes**: 2520 **CIHI-DAD & NACRS ICD-10 codes**: E210, E211, E213, E214, E215 OHIP Dx: 252 OHIP Fee: S792, S795, S796, Z772 CCP: 197, 1971, 1996, 1997 CCI: 1FV59HAX7, 1FV83NZ, 1FV83NZAG, 1FV83PZ, 1FV83PZAG, 1FV87NZ, 1FV87NZAG, 1FV87PZ, 1FV87PZAG, 1FV89NZ, 1FV89NZAG, 1FV89PZ, 1FV89PZAG
Gout	**CIHI-DAD & NACRS ICD-9 codes**: 274 **CIHI-DAD & NACRS ICD-10 codes**: M10 **OHIP Dx codes**: 274

Obesity	**CIHI-DAD & NACRS ICD-9 codes**: 2780 **CIHI-DAD & NACRS ICD-10 codes**: E65, E660, E661, E662, E668, E669 **OHIP Dx codes**: 278
Diabetes Mellitus	**CIHI-DAD & NACRS ICD-9 codes**: 250 **CIHI-DAD & NACRS ICD-10 codes**: E10, E11, E13, E14 **OHIP Dx codes**: 250 **OHIP Fee codes**: K045, K046, K029, K030, Q040
Hypertension	**CIHI-DAD & NACRS ICD-9 codes**: 401, 402, 403, 404, 405 **CIHI-DAD & NACRS ICD-10 codes**: I10, I11, I12, I13, I15 **OHIP Dx codes**: 401, 402, 403
Osteoporosis	**CIHI-DAD & NACRS ICD-9 codes**: 7330 **CIHI-DAD & NACRS ICD-10 codes**: M80, M81, M82 **OHIP Dx codes**: 733
Prior hospital encounter or intervention for stone	**CIHI-DAD, NACRS, & OHIP:** composite of prior hospital encounter for stone and prior intervention for stone removal
Prior hospital encounter for stone	**CIHI-DAD & NACRS ICD-9 codes**: 592,5920, 5921, 5929 **CIHI-DAD & NACRS ICD-10 codes**: N20, N132 **OHIP Dx codes**: 592
Prior intervention for stone removal	**CIHI-DAD & NACRS CCI codes**: 1PE59KQAP, 1PE59KQAQ, 1PE59KQAR, 1PG59KQAP, 1PG59KQAQ, 1PG59KQAR, 1PE57BAAM, 1PE57BAGX, 1PE59BAAG, 1PE59BAAS, 1PE59BAAT, 1PE59BAAZ, 1PG57BAAM, 1PG57BAGX, 1PG59BAAG, 1PG59BAAS, 1PG59BAAT, 1PG59BAAZ, 1PG59BAGX, 1PE59BAAS, 1PE59BAAT,

	1PE59BAAZ, 1PE57DTAG, 1PE57DTAM, 1PE57DTAS, 1PE57DTAZ, 1PE57DTBD, 1PE57DTGX **OHIP Fee codes**: Z630 OR [Z628 AND (E760 or E761 or Z627)] OR [Z624 AND Z627]
Inflammatory bowel disease	**CIHI-DAD & NACRS ICD-9 codes**: 5550, 5551, 5552, 5559, 556 **CIHI-DAD & NACRS ICD-10 codes**: K50, K51 **OHIP Dx:** 555, 556

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; CCI, Canadian Classification of Health Interventions; CCP, Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures; CIHI-DAD Canadian Institute for Health Information Discharge Abstract Database; CORR, Canadian Organ Replacement Register; ICD-9, International Classifications of Diseases, 9th revision codes; ICD-10, International Classification of Diseases, 10th revision codes; IPDB, ICES Physician Database; NACRS, National Ambulatory Care Reporting System; ODB, Ontario Drug Benefit; OHIP Dx, Ontario Health Insurance Plan diagnosis codes; OHIP Fee, Ontario Health Insurance Plan fee for service codes; OLIS, Ontario Laboratories Information System; RPDB, Registered Persons Database

6.2.6 Data analysis

In traditional regression analysis, there must be ten events for every covariate adjusted.[72] Since we anticipated the number of covariates to outnumber the number of events that may be observed, we eliminated the difference in baseline distribution between the two group using propensity scores. There are four common propensity score methods to account for confounding: 1) propensity score matching; 2) inverse probability treatment weighting (IPTW) based on propensity scores; 3) adjusting for propensity score in the model; and 4) stratifying on propensity score. Propensity score matching eliminates a lot more of the systematic differences between the study and control group compared to stratifying on propensity score, and adjusting for propensity score as a covariate in a regression model.[73] Prior studies have shown that propensity score matching eliminates just as much, or modestly more, systematic differences between the two groups compared

to IPTW based on propensity.[73] For these reasons, we first attempted propensity score matching to ensure that the two groups had comparable baseline health. We matched each patient with ADPKD on age (± two years), sex, start date of follow-up (± one years), and log propensity score (± 0.2 standard deviation) a control to select patients with similar indicators for baseline health, and discarded all unmatched patients. However, more than 20% of our ADPKD population was not matched to any control because our control population was very different from our ADPKD cohort; we lost more than 20% of our ADPKD population. As such, propensity score matching was not feasible given the loss in our ADPKD population. As a result, we used IPTW based on propensity scores and used average treatment effect in the treated weights to ensure the distribution of indicators for baseline health were similar between controls and patients with ADPKD. IPTW based on propensity scores involves assigning a weight of one to everyone in the ADPKD group, and a weight of [propensity score/ (1-propensity score)] to the control group (i.e. the inverse of the propensity score) so that the distribution of baseline characteristics in the control group is similar to that in the ADPKD group.[74] This method results in a pseudo-control population that has a similar distribution of measured baseline characteristics as the ADPKD population while retaining all the individuals in the original cohort. In the context of the study, propensity score is the likelihood that a patient would be diagnosed with ADPKD conditional on their baseline characteristics. We calculated propensity scores using logistic regression with ADPKD as the dependent variable, and the following 20 covariates as the independent variables:

(1) *Factors associated with stone and stone intervention*: There are four sets of variables that can be included in a propensity score model: a) all measured baseline covariates; b) covariates associated with exposure; c) covariates associated with outcome only (potential confounders); and d) covariates associated with both the outcome and exposure.[73] Adjusting for potential and/or true confounders results in a more precise estimate.[73] We included and adjusted for potential confounders instead of true confounders as independent variables in our propensity score model since it is difficult to identify all true confounders. Factors associated with our outcomes and those that can be identified using our databases at ICES included: age, sex, acute kidney injury, urinary tract

obstructions, urinary traction, primary hyperparathyroidism, obesity, diabetes mellitus, hypertension, osteoporosis, prior hospital encounter with upper urinary tract stone, prior stone intervention, and inflammatory bowel disease. Studies have shown that lower education level, increased distance from the referral center, income, and urologist density was associated with stone burden.[75] As a result, we also adjusted for average neighbourhood income quintile, rural vs. urban residency, and health service region of Ontario (Local Health Integration Network) as proxies for these risk factors.

(2) *Abdominal imaging in the prior five years*: If one group undergoes abdominal imaging more often than the other group, then stones will be more likely be incidentally found in the group that undergoes abdominal imaging more, and surveillance bias would be introduced. We adjusted for abdominal imaging in the prior five years to minimize the risk of surveillance bias.

(3) *Urology clinic visits in the prior one year*: People who visit the urology clinic would be more likely to be incidentally diagnosed with urological conditions, such as upper urinary tract stones. We adjusted for prior urology clinic visits to minimize the surveillance bias introduced when one group visits the urology clinic more than the other group.

(4) *Primary care physician visits and emergency department visits in the prior one year*: These are indicators for propensity to seek care. Those who are likely to seek care would be more likely to get diagnosed with any conditions; therefore, surveillance bias would be introduced if one group visited the primary care physician and emergency department more than the other group. We adjusted for primary care physicians and emergency department visits as a proxy for propensity to seek care.

When using IPTW based on propensity score, extreme weights can be problematic because few individuals will drive results. According to Stürmer (2014), it is reasonable to considers weights $\geq$10 as a sign of concern.[76] A patient in our control group had a weight of $\geq$ 10 so 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.[77]

We described baseline characteristics for patients with and without ADPKD as mean and standard deviation for continuous variables, and as frequencies and percentages for binary or categorical variables before and after weighting. We assessed the imbalances in baseline characteristics between the two groups using standardized differences, which are insensitive to sample size. The standardized difference is the differences in means or proportions divided by the pooled standard deviation, and a value of greater than 10% suggests important imbalance.[78]

We plotted the cumulative incidence function for stones censoring the observational time for death, end of follow-up, or emigration from the province. While cumulative incidence function provides a visual representation of the rate of outcomes in both groups, it does not quantify the extent to which the rate of outcomes is similar or different between the two groups. In our primary analysis, we compared the rate of outcomes between the ADPKD and control groups using a Cox proportional hazards regression model censoring on end of follow up, death or emigration from the province given the follow-up period was variable and patients died or emigrated from the province during the follow-up. Competing risk is an event that hinders or alters the chance of an event of interest from occurring.[79] Not accounting for competing risk often overestimates the proportion of patients experiencing an event.[79] As a result, in an additional analysis, we treated death as a potential competing event and calculated the subhazard ratio using Fine and Gray's model.[80] The applicability of the Fine and Gray model when using inverse probability exposure weighting remains unclear; therefore, we only conducted this analysis to explore the potential impact of death as a competing event and confirm the reproducibility of the results in our primary analysis.[81] Based on the results of our primary outcomes, accounting for death as a competing event did not alter the hazard ratio estimates. Therefore, we did not account for death as a potential competing event for all subsequent exploratory analyses.

We estimated the 95% confidence intervals using bootstrapping-based methods rather than traditional methods because traditional methods do not account for the within subject correlation introduced by weighting; this results in biased variance estimate and 95% confidence intervals with inaccurate coverage rates.[82] Past studies show that bootstrapping-based approach was the best method to estimate 95% confidence intervals with approximately accurate coverage rate.[82] We estimated the absolute between-group difference in the rate of our outcomes by fitting a Poisson model using the PROC NLMIXED procedure in SAS.

In exploratory subgroup analyses, we tested whether the associations between ADPKD and our outcomes were modified by baseline age groups (18 to 40 years, 41 to 60 years, and >60 years), sex, and prior stone history using 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 2 indicating this was of minimal concern.

Patients with ADPKD generally receive more abdominal imaging than patients without ADPKD, which could explain why upper urinary tract 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 compared to controls using Cox proportional hazards regression.

We performed all analyses using SAS 9.4 (SAS Institute, Inc., Cary, North Carolina). We present the 95% confidence intervals for all estimates, which corresponds to a level of significance of 0.05. Prior to using each Cox proportional hazards model, we ensured the proportional hazards assumption was met. First, we used log-minus-log curve (a graphical method) to visually assess whether the proportional hazard assumption was met. If the log-minus-log curves were not parallel or did not overlap, then the proportional hazard assumption was considered violated. This method is subjective so we also used a second approach where proportional hazards is assessed using a time-

dependent covariate test (statistical test), which includes a time-independent variable and time interaction term. If the p-value for the time-dependent variable and time interaction term was <0.05, then there was no statistical evidence against proportional hazards assumption. When proportional hazard assumption was violated and the hazards of both groups did not cross during following-up, we reported the results as an average hazard ratio over a 15-year period.[83]

6.3 RESULTS

6.3.1 Cohort selection & baseline characteristics

From 4,361 potentially eligible patients with ADPKD, the final cohort included 2,094 patients with ADPKD identified in Ontario (Figure 6-2). 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 1,902 patients in the weighted cohort after truncating weights (Figure 6-3). Table 6-2 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.

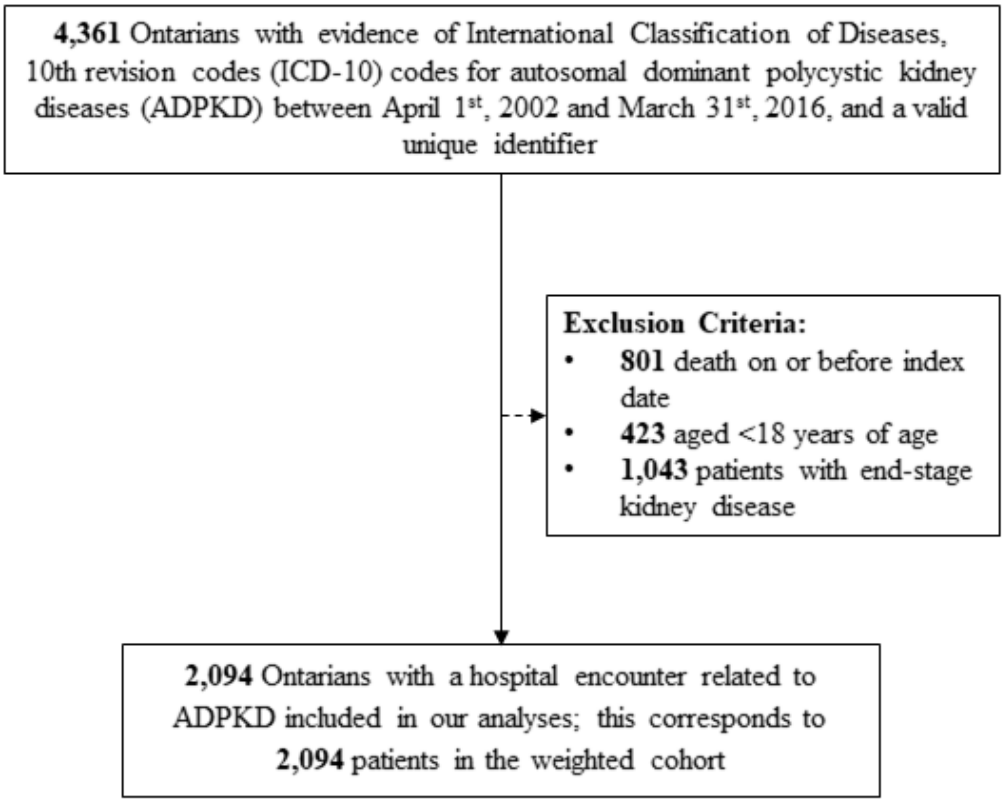


Figure 6-2. Cohort selection of patients with autosomal dominant polycystic kidney disease (ADPKD) using International Classification of Diseases codes for ADPKD.

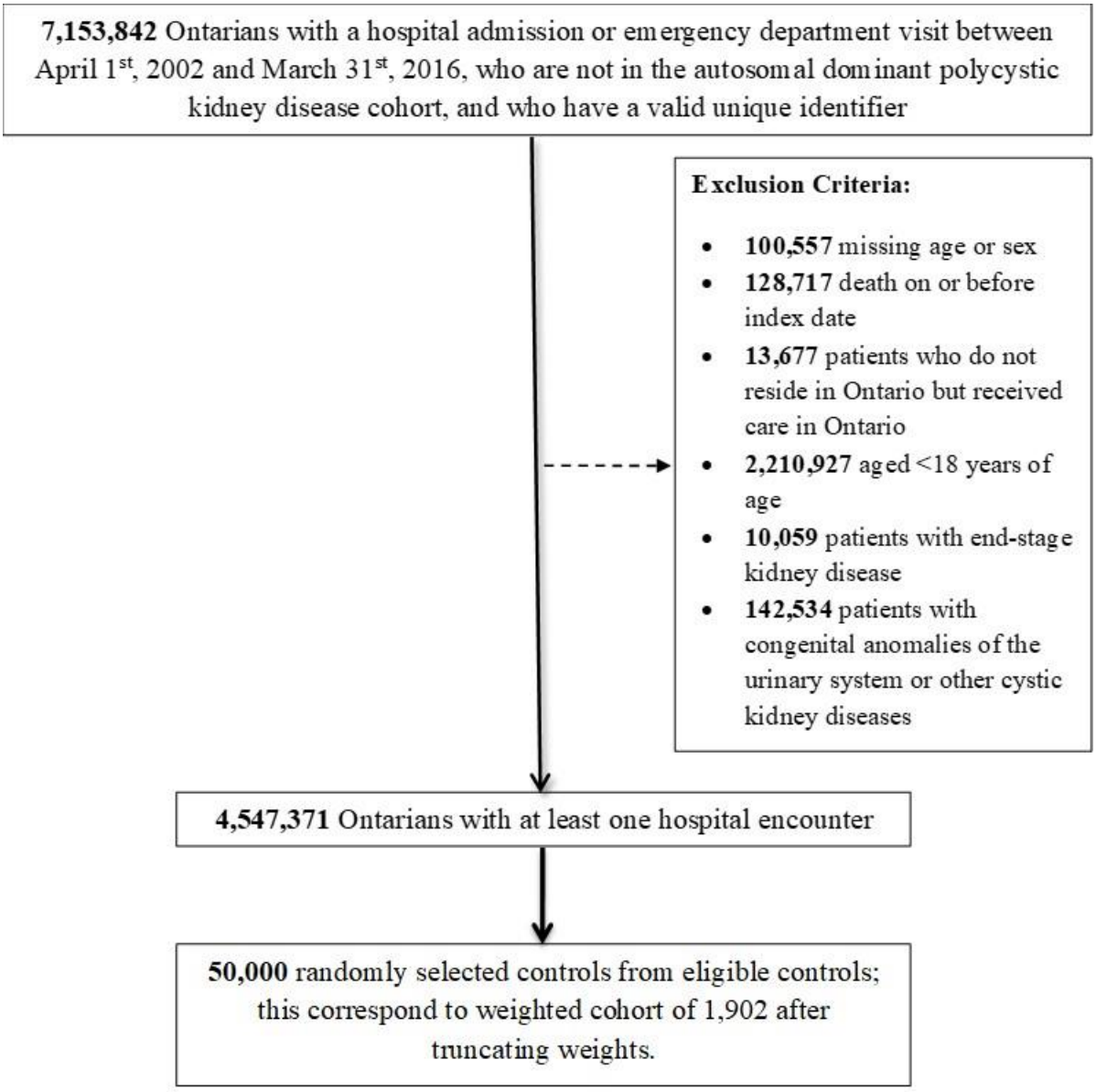


Figure 6-3. Cohort selection of patients without autosomal dominant polycystic kidney disease using International Classification of Diseases, 10th revision codes.

Table 6-2. Characteristics of the autosomal dominant polycystic kidney disease (ADPKD) cohort and controls at the time of cohort entry before and after inverse probability exposure weighting based on propensity scores and truncating extreme weights.

	Before Weighting			After Weighting		
	ADPKD (n=2,094)	**Non-ADPKD (n=50,000)**	**Standardized Difference, %**	**ADPKD (n=2,094)**	**Non-ADPKD (n=2,101)**	**Standardized Difference, %**
Mean (SD) age (years)	57 (18)	52 (20)	25	57 (18)	57 (4)	1
Women, n (%)	1,069 (49)	18,810 (38)	23	1,069 (49)	984 (52)	1
Income fifth[b]						
Quintile 1 (lowest)	436 (21)	10,223 (20)	1	436 (21)	399 (21)	0
Quintile 2	420 (20)	10,234 (21)	1	420 (20)	381 (20)	0
Quintile 3	425 (20)	10,287 (21)	1	425 (20)	386 (20)	0
Quintile 4	368 (18)	9,985 (20)	6	368 (18)	336 (18)	0
Quintile 5 (highest)	445 (21)	9,271 (19)	7	445 (21)	400 (21)	0
Rural Town, n(%)[c]	238 (11)	6,870 (14)	7	238 (11)	222 (12)	1
LHIN, n (%)						
Erie St. Clair	112 (5)	2,692 (5)	0	112 (5)	104 (5)	2
South West	141 (7)	3,903 (8)	4	141 (7)	131 (6)	2
Waterloo Wellington	94 (4)	2,566 (5)	3	94 (4)	88 (4)	1
Hamilton Niagara Haldimand Brant	259 (12)	5,641 (11)	3	259 (12)	232 (11)	4
Central West	98 (5)	2,933 (6)	5	98 (5)	90 (4)	2
Mississauga Halton	134 (6)	3,905 (8)	5	134 (6)	123 (6)	2
Toronto Central	209 (10)	4,317 (9)	5	209 (10)	188 (9)	4
Central	256 (12)	5,890 (12)	1	256 (12)	229 (11)	4
Central East	271 (13)	5,601 (11)	5	271 (13)	243 (12)	4
South East	74 (4)	2,128 (4)	4	74 (4)	70 (3)	1
Champlain	247 (12)	4,619 (9)	8	247 (12)	222 (11)	4
North Simcoe	76 (4)	1,893 (4)	1	76 (4)	66 (3)	3

North East	90 (4)	2,740 (6)	6	90 (4)	84 (4)	2
North West	33 (2)	1,172 (2)	5	33 (2)	32 (2)	0
No of visits to primary care physician in previous year (%)						
0	95 (5)	2,053 (4)	2	95 (5)	84 (4)	1
1 to 2	258 (12)	6,567 (13)	2	258 (12)	229 (12)	1
3 to 4	246 (12)	7,919 (16)	12	246 (12)	228 (12)	1
5 to 6	265 (13)	7,692 (15)	8	265 (13)	243 (13)	0
7 to 8	251 (12)	6,442 (13)	3	251 (12)	231 (12)	0
9 to 10	180 (9)	4,927 (10)	4	180 (9)	169 (9)	1
> 10	799 (38)	14,440 (28)	20	799 (38)	719 (38)	1
No of visits to emergency department in the previous year (%)						
0	350 (17)	18,275 (37)	46	350 (17)	340 (18)	3
1 to 3	1,427 (68)	28,780 (58)	22	1,427 (68)	1,308 (69)	1
4 to 6	252 (12)	2,381 (5)	26	252 (12)	201 (11)	5
7 to 9	44 (2)	350 (1)	12	44 (2)	35 (2)	2
10 to 12	13 (1)	135 (0)	4	13 (1)	12 (1)	0
> 12	8 (0)	79 (0)	4	8 (0)	6 (0)	1
No of visits to urologist visit in the previous year (%)						
0	1,495 (71)	45,296 (91)	5	1,495 (71)	1,406 (74)	6
1 to 2	344 (16)	2,503 (5)	38	344 (16)	282 (15)	4
3 to 4	122 (6)	1,107 (2)	18	122 (6)	105 (6)	1
5 to 6	71 (3)	615 (1)	15	71 (3)	59 (3)	2
7 to 8	34 (2)	278 (1)	1	34 (2)	29 (2)	1
9 to 10	13 (1)	104 (0)	6	13 (1)	10 (1)	1
> 11	15 (1)	97 (0)	7	15 (1)	11 (1)	2
Abdominal imaging in the past five years, n (%)	1,885 (90)	20,810 (42)	119	1,885 (90)	1,693 (89)	3
Comorbidities in the past five years						

Acute kidney injury	17 (1)	69 (0)	10	17 (1)	10 (1)	4
Urinary tract obstruction, n (%)	111 (5)	516 (1)	25	111 (5)	85 (4)	4
Urinary Tract Infection, n (%)	594 (28)	3,877 (8)	56	594 (28)	465 (24)	9
Primary Hyperparathyroidism, n (%)	43 (2)	249 (0)	14	43 (2)	27 (1)	5
Gout, n (%)	290 (14)	1,428 (3)	40	290 (14)	208 (11)	9
Obesity, n (%)	155 (7)	3,653 (7)	0	155 (7)	144 (8)	1
Diabetes Mellitus, n (%)	509 (24)	8,036 (18)	15	509 (24)	460 (24)	0
Hypertension, n (%)	1,662 (79)	19,459 (39)	90	1,662 (79)	1,471 (77)	5
Osteoporosis, n (%)	209 (10)	3,274 (6)	13	209 (10)	178 (9)	2
Prior hospital encounter or intervention for stone, n (%)	281 (13)	1,324 (3)	41	281 (13)	209 (11)	7
Prior hospital encounter for stone, n (%)	278 (13)	1,315 (3)	40	278 (13)	208 (11)	7
Prior intervention for stone, n (%)	58 (3)	403 (1)	15	58 (2)	49 (3)	1
Inflammatory Bowel Disease, n (%)	72 (3)	899 (2)	10	72 (3)	62 (3)	1

Abbreviations: autosomal dominant polycystic kidney disease, ADPKD; standard deviation, SD

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.

[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.

6.3.2 Follow-up period for stone event

The median length of follow-up for an upper urinary tract 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 436 patients with ADPKD and 441 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 65 years (51 to 77). Of the 3,996 total individuals, 2,598 (65%) were alive and event-free at the end of study follow-up (March 31st, 2017), 76 (2%) were censored at time of emigration from the province, 1,170 (29%) died and 152 (4%) had the event of interest during follow up. The total person-years of follow-up was 24,223 (12,254 for patients with ADPKD, 11,969 for non-ADPKD controls). Less than 2% of the ADPKD and control groups experienced two or more stone events or stone intervention events in follow-up (and we only considered the time to the first event).

6.3.3 Follow-up period for stone intervention event

The median length of follow-up was 5.5 years (5.2 years in patients with autosomal dominant polycystic kidney disease [ADPKD], 5.8 years in controls, maximum 15.5 years). A total of 450 patients with ADPKD and 444 controls in the weighted cohort were followed for a period of 10 years or more. The median (interquartile range [IQR]) age at the time of last follow-up for the entire cohort was 65 (50-77). Of the 3,996 individuals (2,094 patients with ADPKD, 1,902 controls), 2,635 (66%) were alive at the end of study follow-up (31 March 2017) and had not experienced a stone intervention event, 76 (2%) were censored at a time of emigration from the province, 1,186 (30%) died and 99 (3%) had the event of interest during follow-up. The total person years of follow-up was 24,483 (12,472 patients with, 12,011 control).

6.3.4 Outcomes

Figure 6-4 and Table 6-3 present the main outcomes. The proportional hazard assumption test was assessed graphically using log-minus-log curves *(*Figure 6-5 and Figure 6-6) and statistically using the time-dependent covariate test. If the log-minus-log curves were not

parallel or overlap each other, and if the time-dependent covariate p-value was <0.05, then there is statistical evidence against the proportional hazard assumption. There was no statistical evidence against proportional hazards assumption for the outcome of hospital encounter with upper urinary tract stones both for the main analysis and when death was treated as a competing event (ADPKD status and time interaction term, P=0.2 and P=0.2, respectively). The same was also true for the outcome of stone intervention (ADPKD status and time interaction term, P=0.7 and P=0.8, respectively).

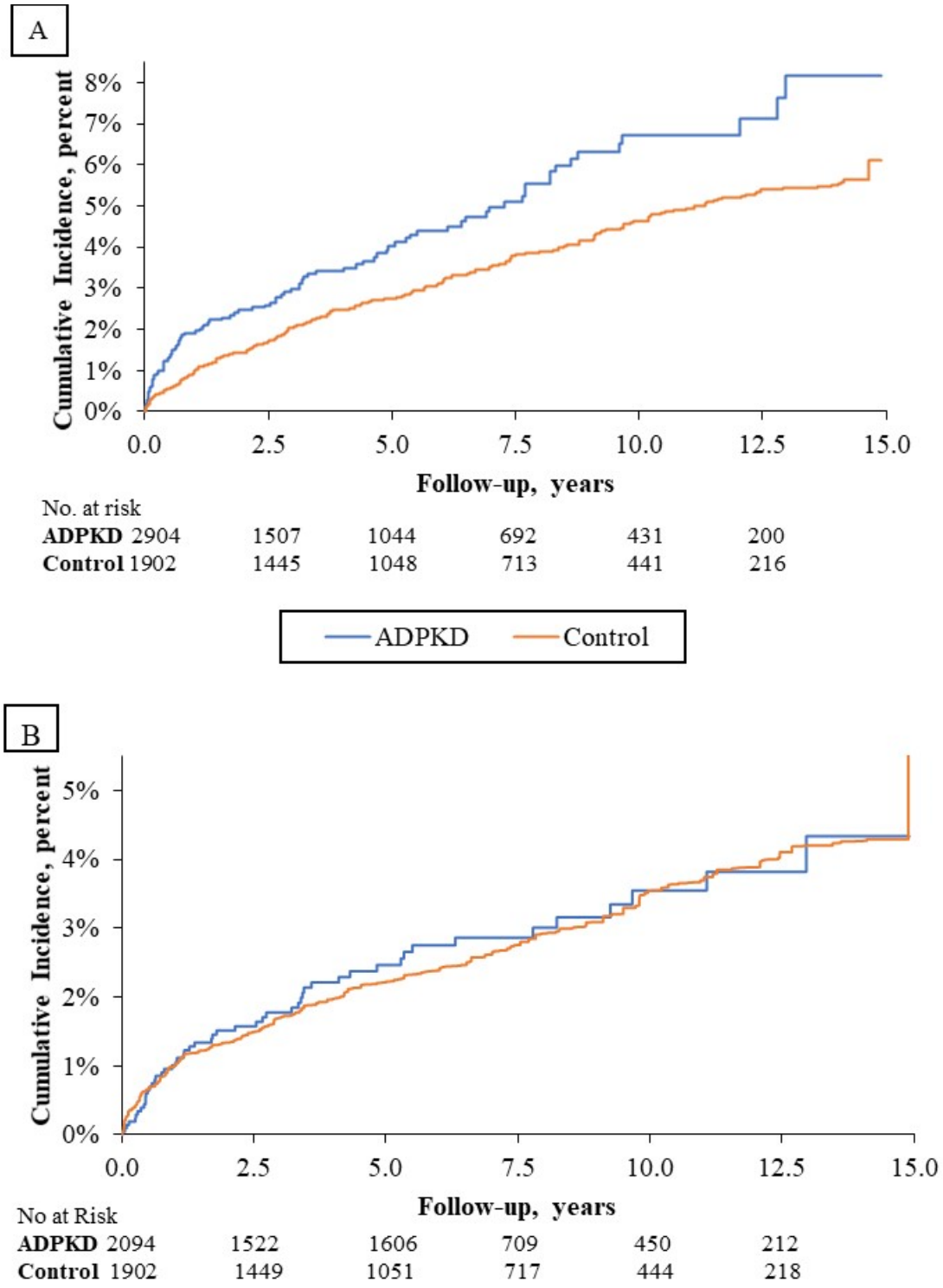


Figure 6-4. Cumulative incidence function of (A) time to first hospital encounter with upper urinary tract stone; and (B) time to first stone intervention.

Table 6-3. Comparison of the hazards of (i) time to first hospital encounter with stone, and (ii) time to first stone intervention between patients with autosomal dominant polycystic kidney disease cohort (ADPKD) and patients without ADPKD with similar baseline health.

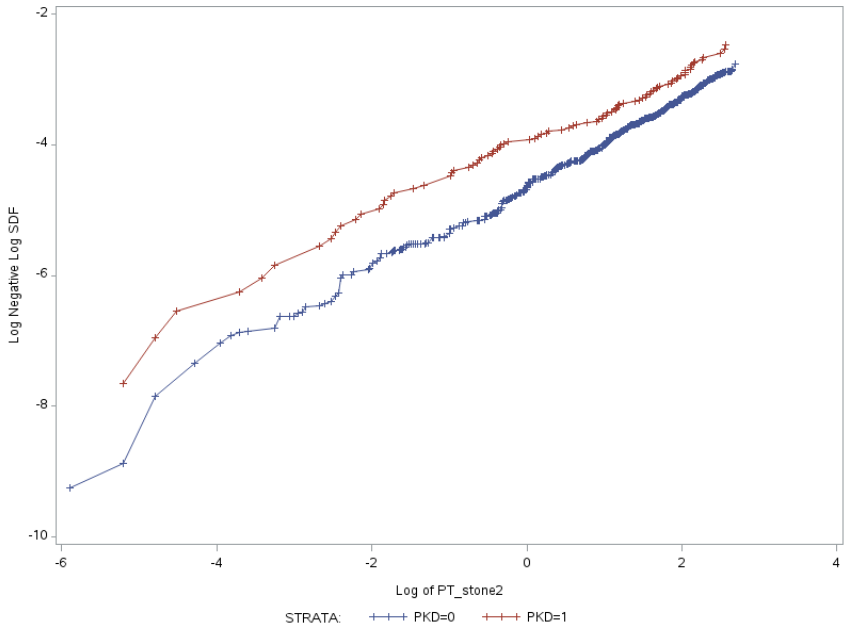
	Hospital encounter for stone		**Stone intervention**	
	ADPKD	**Non-ADPKD**	**ADPKD**	**Non-ADPKD**
Median (IQR) follow-up, years	5.0 (2.2 to 9.1)	5.8 (2.7 to 9.7)	5.2 (2.3 to 9.2)	5.8 (2.7 to 9.7)
Total follow-up, person-years	12,254	11,969	12,472	12,011
No. who died, (%)	676 (32)	494 (26)	688 (33)	498 (26)
No. who emigrated, (%)	37 (2)	39 (2)	37 (2)	39 (2)
No. of unique patients with event, (%)	92 (4)	60 (3)	52 (2)	47 (2)
Type of Intervention				
Shockwave lithotripsy or percutaneous nephrolithotomy or combination of two 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	7.5	5.0	4.2	3.9
Hazards ratio (95% CI)*	1.5 (1.2 to 1.9)	1.0 (Reference)	1.0 (0.8 to 1.4)	1.0 (Reference)
Subhazards ratio (95% CI)	1.4 (1.1 to 1.8)	1.0 (Reference)	1.0 (0.7 to 1.4)	1.0 (Reference)
Risk difference per 1000 person-years (95% CI)	2.5 (0.5 to 4.5)	0.0 (Reference)	0.25 (-1.3 to 1.8)	0.0 (Reference)

Abbreviations: autosomal dominant polycystic kidney disease, ADPKD; confidence interval, CI; interquartile range, IQR; not applicable, N/A

[a] Hazards ratio was obtained by censoring for death, end of follow-up, and emigration from Ontario. The estimates were weighted using inverse probability exposure weighting based on propensity scores. There was no statistical evidence against proportional hazards assumption, for both the hospital encounter with stone outcome (ADPKD status and time interaction term, P=0.2) and stone intervention outcome (ADPKD status and time interaction term, P=0.7).

[b] Hazards ratio was obtained by censoring for emigration and end of follow-up from Ontario, and accounting for death as a competing event. The estimates were weighted using inverse probability exposure weighting based on propensity scores. There was no statistical evidence against proportional hazards assumption for both the hospital encounter with stone outcome (ADPKD status and time interaction term, P=0.2) and stone intervention outcome (ADPKD status and time interaction term, P=0.8).

a) primary analysis



b) additional analysis

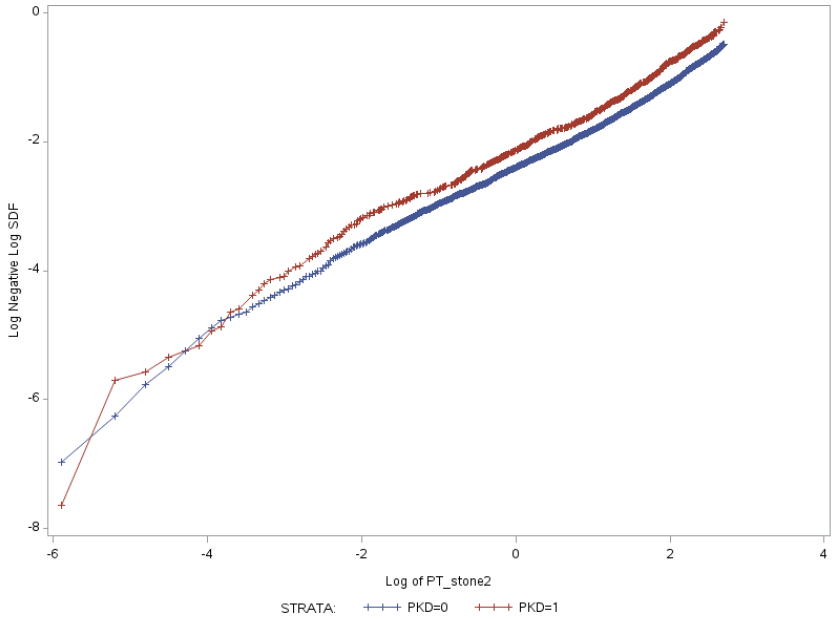
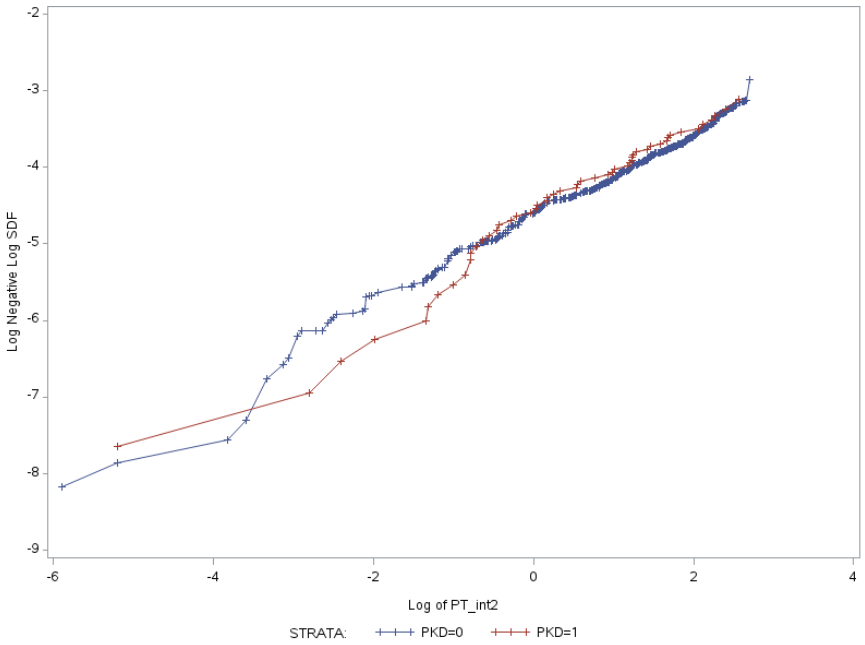


Figure 6-5. Log-minus-log curve of the hospital encounter with upper urinary tract stone outcome.

a) primary analysis



b) secondary analysis

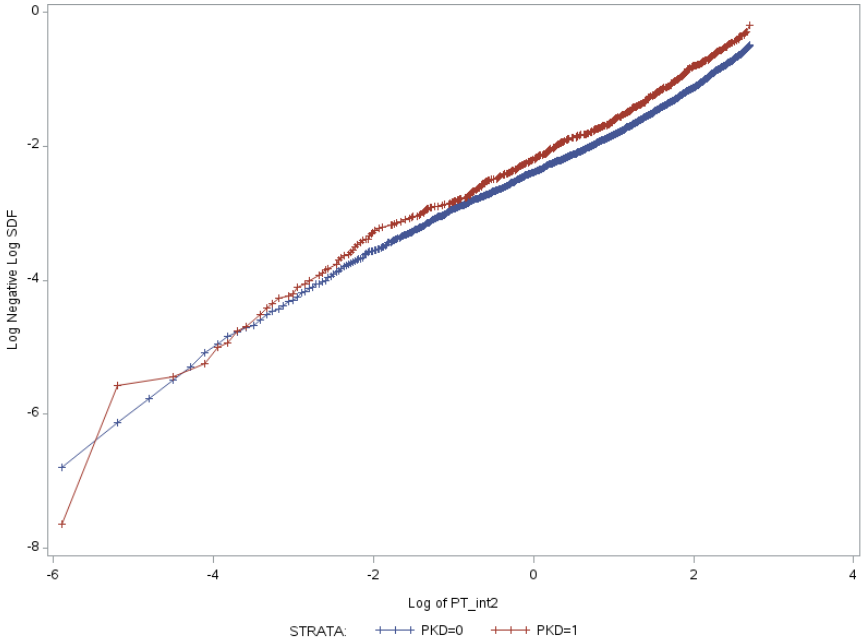


Figure 6-6. Log-minus-log curve of the hospital encounter with stone intervention outcome

There was no statistical evidence against proportional hazards assumption for all exploratory subgroup analyses, and all risk factors except sex for the control group for both the healthcare encounter with stones outcome (ADPKD status and time interaction term, P=0.02) and stone intervention outcome (ADPKD status and time interaction term, P=0.0045). The reported hazard ratio in instances where the proportional hazards assumption is violated is the average hazard ratio over a 15-year period.

The rate of a hospital encounter with upper urinary tract stones was significantly higher in the ADPKD group than the control group (92 of 2,094 patients with ADPKD [4.4%] vs 60 of 1,902 patients without ADPKD [3.2%]; 7.5 vs. 5.0 events per 1000 person-years; hazard ratio [HR] 1.5, 95% confidence interval [CI] 1.2 to 1.9). The results were similar when accounting for death as a competing event (average subHR over 15 years 1.4, 95% CI 1.1 to 1.8).

There was no statistically significant difference, on average, in the rate of stone intervention in patients with ADPKD compared to controls (52 of 2,094 [2.4%] vs 47 of 1,902 [2.5%]; 4.2 vs. 3.9 events per 1000 person-years; average HR over 15 years 1.0; 95% CI 0.8 to 1.4). The results were similar when treating death as a competing event (average subHR over 15 years 1.0, 95% CI 0.7 to 1.4). Ureteroscopy was the most common type of intervention in both groups.

Sex, age, and stone event in the prior five years did not significantly modify the effects of ADPKD on the rate of stones, or stone intervention (Table 6-4).

The rate of abdominal imaging was significantly higher in patients with ADPKD compared to controls (1,826 of 2,094 [87.2%] vs 1,310 of 1,902 [68.9%]; 169.5 vs 121.7 events per 1000 person-years; HR 1.3, 95% CI 1.2 to 1.3).

Table 6-4 Hazard ratio of hospital encounter with upper urinary tract stone and stone intervention among patients with autosomal dominant polycystic kidney disease 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 (95% CI)
	ADPKD	Non-ADPKD	ADPKD	Non-ADPKD	
Hospital encounter with upper urinary tract stone					
Overall	92/2,094	60/1,902	7.5	5	1.5 (1.2 to 1.9)
Sex					
Male	58/1,025	36/918	10.7	6.6	1.6 (0.8 to 1.7)
Female	34/1,069	25/984	5	3.8	1.3 (0.5 to 1.4)
Age, years					
18 to 40	38/440	16/422	11.6	5.1	2.3 (1.5 to 3.3)
41 to 60	35/748	23/571	6.8	5.8	1.2 (0.8 to 1.7)
> 60	19/906	21/909	4.9	4.3	1.1 (0.6 to 1.8)
Stone intervention or hospital encounter with stone in the prior five years					
Yes	53/281	32/209	36.5	24.8	1.4 (1.0 to 1.9)
No	39/1,813	28/1693	3.6	2.6	1.4 (1.0 to 2.0)
Stone intervention					
Overall	52/2,094	47/1,902	4.2	3.9	1.0 (0.8 to 1.4)
Sex					
Male	33/1,025	27/918	5.9	5.0	1.2 (0.8 to 1.7)
Female	19/1,069	20/984	2.7	3.0	0.9 (0.5 to 1.4)
Age, years					
18 to 40	18/440	8/422	5.3	2.5	2.2 (1.2 to 3.8)
41 to 60	21/748	18/571	4.0	4.6	0.9 (0.5 to 1.4)
> 60	13/906	21/909	3.4	4.3	0.7 (0.4 to 1.4)
Stone intervention or hospital encounter with stone in the prior five years					
Yes	34/281	32/209	21.6	24.5	0.8 (0.6 to 1.2)
No	18/1,813	15/1,693	1.7	1.4	1.2 (0.7 to 1.9)

[a] Hazards ratio was obtained by censoring for death, 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.

6.3.5 Multi-variable risk factor analysis

The adjusted hazard ratios for each of the studied risk factors are summarized in Table 6-5. 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. Male sex was associated with a higher risk of hospital encounter with upper urinary tract stone and stone intervention in both the ADPKD and non-ADPKD group.

Table 6-5. Risk factors for hospital encounter with upper urinary tract stones and stone interventions in patients with autosomal dominant polycystic kidney disease (ADPKD) and patients without ADPKD with similar indicators for baseline health when each group was analyzed separately.

Risk Factors	Hospital encounter with stone		Stone Intervention	
	ADPKD	Non-ADPKD	ADPKD	Non-ADPKD
Age				
41 to 60 (vs. 18 to 40)	0.5 (0.3 to 0.7)	1.0 (0.7 to 1.4)	0.6 (0.3 to 1.3)	1.7 (1.1 to 2.5)
60+ (vs. 18 to 40)	0.3 (0.2 to 0.5)	0.7 (0.5 to 1.0)	0.4 (0.2 to 1.0)	1.5 (1.0 to 2.2)
Male *(vs. female)*	2.5 (1.6 to 4.0)	1.7 (1.3 to 2.2)	2.4 (1.3 to 4.4)	1.5 (1.1 to 2.0)
Income quintiles				
Quintile 2 (vs. quintile 1)	0.9 (0.5 to 1.8)	1.4 (0.9 to 2.2)	1.2 (0.5 to 2.9)	1.2 (0.8 to 2.0)
Quintile 3 (vs. quintile 1)	0.9 (0.5 to 1.7)	1.4 (0.9 to 2.1)	0.8 (0.3 to 2.2)	1.4 (0.9 to 2.4)
Quintile 4 (vs. quintile 1)	0.9 (0.4 to 1.8)	1.4 (0.9 to 2.2)	0.8 (0.3 to 2.2)	1.6 (1.0 to 2.7)
Quintile 5 (vs. quintile 1)	1.0 (0.6 to 1.9)	1.2 (0.8 to 1.9)	1.1 (0.4 to 2.7)	1.2 (0.7 to 2.1)
Date of Entry into Cohort				
April 1st, 2007 to March 31st, 2012 (vs. before April 1st, 2007)	1.1 (0.7 to 1.9)	1.0 (0.8 to 1.3)	1.5 (0.7 to 3.1)	0.9 (0.6 to 1.3)
After March 31st, 2012 (vs. before April 1st, 2007)	0.8 (0.4 to 1.5)	1.5 (1.0 to 2.4)	1.1 (0.4 to 3.0)	1.2 (0.8 to 1.9)

Abbreviation: autosomal dominant polycystic kidney disease, ADPKD

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.

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

6.4 DISCUSSION

It is uncertain whether the incidence of hospital encounters with upper urinary tract 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 upper urinary tract stones was significantly higher in patients with ADPKD compared to similar patients without ADPKD, although the rate of stone interventions was not significantly differ 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 favours urinary crystals to form, cause stones to stagnate, and promotes stone growth leading to more upper urinary tract stones. Given their ongoing renal concerns, patients with ADPKD may also be more likely to present to hospital when they develop a stone compared to 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 favour 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.[84,85]

Studies examining the burden of upper urinary tract stones in patients with ADPKD relative to a non-ADPKD population are scarce. To date, only six cross-sectional studies report the prevalence of upper urinary tract 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 upper urinary tract stones and stone

intervention between patients with ADPKD and controls with similar baseline health. It is also the largest study 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 ICD-10 codes that we used to identify patients with ADPKD.[66] 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.[73]

Our study is not without limitations. A small number of events meant some estimates were imprecise. We did not have information on upper urinary tract 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 healthcare 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. 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. 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.

6.5 CONCLUSION

Overall, our results suggest that ADPKD increases the rate of hospital encounters with upper urinary tract 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 upper urinary tract 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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Chapter 7 - Ureteroscopic complications in patients with autosomal dominant polycystic kidney disease[e]

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7.1 INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic kidney disorder with no cure.[1,2] It is characterized by focal cyst development which leads to progressive enlargement of both kidneys, and eventual kidney function loss.[3–5] Much of the current research on patients with ADPKD is focused on delaying time to the onset of end-stage kidney disease (ESKD). However, ADPKD is a systemic disorder with other morbidities that warrant attention to prevent loss of health-related quality of life.[6] One such morbidity is upper urinary tract stones.[7] Stones in patients with ADPKD are a significant determinant of pain, and may be associated with a higher risk of ESKD.[7,8] Currently, there is limited evidence on how best to manage upper urinary tract stones in patients with ADPKD.

In the general population, stones less than four millimeters in size usually do not require a surgical intervention, and will often pass within four weeks of symptom onsets.[9] Pain may be managed with narcotics or nonsteroidal anti-inflammatory drugs (NSAIDs).[9] However, urgent intervention is often required in the presence of infection/urosepsis, intractable pain, vomiting, impending acute renal failure, and/or significant obstruction.[10] Currently, shockwave lithotripsy (SWL), ureteroscopy, and percutaneous nephrolithotomy (PCNL) are potential treatment options; however, ureteroscopy is the most common intervention used in both patients with and without ADPKD.[11]

A comprehensive systematic review conducted by our team confirms there is limited information on the risk of ureteroscopic complications in patients with ADPKD.[12] All studies were either clinical case series or reports, and most studies reported data from a single center. Overall, these limitations lead to uncertainty in how to counsel patients with ADPKD on expected post-operative ureteroscopic complications. In this study, we described the 30-day cumulative incidence of selected ureteroscopic complications, all-cause hospital presentation, all-cause hospital admission, and all-cause emergency department visits following ureteroscopy in patients with compared to patients without ADPKD.

7.2 PATIENTS AND METHODS

7.2.1 Design and setting

We conducted a retrospective cohort study using linked healthcare administrative databases held at ICES (a not-for-profit research institute). Healthcare 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 all people 65 years of age and older. These healthcare encounters are recorded in administrative databases, which are linked using unique, encoded identifiers and held at ICES. The use of ICES data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. No informed consent from patients was also required. We reported this study following guidelines set up for studies conducted using observational routinely-collected data.

7.2.2 Data sources

We created the study cohorts, described baseline characteristics, defined the exposure, and ascertained outcomes using administrative codes detailed in Table 7-1 and seven databases: CIHI-DAD, SDS, NACRS, OHIP, RPDB, CORR, and ODB. A detailed description of each of the Ontario healthcare administrative databases is described in Table A-1. All variables were complete, except for average neighbourhood income (missing in 0.18%) and urban or rural residency status (missing in 0.05%); we assigned the middle average neighbourhood income quintile and urban residence for these missing values, respectively.

Table 7-1. Database and coding definitions for restriction criteria, baseline characteristics and outcome measurements.

Variable	Database & Administrative Codes
Study Population	
Ureteroscopy	**CIHI-DAD & NACRS CCI**: 1PE57BAAM, 1PE57BAGX, 1PE59BAAG, 1PE59BAAS, 1PE59BAAT, 1PE59BAAZ, 1PG57BAAM, 1PG57BAGX, 1PG59BAAG, 1PG59BAAS, 1PG59BAAT, 1PG59BAAZ, 1PG59BAGX, 1PE59BAAS, 1PE59BAAT, 1PE59BAAZ

	OHIP Fee Codes: Z628 AND (E760 or E761 or Z627)
Exposure	
Autosomal dominant polycystic kidney disease	**CIHI-DAD & NACRS ICD-10 codes:** Q612, Q613
Exclusion Criteria	
Shockwave lithotripsy performed in the previous 90 days	**CIHI-DAD & NACRS CCI**: 1PE59KQAP, 1PE59KQAQ, 1PE59KQAR, 1PG59KQAP, 1PG59KQAQ, 1PG59KQAR **OHIP Fee Codes**: Z630
Percutaneous nephrolithotomy performed in the previous 90 days	**CIHI-DAD & NACRS CCI**: 1PE57DTAG, 1PE57DTAM, 1PE57DTAS, 1PE57DTAZ, 1PE57DTBD, 1PE57DTGX **OHIP Fee Codes:** Z624 AND Z627
Open stone surgery performed in the previous 90 days	**CIHI-DAD & NACRS CCI:** 1PE57LAAM, 1PE57LAGX, 1PE57QWGX, 1PE59LAAG, 1PG57LAAM, 1PG57LAGX, 1PG59LAAG, 1PG59LAGX
Kidney transplant	**CIHI-DAD & NACRS CCP:** 6759 **CIHI-DAD & NACRS CCI:** 1PC85 **OHIP fee code:** S435, S434 **CORR – RECIPIENT_TREATMENT dataset** [Treatment_Code]: 171 [Treatment_Date] [Transplanted_Organ_Type_Code] [1-3]: 10, 11, 12, 18, 19
ADPKD (only for control group	**CIHI-DAD & NACRS ICD-9 codes:** 7531 **CIHI-DAD & NACRS ICD-10 codes:** Q611, Q612, Q613 **OHIP Dx codes:** 753, 593
Outcomes	
Acute kidney injury	**CIHI-DAD & NACRS ICD-10 codes:** N17
Urinary tract infection	**CIHI-DAD & NACRS ICD-10 codes:** N10, 'N11, 'N12, N136, 'N151, N159, N160, N300, N308, N309, N340, N390, N410, N411, N412, N413, N431, N45, T835
Sepsis	**CIHI-DAD & NACRS ICD-10 codes:** A021, A392, A393, A394, A400, A401, A402, A408, A409, A410, A411, A412, A403, A414, A4159, A413, A4150, A4151, A4152, A4158, A4180, A4188, A427, A419
Baseline Characteristics	
Age	**RPDB**
Sex	**RPDB**
Rural	**RPDB**
Household income quintiles	**RPDB**
Local Health Integration Network (LHIN)	**RPDB**

Emergency department visits in the previous one year	**NACRS**
Primary care physician visits in the previous one year	**IPDB:** Mainspecialty= GP/FP
Hospital admission in the previous one year	**CIHI-DAD**
ICU admission in the previous one year	**CIHI-DAD CCP codes:** 1361, 1362 **CIHI-DAD CCI codes:** 1GZ31CAND, 1GZ31CRND, 1GZ31GPND **OHIP Fee codes:** G557, G558, G559, G400, G401, G402, G405, G406, G407
Estimated glomerular filtration rate	**OLIS**
Acute interstitial nephritis	**CIHI-DAD & NACRS ICD-9 codes:** 5837, 5838, 5839 **CIHI-DAD & NACRS ICD-10 codes:** N10, N12
Acute kidney injury	**CIHI-DAD & NACRS ICD-9 codes:** 584 **CIHI-DAD & NACRS ICD-10 codes:** N17
Anemia	**CIHI-DAD & NACRS ICD-9 codes:** 280, 281, 282, 283, 284, 285 **CIHI-DAD & NACRS ICD-10 codes:** D50, D51, D52, D53, D55, D58, D59, D61, D62, D63, D64 **OHIP dx codes:** 280, 281, 282, 283, 284, 285
Atrial Fibrillation	**CIHI-DAD & NACRS ICD-9:** 4273 **CIHI-DAD & NACRS ICD-10:** I48
Chronic liver disease	**CIHI-DAD & NACRS ICD-9 codes:** 4561, 4562, 070, 5722, 5723, 5724, 5728, 573, 7824, V026, 2750, 2751, 7891, 7895, 571 **CIHI-DAD & NACRS ICD-10 codes:** B16, B17, B18, B19, I85, R17, R18, R160, R162, B942, Z225, E831, E830, K70, K713, K714, K715, K717, K721, K729, K73, K74, K753, K754, K758, K759, K76, K77 **OHIP dx codes:** 571, 573, 070 **OHIP fee codes:** Z551, Z554
Chronic lung disease	**CIHI-DAD & NACRS ICD-9 codes:** 491, 492, 493, 494, 495, 496, 500, 501, 502, 503, 504, 505, 5064, 5069, 5081, 515, 516, 517, 5185, 5188, 5198, 5199, 4168, 4169 **CIHI-DAD & NACRS ICD-10 codes:** I272, I278, I279, J40, J41, J42, J43,J44, J45, J47, J60, J61, J62, J63, J64, J65, J66, J67, J68, J701, J703, J704, J708, J709, J82, J84, J92, J941, J949, J953, J961, J969, J984, J988, J989, J99 **OHIP dx codes:** 491, 492, 493, 494, 496, 501, 502, 515, 518, 519 **OHIP fee codes:** J889, J689
Coronary artery disease	**CIHI-DAD & NACRS ICD-9 codes:** 412, 410, 413, 414, 4292, 4296, 4297, 411

	CIHI-DAD & NACRS ICD-10 codes: I20, I21, I22, I23, I24, I25, Z955, Z958, Z959, R931, T822 **CIHI-DAD & NACRS CCI codes:** 1IJ26, 1IJ27, 1IJ54, 1IJ57, 1IJ50, 1IJ76 **CIHI-DAD & NACRS CCP codes:** 4801, 4802, 4803, 4804, 4805, 481, 482, 483 **OHIP fee codes:** R741, R742, R743, G298, E646, E651, E652, E654, E655, G262, Z434, Z448 **OHIP dx codes:** 410, 412, 413
Cystoscopy	**OHIP fee codes:** Z606, Z607, Z628, Z632, Z633, Z634
Depression	**CIHI-DAD & NACRS ICD-9 codes:** 2962, 2963, 3000, 3002, 3003, 3004, 3091, 311 **CIHI-DAD & NACRS ICD-10 codes:** F063, F064, F320, F321, F322, F323, F328, F329, F330, F331, F332, F333, F334, F338, F339, F341, F400, F401, F402, F408, F409, F410, F411, F412, F413, F418, F419, F420, F421, F422, F428, F429, F430, F431 **OHIP dx codes:** 311 **OMHRS DSM-IV codes:** 29189, 29284, 29289, 29383, 29384, 29620, 29621, 29622, 29623, 29624, 29625, 29626, 29630, 29631, 29632, 29633, 29634, 29635, 29636, 30000, 30001, 30002, 30021, 30022, 30023, 30029, 30030, 30040, 30113
Diabetes Mellitus	**CIHI-DAD & NACRS ICD-9 codes**: 250 **CIHI-DAD & NACRS ICD-10 codes**: E10, E11, E13, E14 **OHIP Dx codes**: 250 **OHIP Fee codes**: K045, K046, K029, K030, Q040
Hemorrhage	**CIHI-DAD & NACRS ICD-9 codes:** 430, 431, 432, 5307, 5310, 5312, 5314, 5316, 5320, 5322, 5324, 5326, 5330, 5332, 5334, 5336, 5340, 5342, 5344, 5346, 5780, 5781, 5693, 5789, 7191, 7192, 4590, 5997, 5307, 5310, 5312, 5314, 5316, 5320, 5322, 5324, 5326, 5330, 5332, 5334, 5336, 5340, 5342, 5344, 5346, 5693, 53501, 53511, 53521,7847, 7863, 6238, 6262 **CIHI-DAD & NACRS ICD-10 codes:** I600, I601, I602, I603, I604, I605, I606, I607, I609, I61, I62, I850, I9820, I983, K2210, K2211, K2212, K2214, K2216, K226, K228, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K3180, K6380, K920, K921, K5520, K625, K922, M2509, M2501, M2502, M2503, M2504, M2505, M2506, M2507, M2508, M2500, M1229, M1221, M1222, M1223, M1224, M1225, M1226, M1227, M1228, M1220, R58, N020, N021, N022, N023, N024, N025, N026, N027, N028, N029, R310, R311, R318, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K625, R040, R042, R048, R049, N898, N920, N921

	CIHI-DAD & NACRS CCP codes: 1302, 1303, 1304, 1305, 1306, 1307, 1308, 1309 **CIHI-DAD & NACRS CCI codes:** 1LZ19HMU1, 1LZ19HMU2, 1LZ19HMU9, 1LZ19HHU9A, 1LZ19HHU9J, 1LZ19HHU1A, 1LZ19HHU1J, 1LZ19HHU3J, 1LZ19HHU4J, 1LZ19HHU2A, 1LZ19HHU2J, 1LZ19HHU5J
Hypertension	**CIHI-DAD & NACRS ICD-9 codes**: 401, 402, 403, 404, 405 **CIHI-DAD & NACRS ICD-10 codes**: I10, I11, I12, I13, I15 **OHIP Dx codes**: 401, 402, 403
Kidney tumor	**CIHI-DAD & NACRS ICD-9 codes:** 1890, 1891, 2230 **CIHI-DAD & NACRS ICD-10 codes:** C64, C65, D300 **OHIP Dx:** 189, 2230
Obesity	**CIHI-DAD & NACRS ICD-9 codes**: 2780 **CIHI-DAD & NACRS ICD-10 codes**: E65, E660, E661, E662, E668, E669 **OHIP Dx codes**: 278
Percutaneous tube/Ureteral stent	**OHIP Fee codes:** E773, E776, E818, Z623, J046, Z629
Prostatic hyperplasia	**CIHI-DAD & NACRS ICD-9 codes:** N40 **CIHI-DAD & NACRS ICD-10 codes:** 600 **OHIP Dx codes:** 600
Surgery	**OHIP Fee codes:** S002, S003, S004, S005, S006, S007, S010, S011, S012, S013, S014, S015, S018, S019, S020, S021, S023, S024, S025, S028, S030, S031, S032, S033, S034, S035, S036, S042, S043, S044, S045, S046, S047, S049, S050, S057, S058, S059, S061, S062, S063, S065, S066, S067, S068, S069, S103, S104, S113, S114, S115, S116, S118, S119, S208, S209, S222, S223, S225, S226, S227, S228, S229, S231, S233, S234, S236, S237, S241, S242, S243, S246, S247, S248, S249, S251, S253, S256, S257, S258, S259, S260, S265, S266, S267, S268, S269, S270, S271, S272, S273, S274, S275, S276, S278, S280, S281, S282, S283, S284, S285, S287, S291, S292, S293, S294, S295, S297, S298, S299, S300, S301, S302, S303, S304, S305, S306, S307, S308, S309, S310, S311, S312, S313, S314, S315, S316, S317, S318, S319, S320, S321, S322, S323, S325, S326, S328, S329, S330, S332, S333, S334, S335, S336, S337, S338, S339, S340, S342, S343, S344, S345, S346, S347, S348, S349, S355, S372, S400, S401, S402, S403, S404, S405, S406, S407, S408, S409, S410, S411, S412, S413, S415, S416, S417, S418, S420, S421, S422, S423, S424, S426, S427, S428, S429, S430, S431, S432, S433, S434, S435, S436, S437, S438, S440, S441, S442, S443, S444, S445, S446, S447, S448, S449, S450, S451, S452, S453, S454, S455, S456, S457, S458, S459, S460, S461, S462, S463, S465, S466, S467, S468, S470, S471, S476, S477, S478, S479, S480, S481, S482, S483, S484, S485, S487, S488, S489,

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	Z411, Z412, Z413, Z414, Z415, Z422, Z423, Z424, Z425, Z426, Z427, Z428, Z429, Z430, Z431, Z432, Z433, Z434, Z435, Z436, Z437, Z438, Z439, Z440, Z441, Z442, Z443, Z444, Z445, Z446, Z447, Z448, Z449, Z450, Z451, Z452, Z453, Z454, Z455, Z456, Z457, Z458, Z459, Z460, Z461, Z462, Z463, Z464, Z465, Z466, Z470, Z475, Z477, Z478, Z480, Z496, Z497, Z498, Z499, Z512, Z513, Z514, Z515, Z520, Z523, Z524, Z525, Z526, Z527, Z528, Z529, Z530, Z531, Z532, Z533, Z534, Z535, Z536, Z537, Z538, Z539, Z540, Z541, Z542, Z543, Z544, Z545, Z546, Z547, Z548, Z549, Z550, Z551, Z552, Z553, Z554, Z555, Z556, Z557, Z558, Z559, Z560, Z561, Z562, Z563, Z564, Z565, Z566, Z567, Z568, Z569, Z570, Z571, Z572, Z573, Z574, Z575, Z576, Z577, Z578, Z579, Z580, Z581, Z582, Z583, Z584, Z585, Z586, Z587, Z590, Z591, Z592, Z593, Z594, Z595, Z596, Z597, Z600, Z601, Z602, Z603, Z604, Z605, Z606, Z607, Z608, Z609, Z610, Z611, Z612, Z615, Z616, Z617, Z618, Z619, Z620, Z621, Z622, Z623, Z624, Z625, Z626, Z627, Z628, Z629, Z630, Z631, Z632, Z633, Z634, Z635, Z636, Z637, Z638, Z640, Z662, Z700, Z701, Z702, Z703, Z704, Z705, Z706, Z707, Z708, Z709, Z710, Z711, Z712, Z713, Z714, Z715, Z716, Z717, Z718, Z719, Z720, Z721, Z722, Z723, Z724, Z725, Z726, Z727, Z728, Z734, Z735, Z736, Z737, Z738, Z739, Z740, Z741, Z742, Z743, Z744, Z745, Z746, Z747, Z748, Z749, Z750, Z751, Z752, Z753, Z754, Z755, Z756, Z757, Z758, Z759, Z760, Z761, Z762, Z763, Z764, Z765, Z766, Z767, Z768, Z769, Z771, Z772, Z773, Z774, Z775, Z776, Z777, Z778, Z779, Z780, Z781, Z782, Z783, Z784, Z785, Z787, Z788, Z800, Z801, Z802, Z803, Z804, Z805, Z806, Z807, Z808, Z809, Z810, Z811, Z812, Z813, Z814, Z815, Z816, Z817, Z818, Z819, Z820, Z821, Z823, Z824, Z825, Z826, Z827, Z869, Z870, Z873, Z941, Z942, Z943, Z944
Urinary tract infection	**CIHI-DAD & NACRS ICD-9 codes:** 5901, 5900, 5908, 5902, 5909, 5950, 5958, 5959, 5970, 5990, 6016, 6011, 6012, 6013, 6040, '6049 **CIHI-DAD & NACRS ICD-10 codes:** N10, N11, N12, N136, N151, N159, N160, N300, N308, N309, N340, N390, N410, N411, N412, N413, N431, N45, T835
Urinary tract obstruction	**CIHI-DAD & NACRS ICD-9 codes**: 591, 5934, 5996 **CIHI-DAD & NACRS ICD-10 codes**: N130, N131, N132, N133, N138 **OHIP Dx codes**: 591
Angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker	**ODB**
Antibiotics	**ODB**
Anti-diabetics	**ODB**

Calcium channel blocker	**ODB**
Diuretic	**ODB**
Proton pump inhibitors	**ODB**

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; CCI, Canadian Classification of Health Interventions; CCP, Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures; CIHI-DAD Canadian Institute for Health Information Discharge Abstract Database; CORR, Canadian Organ Replacement Register; ICD-9, International Classifications of Diseases, 9th revision codes; ICD-10, International Classification of Diseases, 10th revision codes; IPDB, ICES Physician Database; NACRS, National Ambulatory Care Reporting System; OHIP Dx, Ontario Health Insurance Plan diagnosis codes; OHIP Fee, Ontario Health Insurance Plan fee for service codes; Registered Persons Database, RPDB

7.2.3 Population and timeline

We identified all patients who underwent ureteroscopy between April 1st, 2002 and March 31st, 2018 using OHIP fee and Canadian Classification of Health Intervention (CCI) codes. OHIP fee codes are submitted by physicians so they are paid for the interventions/procedures they perform. The OHIP fee codes for ureteroscopy have been extensively used in prior studies, and are expected to have excellent validity similar to other fee-for-service codes.[13–15] CCI is a health-related intervention classification system developed by Canadian Institute for Health Information for administrative purposes. An accrual end date of March 31st, 2018 ensures that each patient had the potential for at least 30 days of follow-up. We excluded the following patients:

(1) Missing or invalid encrypted unique identifiers, missing date of birth or sex, patients aged over 105 years, and those who died before cohort entry date for data cleaning purposes;
(2) Visiting non-Ontarians who received care from a healthcare facility in Ontario to limit our study population to Ontarians. We will not have follow-up data on non-Ontarians;
(3) Patients aged 18 and under to exclude patients with autosomal recessive polycystic kidney disease who may have been misclassified as patients with ADPKD;
(4) Patients with database codes for open stone surgery, SWL, and PCNL in the previous 90 days to ensure that ureteroscopy was the first stone intervention performed for the stone; and

(5) Kidney transplant recipients to ensure the ureteroscopy was performed in the polycystic kidneys.

Any stone intervention codes that appeared within 90 days of each other were considered interventions performed for the same stone.

The cohort entry date, to reflect the time of the ureteroscopic procedure, was either the hospital discharge date (for patients who underwent ureteroscopy in a hospital), registration date (for patients who underwent ureteroscopy at the emergency department), or the date of the ureteroscopy (for patients who had the procedure performed in the outpatient setting). We looked back from cohort entry date until April 1st, 2002 (earliest date when could identify patients with ADPKD using our administrative databases and hence also defined our accrual start date) for International Classification of Diseases, 10th revision (ICD-10) codes related to ADPKD, and classified patients as having or not having ADPKD.[16] ICD-10 codes related to ADPKD in our province have a positive predictive value of 85% (95% confidence interval [CI]: 79% to 89%), only identify patients who presented at the hospital with ADPKD, and differentiate patients with ADPKD from patients with other cystic kidney diseases.[16,17] After classifying each patient as affected or not affected with ADPKD, we excluded patients with OHIP diagnosis codes for congenital anomalies of the urinary system (753) and other renal cystic disease (593) from the patients without ADPKD cohort only; although these OHIP diagnosis codes identify a lot of patients with ADPKD, the codes also indiscriminately capture a lot of patients with similar conditions.[17] Therefore, excluding patients with OHIP diagnosis 753 and 593 would ensure that there are no patients with ADPKD in the control group. We also excluded patients with baseline characteristics that were present in one group but not the other as an approach to account for confounders (see Table 6-2). For patients who underwent more than one ureteroscopy, we included only the first ureteroscopy event. We followed each patient for 30 days from cohort entry date to ascertain outcomes. A follow-up of 30 days would ensure that there is sufficient time to ascertain outcome yet still be somewhat confident that the observed outcome is due to the intervention.

Table 7-2. List of baseline characteristics that were present in one study group but not the other group.

Category	Variables
Health care use[a]	Intensive care unit admission
Comorbidities[b]	Brain injury, cirrhosis, chronic obstructive pulmonary disease, hepatic failure, hepatorenal syndrome, HIV, microangiopathy, multiple sclerosis, neurogenic bladder, peripheral vascular disease, pneumonia, renal vein thrombosis, rheumatoid arthritis, schizophrenia or other psychotic disorders, sclerosis, sickle cell disease, spinal cord injury, urinary diversion, vasculitis, vesicoureteral reflux, vitamin D deficiency
Medications[c]	Aliskiren, anti-convulsant, anti-histamine, anti-neoplastic medications, carmustine, cisplatin, cyclosporine, glucocorticoid, gold compounds, methotrexate, leucovorin calcium, lithium, tacrolimus, or TMP-SMX antibiotics

[a] The look-back period for health care use was 1-year.
[b] The look-back period for comorbidities was 5-years.
[c] The look-back period for medications was 120 days.

7.2.4 Outcomes

Outcomes assessed in the 30-days following ureteroscopy were hospital presentation with ureteroscopic complications (which was a composite outcome of either emergency department visit or hospital admission with acute kidney injury [AKI], urinary tract infection [UTI], or sepsis), all-cause hospital presentation (which is either emergency department visit or hospital admission for any reason), all-cause hospital admission, and all-cause emergency department visit. We identified hospital presentation with AKI, UTI, and sepsis using ICD-10 codes.[18–20] The sensitivity and specificity of ICD-10 codes for each of the components of the composite outcome is as followed:

- **Sepsis presented during hospital admission or emergency department visit**: Sepsis is a life-threatening condition characterized by a systemic inflammatory response to a severe infection.[21] I will identify all hospital encounters for sepsis using the validated ICD-10 codes using CIHI-DAD and CIHI-NACRS (Table F-1). Based on a previous validation study of ICD-10 codes related to sepsis, the sensitivity ranged from 5.9 to 51.1%, specificity > 92%, positive predictive value ranged from 9.8 to 93.9%, and negative predictive value ranged from 86.8 to 98.3%.[22]

- **AKI presented during hospital admission or emergency department visit**: AKI is characterized by a sudden increase in serum creatinine.[23] It is associated with increased mortality and longer hospital stay.[23] I will identify patients with AKI using the validated ICD-10 codes with moderate sensitivity for patients who present with AKI at the emergency department (37.9%; 95% CI 32.1% to 43.1%), and hospital admission (61.1%; 95% CI: 57.5% to 65.5%), and high specificity (>95%) in both settings.
- **UTI presented during hospital admission or emergency department visits**: I will identify all urinary tract infections presented at hospital admissions (CIHI-DAD), or emergency department visits (CIHI-NACRS) using the validated ICD-10 codes with a sensitivity of 49.5% (95% CI: 39.5% to 59.5%), specificity of 96.6% (95% CI: 94.5% to 98.1%), and a positive predictive value of 77.3% (95% CI: 65.3% to 86.7%) (Table F-1).[24] I will consider all recurrent events.[24] However, two or more codes billed within seven days will be considered as hospital encounters for a single infection.[25]

Since the sensitivity of each of the ICD-10 codes for each of the component of the composite outcome is low, the estimated 30-day risk of ureteroscopic complication would be underestimated. However, the specificity of each of the ICD-10 codes for the three component is >95%, indicating that the codes differentiate patients with the conditions from those without the conditions. Although the risk of 30-days ureteroscopic outcome would be underestimated, the ICD-10 codes are likely capturing the more severe cases of AKI, UTI, and sepsis.

7.2.5 Data analysis

We assessed the baseline characteristics of both cohorts as mean and standard deviation for continuous variables, and as frequencies and percentages for binary or categorical variables. We used standardized difference, which are insensitive to sample size, to compare the baseline characteristics between patients with and without ADPKD. A standardized difference greater than 10% indicates important imbalance.

We assessed the unadjusted and adjusted relative and absolute risk difference of outcomes and its respective 95% confidence intervals using modified Poisson regression with robust variance estimator, and binomial regression model with an identity link function, respectively. Although logistic regression is the most common model used to analyze binary outcome, we used modified Poisson to compare relative risk because modified Poisson model provides relative risk directly which is more easily interpretable than odds ratio. The outcomes were the dependent variable and the variables listed in Table 6-3 (risk factors of our outcome) were independent variables.

Table 6-3. List of variables considered to be adjusted in the regression models.

Category	Variables
Demographic and Socioeconomic variables	Date of cohort entry, age, sex, neighbourhood income quintile, rural vs. urban residency, health service region of Ontario (local health integration network),
Health care use[a]	Hospital admission, emergency department visit, and primary care physician visit
Comorbidities[b]	Acute interstitial nephritis, acute kidney injury, anemia, atrial fibrillation, chronic liver disease, chronic lung disease, coronary artery disease, depression, diabetes mellitus, hemorrhage, hypertension, kidney tumor, obesity, prostatic hyperplasia, urinary tract infection, urinary tract obstruction
Procedures[b]	Cystoscopy, stent placed on cohort entry date, surgery
Medications[c]	Angiotensin converting enzyme inhibitor or angiotensin receptor blockers, proton pump inhibitors, diuretics, anti-diabetic medications, antibiotics, and calcium channel blocker
Lab Values	Estimate glomerular rate greater than or less than 60 mL/min/1.73m^2

[a] The look-back period for health care use was 1-year.
[b] The look-back period for comorbidities was 5-years.
[c] The look-back period for medications was 120 days.

We assessed for multicollinearity between all considered covariates using variance inflation factor (a variance inflation factor of >2 indicates presence of multicollinearity. The variance inflation factor was greater than two for proton pump inhibitors, diuretics, anti-diabetic medication, antibiotics, and calcium channel blockers. After omitting the latter four variables, the variance inflation factor was less than two for all remaining covariates in the adjusted model.

As post-hoc analysis, we examined the most common reasoning for presenting to the emergency department and median [interquartile range, IQR] time to the outcomes for both patients with and without ADPKD. All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc, Cary, NC). We present the 95% confidence interval for all estimates, which corresponds to a significance level of 0.05.

7.3 RESULTS

7.3.1 Cohort selection and baseline characteristics

Our cohort included 73 patients with ADPKD, and 81,445 patients without ADPKD who underwent ureteroscopy (Figure 7-1). Ureteroscopy was performed across 40 unique institutions for patients with ADPKD, and across 228 unique institutions for patients without ADPKD. The characteristics of both groups are summarized in Table 7-4. Compared to patients without ADPKD, patients with ADPKD were younger (median age 44 vs. 53 years), and equally likely to come from a rural area (12% vs. 12%). About 40% of the patients with ADPKD and 39% of the patients without ADPKD were women.

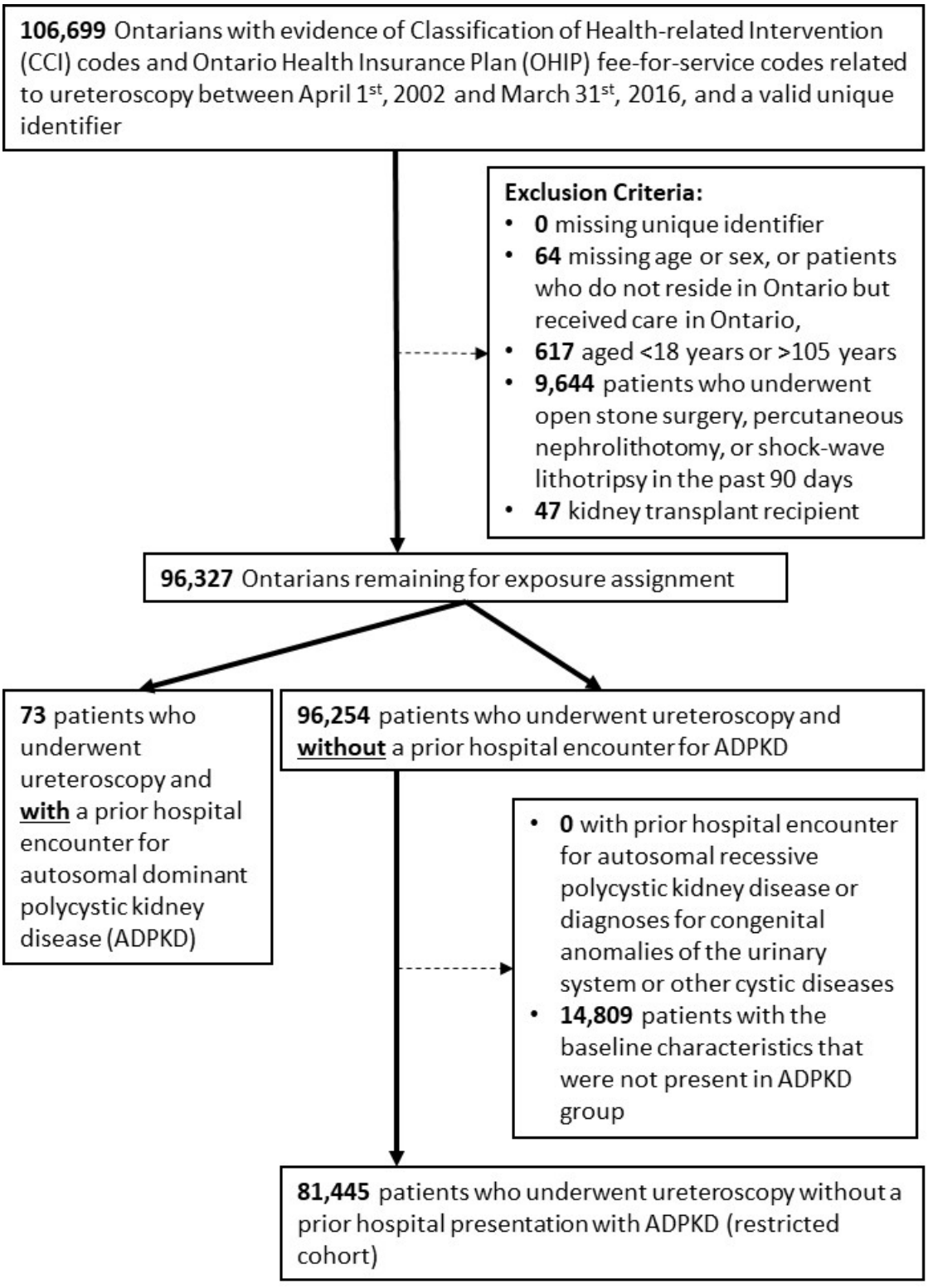

Figure 7-1. Cohort selection.
*Control groups were restricted to baseline characteristics present in ADPKD group to improve comparability between both groups

Table 7-3. Characteristics of patients with and without autosomal dominant polycystic kidney disease at the time of cohort.

	ADPKD		Standardized Difference[a] (%)
	Yes (n=73)	No (n= 81,445)	
Median (IQR) age, years	44 (38-60)	53 (42-64)	37
Women, n (%)	29 (40)	31,521 (39)	2
Income fifth:[b]			
Quintile 1 (lowest)	16 (22)	15,034 (19)	0
Quintile 2	18 (25)	16,669 (21)	0
Quintile 3	14 (19)	16,610 (20)	0
Quintile 4	6 (8)	17,007 (21)	0
Quintile 5 (highest)	19 (26)	16,125 (20)	0
Rural Town[c], n (%)	9 (12)	9,891 (12)	1
Median no. of visits to primary care physician in prior year (IQR)	8 (3-12)	8 (3-13)	11
No. of hospital admissions in the prior year (%)			
0	37 (51)	65,359 (80)	64
1	24 (33)	12,687 (16)	40
2+	12 (16)	3,399 (4)	41
Median no. of visits to emergency department in the prior year (IQR)	1 (1-3)	1 (1-2)	11
Procedures in the prior five years unless specified otherwise, n (%)			
Cystoscopy	61 (84)	68,631 (84)	2
Any type of surgery	41 (56)	33,795 (41)	30
Comorbidities, in the prior five years, n (%)			
Acute interstitial nephritis	10 (14)	3,006 (4)	36
Acute kidney injury	14 (19)	2,261 (3)	54
Anemia	10 (14)	7,919 (10)	12
Atrial fibrillation	6 (8)	6,645 (8)	0
Chronic liver disease	7 (10)	3,130 (4)	23
Chronic lung disease	9 (12)	15,303 (19)	18
Coronary artery disease	12 (16)	12,209 (15)	4
Depression	7 (10)	7,925 (10)	0
Diabetes mellitus	13 (18)	18,422 (23)	12
Hemorrhage (any type)	24 (33)	14,013 (17)	37
Hypertension	42 (58)	33,057 (41)	34
Kidney tumor	6 (8)	1524 (2)	29
Obesity	7 (10)	7,417 (9)	2
Prostatic hypertrophy	7 (10)	9,905 (12)	8
Urinary tract infection	25 (34)	14,674 (18)	38

	ADPKD		Standardized Difference[a] (%)
	Yes (n=73)	No (n= 81,445)	
Urinary tract obstruction	33 (45)	26,261 (32)	27
Medication use in the prior 120 days, n (%)[d]			
ACE inhibitors or ARBs	10 (31)	9,803 (31)	0
Antibiotics	15 (47)	14,800 (47)	0
Calcium channel blockers	7 (22)	4,985 (16)	15
Diabetic medications[e]	6 (19)	5,564 (18)	3
Proton pump inhibitors	6 (19)	4,694 (15)	11
Kidney function, n (%)[f]			
$\geq$ 60 mL/min/1.73m²	34 (83)	33,402 (88)	14
< 60 mL/min/1.73m²	7 (17)	4,753 (12)	14

Abbreviations: angiotensin II receptor blockers, ARBs; angiotensin converting enzyme inhibitors, ACE inhibitors; autosomal dominant polycystic kidney disease, ADPKD; interquartile range, IQR

Date of cohort entry is discharge date for patients that underwent ureteroscopic procedure during same day surgery, or inpatient setting, registration date for patients that underwent ureteroscopy in the emergency department, and procedure date for patients who underwent ureteroscopy in an outpatient setting.

[a] Unlike hypothesis testing, standardized difference is not influenced by sample size. A standardized difference of <10% indicates negligible difference.

[b] Average neighbourhood income was categorized into fifths on index date. Income quintile was missing for 0.18% of the entire study cohort. For these individuals, middle income quintile was assigned.

[c] Rural/urban residency status was missing for 0.05% of the entire study cohort. For these individuals we assumed they resided in an urban area

[d] Data on prescription filled was only available in 32 patients with ADPKD, and 31,411 patients without ADPKD.

[e] Diabetic medications represent a combination of insulin and anti-glycemic medications.

[f] Data on kidney function was only available in 41 patients with ADPKD and 38,155 patients without ADPKD.

7.3.2 Follow-up

None of the 73 (0%) patients with ADPKD and 142 of 81,445 (0.2%) patients without ADPKD died during 30-day follow-up.

7.3.3 Outcome

The risk of ureteroscopic complications was not significantly different between patients with and without ADPKD, although the estimates were imprecise (6 of 73 [8%] patients with ADPKD vs. 3,537 of 81,445 [4%] patients without ADPKD; adjusted RR 1.52, 95% CI 0.72 to 3.24) (Table 7-5). Median [IQR] time to ureteroscopic complication among those who had one was 16 (5 to 20) days in patients with ADPKD vs. 8 (4 to 15) days in patients without ADPKD.

Compared to patients without ADPKD, patients with ADPKD were more likely to present to hospital after their procedure (26 of 73 [36%] patients with ADPKD vs. 16,345 of 81,445 [20%] patients without ADPKD; adjusted RR 1.62, 1.19 to 2.20), which included a statistically significant increase in the risk of presenting to the emergency department (33% vs. 19%; adjusted RR 1.58, 95% CI 1.15 to 2.19) but not hospital admissions (8 of 73 [11%] vs. 4,076 of 81,445 [5%]; adjusted RR 1.78, 0.92 to 3.43) (Table 7-5). The most common diagnosis for those coming to the emergency room was renal colic or abdominal pain; nine patients with ADPKD and 3,908 patients without ADPKD presented to the emergency department with one of these diagnoses. Median [IQR] time to emergency department visit (6 [2 to15) days in patients with ADPKD vs 5 (2 to 11) days in patients without ADPKD) is approximately the same between patients with and without ADPKD.

Table 7-4. Unadjusted, and adjusted 30-days risk of ureteroscopic complications, hospital presentation, hospital admission, and emergency department visits in patients with compared to patients without autosomal dominant polycystic kidney disease (ADPKD).

	Events, n (%)		Unadjusted Relative Risk (95%CI)	Unadjusted Risk Difference (95% CI)	Adjusted Relative Risk (95% CI)
	ADPKD				
	Yes (n=73)	No (n=81,445)			
Outcome					
Ureteroscopic complication	6 (8)	3,537 (4)	1.89 (0.88 to 4.08)	0.04 (-0.02 to 0.10)	1.52 (0.72 to 3.24)
All-cause hospital presentation	26 (36)	16,345 (20)	1.77 (1.30 to 2.42)	0.16 (0.05 to 0.27)	1.62 (1.19 to 2.20)
All-cause hospital admission	8 (11)	4,076 (5)	2.19 (1.14 to 4.21)	0.06 (-0.01 to 0.13)	1.78 (0.92 to 3.43)
All-cause emergency department visits	24 (33)	15,479 (19)	1.73 (1.25 to 2.40)	0.14 (0.03 to 0.25)	1.58 (1.15 to 2.19)

Abbreviations: autosomal dominant polycystic kidney disease, ADPKD; confidence interval, CI

[a] Estimates were obtained using modified Poisson regression with outcomes as the dependent variable and ADPKD as the independent variable.

[b] Estimates were obtained using binomial regression with identity link function with outcomes as the dependent variable and ADPKD as the independent variable.

[c] Estimates were obtained using modified Poisson regression with outcomes as the dependent variable and the following as the independent variables: ADPKD, date of cohort entry, age, sex, rural residency status, income quintile, LHIN, healthcare encounter in the prior one year (hospital admission, emergency department visit, primary care physician visit, and intensive care unit visit), comorbid conditions (acute interstitial nephritis, acute kidney injury, anemia, atrial fibrillation, chronic liver disease, chronic lung disease, coronary artery disease, depression, diabetes mellitus, hemorrhage, hypertension, kidney tumor, obesity, prostatic hyperplasia, urinary tract infection, urinary tract obstruction), procedures performed in the prior five years (cystoscopy, percutaneous stent, and surgery), prescription filled in the prior 120 days (angiotensin converting enzyme inhibitor or angiotensin receptor blockers, proton pump inhibitors), and estimated glomerular filtration rate value greater than or less than 60 *mL/min/1.73m²*

7.4 DISCUSSION

The distorted kidney anatomy in patients with ADPKD may make performing ureteroscopy challenging compared to the general population. We described the 30-day risk of ureteroscopic complications, all-cause hospital presentation, all-cause hospital admission, and all-cause emergency department visit in patients with ADPKD, and compared it to patients without ADPKD. In general, all outcomes were common (although not necessarily statistically significant) in the ADPKD population. Specifically, the 30-days risk of ureteroscopic complications was not significantly different between patients with and without ADPKD, however, patients with ADPKD were more likely to present to hospital after ureteroscopy, which was driven by a statically significant increase in risk of presenting to the emergency department.

Our group recently conducted a thorough systematic review summarizing the outcomes of the three commonly used stone interventions in patients with ADPKD. Currently, there are only six case series describing the post-ureteroscopy outcome in a total of 43 patients with ADPKD with the largest case series consisting of 13 patients with ADPKD.[26–32] According to the six published case series, the overall risk of complication ranged between 0% and 27%; post-operative complications described in the literature includes fever, pain, and hematuria.[26–32] While case series and report provide insight into post-operative outcomes of ureteroscopy experienced by patients with ADPKD, it does not provide strong empirical evidence into whether ADPKD is truly associated with ureteroscopic complications. Our cohort study is the first and largest study to date to examine this association (approximately six times larger than the largest published case series). Additionally, our study had minimal loss to follow-up; no patient with ADPKD died, and it is unlikely that many people would have travelled out of Ontario during the 30-day follow-up.

There may be reasons why patients with ADPKD presented to the emergency department after ureteroscopy more than patients without ADPKD. It is possible that patients with ADPKD may experience a ureteroscopic related complications that is not part of our composite outcome. For example, pain is a post-ureteroscopic complication according to

the two case series published in the literature; as this was is nonspecific we did not include it in our composite outcome.[28,32] Our post-hoc analysis showed that pain is the most common reason for presenting to the emergency department and confirm that presenting to the emergency department with pain is more prevalent in patients with ADPKD compared to patients without ADPKD.

Our study is not without limitations. First, the codes for ureteroscopy have not been formally validated, so we had to rely on clinical expertise and knowledge of billing practices to define the outcomes. However, we expect the codes for ureteroscopy to have excellent validity similar to other fee-for services codes. The study is also limited by what is available in the healthcare administrative databases. We could not adjust for all important covariates, such as surgeon characteristics, and the accuracy and validity of each covariate was not perfect; this may have introduced residual confounding and affected the association between ADPKD and outcomes. We selected ureteroscopy complications that we thought would represent common issues encountered post-operatively, and rare complications such as ureteral perforation, or common complications such as retained stone fragments/incomplete stone treatment could not be accurately measured with administrative data. Lastly, the low event number led to imprecision around the relative risk estimates. As a result, future studies with larger number of patients are needed.

7.5 CONCLUSION

In this study of patients who underwent ureteroscopy for upper urinary tract stones, those with ADPKD did not have a statistically significant higher 30-day risk of selected ureteroscopic complications. However, they did have a significantly higher 30-day risk of all-cause hospital presentation and all-cause emergency department visits. Past case-series and reports and the results of this current study do not provide strong evidence against the use of ureteroscopy to remove upper urinary tract stones in patients with ADPKD. However, future studies with a larger number of patients are needed.

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Chapter 8 - Discussion and conclusions

8.1 SUMMARY OF KEY FINDINGS

This doctoral thesis identifies knowledge gaps and explores the epidemiology of upper urinary tract stone and stone interventions, and the consequences of upper urinary tract stone management in patients with ADPKD. Our first systematic review of 49 studies showed that the prevalence estimates ranged widely from 3% to 59% for upper urinary tract stones and from 1% to 8% for stone interventions in the literature.[1] The between-study difference in prevalence estimates is due to inconsistent stone definitions, different distributions of stone risk factors, potential recall bias in studies that relied on patient self-reported data to identify stone events, and relying on past imaging reports done for reasons other than stone identifications. UTI and flank pain were the predominant precursor to diagnosis of stone, and uric acid stones are the most prevalent stone compositions in patients with ADPKD. Only six studies compared the prevalence of upper urinary tract stones in patients with ADPKD to unaffected family members.[2–7] The two of six studies with controls that statistically compared the prevalence of upper urinary tract stones between the two groups showed no significant difference.[2–7] However, none of the studies adjusted for confounders. The wide-ranging prevalence estimates along with the discovery that no published studies clearly reported stone incidence confirms that there is poor consensus on how often patients with ADPKD develop or undergo intervention for upper urinary tract stones.

Our second systematic review of 25 studies describing 311 patients (32 patients that underwent SWL, 42 patients that underwent ureteroscopy, and 237 patients that underwent PCNL) showed that percentage of patients who were stone-free after one session ranged from 0-69% after SWL, 73-100% after ureteroscopy, and 45-100% after PCNL.[8] The percentage of patients with ADPKD that experienced at least one post-operative complication ranged from 0-33% for SWL, 0-27% for ureteroscopy, and 0-100% for PCNL. The wide-ranging estimates, which were limited by the sample size, shows that the efficacy and safety of stone interventions in patients with ADPKD remains uncertain.[8]

The methodological quality of the published studies included in both systematic reviews was poor.[1,8] Our systematic reviews call for more methodologically robust studies to

better characterize the risk of upper urinary tract stones and stone intervention in patients with ADPKD, and to better understand the consequences of these three common stone interventions in patients with ADPKD. Conducting large cohort studies using healthcare administrative databases can help address this knowledge gap. However, validation of whether administrative codes related to ADPKD can reliably identify patients with ADPKD is first required. Our validation study shows that most patients with ICD-10 codes Q61.2 (ADPKD) and Q6.13 (unspecified polycystic kidney disease) truly had ADPKD according to our strict clinical criteria.[9] Another validation study that we conducted showed that ICD-10 codes related to ADPKD differentiate patients with ADPKD from patients with similar conditions.[10] The second validation study also showed that OHIP diagnosis codes for congenital anomalies of the urinary system and other cystic kidney diseases identifies most patients with ADPKD but is indiscriminately also identifying patients without ADPKD.[10] Therefore, we can use the ICD-10 codes related to ADPKD to build a robust cohort of patients with ADPKD and hospital encounters. We can also use OHIP diagnosis codes for congenital anomalies of the urinary system and other cystic kidney diseases as exclusion codes to exclude patients with ADPKD from the control group to ensure that the ADPKD and control groups are mutually exclusive. We used the ICD-10 codes to assemble our ADPKD cohorts for our two cohort studies and OHIP diagnosis codes to exclude patients with ADPKD from the control cohort.

Our first cohort study fills some of the knowledge gap identified in our first systematic review. The results show that ADPKD is associated with an increased rate of hospital encounter with upper urinary tract stone in patients with ADPKD than patients without ADPKD with otherwise similar baseline health.[11] The cysts may be compressing the collecting system leading to urinary stasis, which favours urinary crystals to form, stones to stagnate, and promote stone growth. Given their ongoing renal concerns, patients with ADPKD may be more likely to present to hospital when they develop a stone compared to patients without ADPKD. The increased surveillance may also explain the increased rate of hospital encounter with upper urinary tract stones. The results also showed 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 favour 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.[12,13] Our first cohort study also showed that ureteroscopy is the most common type of stone intervention used to treat stone in both patients with and without ADPKD.

Our second cohort study examined the post-operative ureteroscopic complications, all-cause hospital presentation, all-cause hospital admission, and all-cause emergency department visit of the most commonly performed stone intervention, ureteroscopy. The results show that risk of ureteroscopic complication did not differ between patients with and without ADPKD. Patients with ADPKD were more likely to present to the hospital after the intervention, which included an increased risk of presenting to the emergency department but not hospital admission.[14] There may be reasons why patients with ADPKD presented to the emergency department after ureteroscopy more than patients without ADPKD. It is possible that patients with ADPKD may experience a ureteroscopic related complications that is not part of our composite outcome. For example, pain is a post-ureteroscopic complication according to the two case series published in the literature; as this was is nonspecific we did not include it in our composite outcome.[15,16] Our post-hoc analysis showed that pain is the most common reason for presenting to the emergency department and confirm that presenting to the emergency department with pain is more prevalent in patients with ADPKD compared to patients without ADPKD. Interestingly, this does not appear to be driven by stent related pain, as the placement of ureteral stents was similar between groups.

8.2 IMPLICATIONS

8.2.1 Laid the foundation for future research in ADPKD using administrative databases

Understanding the performance of administrative codes related to ADPKD is important to ensure our ADPKD study cohort is robust; this affects the internal validity of the study.

Chapter 5 of this thesis show that patients with ICD-10 codes related to ADPKD truly have ADPKD according to a strict clinical criterion.[9] Another validation study conducted by our team shows that ICD-10 codes also differentiate patients with ADPKD from patients with similar conditions, but only identifies a subset of the ADPKD population.[10] The study also shows that OHIP diagnosis codes for congenital anomalies of the urinary system and other cystic kidney diseases capture most patients with ADPKD, but also a lot of patients with similar conditions.[10] Therefore, future studies that use administrative databases can use ICD-10 codes to build a robust cohort of patients with ADPKD and can use OHIP diagnosis codes to exclude patients with ADPKD.

8.2.2 Implications for clinical practice guidelines

Many popular educational materials and clinical practice guidelines state that upper urinary tract stones are common in patients with ADPKD, and its prevalence may be five to ten times higher than the general population.[17,18] Our systematic review and meta-analysis of the prevalence and incidence of upper urinary tract stones in patients with ADPKD (Chapter 2) revealed that these assertions are based on weak evidence.

Results from our first cohort study (Chapter 6) did show that rate of hospital encounter with upper urinary tract stone is higher in patients with ADPKD compared to patients without ADPKD with similar baseline health. However, the percentage of patients with ADPKD who experienced at least one hospital encounter with a stone (4%) and stone intervention (2%) is still relevantly uncommon. We acknowledge that the way stone is defined in the study does not identify many stone events, such as when the stone is passed at home or when it only requires care in an outpatient clinic, We recommend repeating this study in the future with more rigorous methodology.

Although clinically significant stones are fairly uncommon in patients with ADPKD, stones remain a major determinant of pain.[24] Stones are also known to accelerate disease progression in patients with CKD and this is suggested to be true in patients with ADPKD. [25,26] According to the exploratory risk factor analysis in Chapter 6, male sex is a risk factor for hospital encounter with stone and stone intervention. Therefore, a nephrologist may wish to monitor high-risk stone formers, such as males, with ADPKD

for upper urinary tract stones. They may also place a greater emphasis on preventing upper urinary tract stone formation by monitoring and managing any metabolic abnormalities. For example, hypocitraturia is a prevalent metabolic abnormality observed in patients with ADPKD and upper urinary tract stones.[19–22] Hypocitraturia is when there is a low amount of citrate in the urine, and citrate is an inhibitor of stone formation. Screening for hypocitraturia and treating it with potassium citrate may help prevent upper urinary tract stones in high-risk stone formers with ADPKD. Nephrologists may also consider the use of foam sclerotherapy to eliminate predominant cysts that obstruct upper urine flow.[23] Foam sclerotherapy is a procedure that reduces cyst volume by removing the fluid within the cyst and by instilling sodium tetradecyl sulfate to ablate cyst lining.[23]

Even if stones are not frequent in patients with ADPKD, we still need to ensure that interventions are safe and efficacious in those patients who require intervention. If upper urinary tract stones do develop and grow to the extent that surgical intervention is needed, it is clear that we cannot draw conclusions about whether the three common stone interventions (SWL, ureteroscopy, and PCNL) are safe and efficacious in patients with ADPKD based on the evidence available from the published literature (Chapter 3). Our final cohort study (Chapter 7) provided preliminary results on the risk of complications after the most common stone intervention.[14] The results show that ADPKD is not associated with a significant increase in ureteroscopic complications but is associated with an increased 30-day risk of all-cause emergency department visits.[14] Post-hoc analysis showed that the most common reason for emergency department is pain, which can be managed with medications. Therefore, based on the preliminary insight from our final cohort study, there are not sufficient evidence against performing ureteroscopy in patients with ADPKD. However, this needs to be further investigated in future studies.

8.2.3 Clinical prognostication

Identifying risk factors for upper urinary tract stones in patients with ADPKD can help target patients who may warrant closer monitoring and increased efforts to prevent upper urinary tract stone formation. Our exploratory analysis from Chapter 6 shows that men (vs. women) are at higher risk of being hospitalized with upper urinary tract stones and

undergo stone interventions. Nephrologists may wish to monitor males with ADPKD more closely for any metabolic abnormalities or any cyst that may obstruct the collecting system.

8.3 STRENGTHS

The strength of this thesis is described in detail in the discussion section of each chapter of the thesis. However, the key strengths are highlighted below.

First, we conducted two comprehensive systematic review to gain a thorough understanding of the current literature on the epidemiology and management of upper urinary tract stones in patients with ADPKD. We used a very comprehensive search strategy to identify relevant literature, and two reviewers independently screened and abstracted data carefully using a robust form in duplicate to minimize human error and bias.

Second, we validated administrative codes related to ADPKD and our study showed that patients identified ADPKD-related ICD-10 codes truly have ADPKD (Chapter 5). The same codes also differentiate patients with ADPKD from patients with conditions similar to ADPKD. We used the codes validated in Chapter 5 to assemble our study population for chapter 6 and 7; therefore, our study populations were robust and internal validity of the studies were not compromised by the administrative codes used to assemble our study population.

Third, to the best of our knowledge, Chapter 6 was the first and largest, longitudinal study that adjusted for covariates, and compared the rate of hospital encounter with upper urinary tract stones and stone intervention between patients with ADPKD and controls with similar baseline health. Additionally, Chapter 7 was the first and largest cohort study to date examining the association between ADPKD and complications post-ureteroscopy. Both studies had minimal or no loss to follow-up.

8.4 LIMITATIONS

Limitations of the thesis is described in details in the discussion section of each data chapter, and are reiterated in this section of the thesis.

First, our two systematic reviews only included conference proceedings and original journal articles published in English.

Second, we only reviewed medical charts from two hospitals within the London Health Sciences Center for our validation study (Chapter 4). While coding practices are standardized across hospitals in Ontario, there still may be slight difference in coding practices between the two hospitals and other hospitals across Ontario. Additionally, coding practices vary across the world. For example, in Ontario, physician fee diagnostic and fee-for service codes (OHIP codes) are submitted by physicians for the remuneration for the services they provide. ICD-10 codes are traditionally used for administrative purposes, such as assessing healthcare use and needs in hospital settings. In other regions, ICD-10 codes are used in outpatient settings as well. Therefore, findings from our validation study must be generalized to other regions with caution.

Third, ICD-10 codes for ADPKD only identifies patients with a hospital encounter with ADPKD and does not identify patients with ADPKD who did not have any hospital encounter. Therefore, findings from chapter 6 and 7 must be generalized to patients with ADPKD without any hospital encounter with caution.

Fourth, codes for stone interventions has not been formally validated, so we had to rely on clinical expertise and knowledge from billing practices to define stone intervention. However, we expect the codes for stone intervention to have excellent validity similar to other fee-for service codes.

Fifth, chapters 6 and 7 were limited by what is available in healthcare administrative databases held at ICES. Therefore, we could not adjust for all important covariates, such as stone size and location, water intake for chapter 6, and surgeon characteristics for Chapter 7. Additionally, the validity of all the included covariates is not perfect, and therefore there may be residual confounding.

Sixth, the number of upper urinary tract stones events is under-reported in chapter 6 because we used ICD-10 codes to identify upper urinary tract stone events. ICD-10 codes only identify patients who had a hospital encounter with upper urinary tract stones and does not capture upper urinary tract stone events presented at an outpatient clinic or that simply passed at home.

Last, the small number of events in both chapters 6 and 7 led to some imprecise estimates.

8.5 FUTURE DIRECTIONS

While this thesis addressed many knowledge gaps, and addressed many questions about the epidemiology of upper urinary tract stones in patients with ADPKD, there still remains many unanswered questions.

First, linking a registry of a large number of patients with ADPKD and their unaffected family members with precise collection of baseline and outcome measures will provide a better estimate of risk. In our studies, we were limited by what was available through healthcare administrative databases held at ICES. As a result, we could not identify patients with ADPKD with a wide spectrum of disease. We also could not adjust for important confounders such as diet and water intake. By comparing the outcomes to an unaffected family member, we would be indirectly adjusting for lifestyle and by linking a registry with prospectively collected baseline data we can supplement the data from administrative databases with registry data to minimize residual confounding.

Second, while we know that upper urinary tract stones accelerate disease progression in patients with CKD, this is only suggested to be true in patients with ADPKD.[25,26] Future studies should determine whether upper urinary tract stones truly accelerate disease progression to ESKD in patients with ADPKD.

Third, while Chapter 6 gives some insights into risk factors for upper urinary tract stone in patients with ADPKD, more ADPKD-specific risk factors for upper urinary tract

stones, such as total kidney volume and mutation type, should be explored. Identifying risk factors for upper urinary tract stones would help clinicians identify which particular patients should be monitored more closely and targeted for preventative therapy for upper urinary tract stones.

Fourth, while chapter 7 provided preliminary insight into the complication rates of ureteroscopy in patients with ADPKD compared to patients without ADPKD with otherwise similar baseline health, the estimates were imprecise. The same study should be repeated with a larger sample size achieved by conducting national level study or a longer accrual period in the future to get a better understanding of the complication rates of ureteroscopy in the future.

Last, this thesis did not explore the success and complication rates of SWL and PCNL. Chapter 3 confirms that evidence for the success and complication rates of SWL and PCNL is limited. Therefore, future, large, multi-center, prospective or retrospective cohort studies should be conducted to understand the safety and efficacy of SWL and PCNL in patients with ADPKD.

8.6 CONCLUSION

Kidney failure is not the only manifestation of ADPKD. ADPKD is a systemic disorder with many other manifestations that warrant attention to maintain or improve quality of life. This thesis confirms that hospital encounters with upper urinary tract stones are a manifestation of ADPKD. The urologists are not more or less likely to manage stones compared to patients with otherwise similar baseline health. The distorted kidney anatomy may make performing stone interventions more challenging. Of all three commonly used interventions (SWL, ureteroscopy, and PCNL), ureteroscopy is the most prevalent intervention used to manage stones in both patients with and without ADPKD. Our final thesis study shows that ADPKD is not associated with a statistically significant increase in ureteroscopic complications and all-cause hospital admission but is associated with an increased 30-days risk of all-cause hospital presentation and emergency

department visits. Currently, there is insufficient evidence to show that we should discontinue using ureteroscopy to manage upper urinary tract stones. The knowledge gained from this thesis identifies this knowledge gap and lays the foundation for future studies on ADPKD using healthcare administrative databases. It clarifies the rate of hospital encounters with upper urinary tract stones and the rate of stone interventions, and provides the best evidence we have to date to inform clinical practice.

8.7 TAKE HOME MESSAGE

- We can reasonably identify patients with a hospital encounter with ADPKD using ICES data
- Incidence and prevalence of upper urinary tract stone and stone intervention in ADPKD, and the safety and efficacy of the three common stone interventions (SWL, ureteroscopy, and PCNL) are unclear.
- The rate of a hospital encounter with upper urinary tract stone is higher in patients with ADPKD than patients without ADPKD with similar baseline health. The percentage of patients with ADPKD who experience a clinically significant stone event remains relatively uncommon (4%)
- Urologists are not more or less aggressive in their management of stones in patients with ADPKD compared to patients without ADPKD.
- Patients with ADPKD are more likely to visit to the emergency department within 30 days of ureteroscopy for stone disease compared to patients without ADPKD with similar baseline health.

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Appendices

APPENDIX A: Detailed descriptions of ICES data sources used in Chapters 5 to 7

Table A-1. Detailed description of ICES data sources used in Chapters 5 to 7.

DATABASE	DESCRIPTION
Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD), CIHI Same Day Surgery (SDS), and CIHI National Ambulatory Care Reporting System (NACRS)	CIHI-DAD contains administrative, demographic, and clinical information on hospital discharges of patients admitted to acute care hospitals in Ontario, SDS contains information on same day surgery, and NACRS contains information on all emergency department visits. The diagnostic and procedural information are coded using the 9th edition of the Canadian Modified International Classification of Diseases (ICD-9-CM) and the Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (CCP) codes, respectively, prior to April 1st, 2002, and coded using the 10th edition of the Canadian Modified International Classifications of Diseases (ICD-10-CM) and the Canadian Classification for Health Interventions (CCI) codes, respectively, from April 1st, 2002 and onwards.[119]
Ontario Health Insurance Plan (OHIP) Database	OHIP contains most claims covered under the provincial health insurance plan. Approximately 95% of the specialist and 50% of the family care physicians in Ontario get paid on a fee for service basis.
Ontario Registered Persons Database (RPDB)	RPDB contains reliable demographic and vital statistics, such as birth and death data, of all Ontarians with a valid health card number.
ICES Physician Database (IPDB)	IPDB is created by ICES and contains information about all physicians, including practice location, and clinical specialties. It comprises information from the OHIP Corporate Provider Database (CPDB), the Ontario Physician Human Resource Data Centre database, and the OHIP database of physician billing.
Canadian Organ Replacement Register (CORR)	CORR is a national information system that contains detailed information on everyone who has received an organ transplantation or is on chronic dialysis.[120] At ICES, we only have access to data from Ontario.
Ontario Drug Benefits (ODB)	ODB contains information on outpatient prescriptions dispensed to patients aged 65 years and older, patients who live in a Long-Term Home or Home for Special Care, patients enrolled in Home Care Program, patients enrolled in the Trillium Drug Program, and patients who receive social assistance from Ontario Works or the Ontario Disability Support program. The data available from this database is highly reliable with an error rate of <1%.[122]

The health card number of Ontarians is encoded using a unique ICES key number, which is used as a common identifier to link databases at ICES together.

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APPENDIX B: Copyright information

B.1 COPYRIGHT INFORMATION FOR CHAPTER 2, 3, and 5

Curriculum Vitae

Name:	Vinusha Kalatharan
Post-secondary Education and Degrees:	The University of Western Ontario London, Ontario, Canada 2009-2013 BMSc
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Honours and Awards:	Western Graduate Research Scholarship 2013-2018
	Schulich Graduate Scholarship 2015-2016
	Ontario Graduate Scholarship 2014-2017
	Canadian Institute for Health Research Travel Award 2016
	Ontario Graduate Scholarship (declined) 2017-2018
	Canadian Institute of Health Research Doctoral Scholarship 2017-2020
	Kidney Foundation of Canada Allied Health Doctoral Scholarship (declined) 2017-2018
	Kidney Research Scientist Core Education and National Training (KRESCENT) Award 2017-2020
Related Work Experience	Graduate Research Assistant London Health Sciences Centre ICES Western 2013-2019
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