LEVERAGING REAL-WORLD DATA TO ASSESS HEALTH CARE RESOURCE UTILIZATION AND COST OUTCOMES AMONG PATIENTS LIVING WITH AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE IN THE UNITED STATES

by

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ABSTRACT

LAURA ANN CLARK. Inpatient Resource Use and Cost Outcomes Among Kidney Transplant Recipients with vs. without Autosomal Dominant Polycystic Kidney Disease. (Under the direction of DR. REUBEN HOWDEN)

Introduction: Autosomal dominant polycystic kidney disease (ADPKD) is a rare genetic condition impacting 1 in 400 live births in the United States (US) and it causes variable declines in kidney function to end-stage renal disease (ESRD). ADPKD accounts for approximately 5 to 10% of patients diagnosed with ESRD in the US and Europe. Between 50 and 70% of the ADPKD population require renal replacement therapy (RRT) (i.e., dialysis and kidney transplantation [KTP]) by their fourth to seventh decades of life, which exponentially increases the burden experienced by patients, caregivers, HCPs, and payers in the US. Patients with ADPKD, ESRD, and dialysis have been observed to have fewer 30-day unplanned hospital readmissions than patients without ADPKD, but the cost of index hospitalizations ($15,093 vs. $12,394) and 30-day all-cause readmissions ($17,391 vs. $16,455) was observed higher among those with ADPKD compared to those without ADPKD. Patients with ADPKD have been observed to have a higher rate of KTP within the first year of initiating dialysis compared to the total ESRD population in the US (25% vs. 5%, respectively). However, literature on the inpatient resource use and cost outcomes of patients with ADPKD and receiving KTP in the US is limited. This study aimed to leverage real-world data to generate estimates of inpatient resource use and cost of hospitalization for KTP surgery and 30-day all-cause readmissions among patients with vs. without ADPKD in the US.

Methods: This study was a retrospective, longitudinal, case-cohort analysis of patients ≥18 years of age with an index hospitalization for KTP surgery between 01 January – 31

December 2018 in the Premier Healthcare Database (PHD). Patients with and without ADPKD were characterized at index hospitalization for KTP and 30-day all-cause readmissions within 30-days of index hospitalization for KTP surgery were identified between 01 January 2018 – 31 January 2019 in the PHD. Inpatient resource use (i.e., length of stay [LOS]) and total patient cost were compared for those with vs. without ADPKD at index hospitalization for KTP surgery. 30-day all-cause readmission outcomes (readmission rate, LOS, and total patient cost at readmission) were also compared for those with vs. without ADPKD. Descriptive (chi-square and Wilcoxon Signed-Rank Sum test) were applied for assessment of differences in outcomes at index hospitalization for KTP surgery and 30-day all-cause readmissions with alpha level set at ≤ 0.05. Inferential (logistic, negative binomial, and quantile regression) statistics were applied to assess the association between ADPKD diagnosis and 30-day all-cause readmission outcomes (i.e., readmission rate, LOS, total patient cost at readmission).

Results: A total sample of 3,512 patients receiving KTP were obtained and stratified as ADPKD (n=285) and non-ADPKD (n=3,227) for comparison of patient demographics, Elixhauser comorbidities, hospital characteristics, inpatient resource use (i.e., LOS), and total patient cost at index hospitalization for KTP surgery. No significant difference was observed in the median (IQR) age of patients with vs. without ADPKD at index hospitalization for KTP surgery (56 [47-62] vs. 55 [43-63] years; $p = 0.1658$). However, a higher proportion of patients with ADPKD were aged 55-64 and 45-54 years old compared to patients without ADPKD (35% vs. 29% and 28% vs. 21%, respectively; $p < 0.0001$). A higher proportion of patients with ADPKD were female compared to those without ADPKD (46% vs. 38%, respectively; $p = 0.0050$). Patients without ADPKD were

found to have a greater comorbidity presence and poorer health status with a higher proportion of patients without ADPKD having congestive heart failure (11% vs. 7%; p = 0.0498), valvular disease (5% vs. 3%; p = 0.0452), complicated hypertension (90% vs. 78%; p < 0.0001), complicated diabetes (45% vs. 9%; p < 0.0001), rheumatoid arthritis (7% vs. 1%; p < 0.0001), weight loss (4% vs. 1%; p = 0.0427), and alcohol abuse (2% vs. 0%; p = 0.0315) compared to those with ADPKD. However, a higher proportion of patients with ADPKD were identified to have uncomplicated hypertension compared to those without ADPKD (17% vs. 7%, respectively; p < 0.0001). The unadjusted median (IQR) LOS (4 [4-6] vs. 5 [4-7] days, respectively; p = 0.0006) and total patient cost ($103,000 [$72,000-$128,000] vs. $113,000 [$75,000-$139,000], respectively; p = 0.0010) at index hospitalization for KTP surgery were significantly lower among patients with ADPKD. A total of 1,582 patients (45.05%) of the total cohort were observed to have at least one all-cause readmission within 30-days of index discharge for KTP surgery. A lower proportion of patients with ADPKD (n=112) were observed have at least one all-cause readmission within 30-days of index discharge for KTP surgery compared to those without ADPKD (n=1,470) (39.30% vs. 45.55%, respectively; p = 0.0419). After adjustment for factors associated with the probability of ADPKD diagnosis, a 0.01% lower odds of at least one all-cause readmission within 30-days of index discharge for KTP surgery was observed, but it was no significant (OR: 0.99, 95% CI: 0.76 to 1.28, p = 0.9272). There was no significant difference in the unadjusted median (IQR) LOS (3 [2-6] vs. 3 [2-5] days, respectively; p = 0.4421) of 30-day all-cause readmissions among patients with ADPKD vs. without ADPKD. After adjustment for factors associated with the probability of ADPKD diagnosis, a 15% lower odds of a longer mean LOS at 30-day all-cause

readmission was observed, but it was not significant (IRR: 0.85, 95% CI: 0.72 to 1.01, p = 0.0687). There was no significant difference in the unadjusted median (IQR) total patient cost ($8,575 [$4,904-$14,744] vs. $8,550 [$4,774-$16,940], respectively; p = 0.5364) of 30-day all-cause readmissions among patients with ADPKD vs. without ADPKD. After adjustment for factors associated with the probability of ADPKD diagnosis, a higher incremental median total patient cost was observed, but it was not significant ($1,252; 95% CI: -$1,057 to $3,088; p≥ 0.05).

Conclusions: Patients with ADPKD and receiving KTP impose less inpatient resource use and cost burden to hospitals at index hospitalization for KTP surgery compared to those without ADPKD. Nearly half of patients included in this cohort experienced a 30-day all-cause readmission following KTP surgery, thus, there is a need for improvement in the quality of KTP care delivered across hospitals in the US. There was no association found between ADPKD diagnosis and the odds of at least one 30-day all-cause readmission. Furthermore, no association was found between ADPKD diagnosis and the burden imposed to hospitals (i.e., mean LOS and incremental median total patient cost) at 30-day all-cause readmissions. Lower comorbidity burden at index hospitalization for KTP surgery among patients with ADPKD likely impacted the readmission results. Ultimately, the economic burden to hospitals financially responsible for 30-day all-cause readmissions was determined equivalent for KTP patients with and without ADPKD in this study.

DEDICATION

To my first mentor, best friend, and father - Tim Brooks. Thank you for 15 wonderful years of love, support, and encouragement to chase after my dreams. It was these years that laid the foundation of my empathy and compassion for mankind, passion for human physiology, research, and writing. The greatest lessons learned were to never give up and dig deep when life gets rocky, to eagerly listen to the experiences of others, and somehow find their relevance and meaning in my life. It is because of these lessons that I connected with JoAnn, Patty, and Celia, amazing ladies living with autosomal dominant polycystic kidney disease, and began my PhD journey. I also dedicate this dissertation to JoAnn, Patty, and Celia. Words will never express my gratitude for your time and vulnerability when sharing your experiences with autosomal dominant polycystic kidney disease. Your experiences informed the development of my dissertation aims and these real-world data concepts are a reflection of not just your experiences, but that of others also living with autosomal dominant polycystic kidney disease in the United States.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AA	Alcohol Abuse
ADH	Antidiuretic Hormone
ADM_MON	Admission Month
ACE-I	Angiotensin Converting Enzyme Inhibitor
ADPKD	Autosomal Dominant Polycystic Kidney Disease
ADPKD-OM	Autosomal Dominant Polycystic Kidney Disease – Outcomes Model
AHA	American Hospital Association
AIDS	Autoimmune Deficiency Syndrome
AKF	Acute Kidney Failure
AKI	Acute Kidney Injury
ALT	Alanine Aminotransferase
ARB	Angiotensin Receptor Blocker
ARPKD	Autosomal Recessive Polycystic Kidney Disease
AV	Arteriovenous
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CAD	Coronary Artery Disease
cAMP	Cyclic Adenosine Monophosphate
CCI	Charlson Comorbidity Index
CDC	Centers for Disease Control and Prevention
CHF	Congestive Heart Failure
CIs	Confidence Intervals
CKD	Chronic Kidney Disease
CMS	Centers for Medicare and Medicaid Services
CNI	Calcineurin Inhibitors
COPD	Chronic Obstructive Pulmonary Disease
CPI	Consumer Price Index
CPT	Current Procedural Terminology
CRISP	Consortium for Radiologic Imaging for the Study of Polycystic Kidney Disease
CT	Computed Tomography
CVC	Central Venous Catheter
CVD	Cardiovascular Disease
DC	Diabetes, Complicated
DCGF	Death-Censored Graft Failure
DHPLC	Denaturing High Performance Liquid Chromatography
DISC_MON	Discharge Month
DIVAT	Données Informatisées et VAlidées en Transplantation
DNA	Deoxyribonucleic Acid
DRG	Diagnosis Related Group
DU	Diabetes, Uncomplicated

DVT	Deep Vein Thrombosis
Dx	Diagnosis
ED	Emergency Department
eGFR	Estimated Glomerular Filtration Rate
EPO	Erythropoietin
EPTS	Estimated Post-Transplant Survival
ERA-EDTA	European Renal Association-European Dialysis and Transplant Association
ESA	Erythropoietin Stimulating Agent
ESRD	End-Stage Renal Disease
FFS	Fee-for-Service
GBD	Global Burden of Disease
GDP	Gross Domestic Product
GINA	Genetic Information Nondiscrimination Act
GLM	Generalized Linear Model
HALT-PKD	Halt Progression of Polycystic Kidney Disease
HCP	Health Care Provider
HCPCS	Health Care Common Procedure Coding System
HCUP	Health Care Cost and Utilization Project
HCRU	Health Care Resource Utilization
HD	Hemodialysis
Hgb	Hemoglobin
HHO	Home Health Organization
HIPPA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HMO	Health Maintenance Organization
HRQoL	Health-Related Quality of Life
htTKV	Height-Adjusted Total Kidney Volume
HTN	Hypertension
HTN-C	Hypertension, Complicated
HTN-U	Hypertension, Uncomplicated
ICA	Intracranial Aneurysm
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
ICD-10-PCS	International Classification of Diseases, 10th Revision, Procedural Coding System
IHD	Ischemic Heart Disease
IP	Inpatient Visits
IQR	Interquartile Range
IRR	Incidence rate ratio
IV	Intravenous

KAS	Kidney Allocation System
KDPI	Kidney Donor Profile Index
KPSC	Kaiser Permanente Southern California
RRT	Renal Replacement Therapy
KTP	Kidney Transplant
LDS	Limited Dataset
LOS	Length of Stay
LVH	Left Ventricular Hypertrophy
LVMI	Left Ventricular Mass Index
MAP	Mean Arterial Pressure
MDRD	Modification of Diet in Renal Disease
MEDREQ_KEY	Patient-Level Identifier
MI	Myocardial Infarction
MLD	Mild Liver Disease
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
N/A	Not Applicable
NAMCS	National Ambulatory Medical Care Survey
NEDS	Nationwide Emergency Department Sample
NIS	National Inpatient Sample
NN	Native Nephrectomy
NODAT	New Onset Diabetes After Transplant
NR	Not Reported Due to Low Sample Size (n<11)
NRD	Nationwide Readmissions Database
NS	Not Significant
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OOP	Out-Of-Pocket
OP	Outpatient Visits
OPO	Organ Procurement Organization
OPTN	Organ Procurement and Transplant Network
OR	Odds Ratio
OV	Office Visits
PAT_KEY	Encounter-Level Identifier
PD	Peritoneal Dialysis
PHD	Premier Healthcare Database
PKD	Polycystic Kidney Disease
PKD-U	Polycystic Kidney Disease - Unspecified
PLD	Polycystic Liver Disease
PPO	Preferred Provider Organization
PPY	Per Patient Year
PPPY	Per Patient Per Year
PVD	Peripheral Vascular Disease
Q	Quarter
QoL	Quality of Life

RA	Rheumatoid Arthritis
RAAS	Renin Angiotensin Aldosterone System
RBCs	Red Blood Cells
RCC	Renal Cell Carcinoma
REPRISE	Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy
REMS	Risk Evaluation and Mitigation Strategy
RoA	Route of Administration
RoM	Risk of Mortality
RRB	Railroad Retirement Board
SAS	Statistical Analysis Software
SD	Standard Deviation
SE	Standard Error
SID	State Inpatient Database
SD	Standard Deviation
SNFs	Skilled Nursing Facilities
SNP	Special Needs Plan
SoI	Severity of Illness
TEMPO	Tolvaptan Efficacy and Safety in Management of ADPKD and Its Outcomes
TKV	Total Kidney Volume
UNOS	United Network for Organ Sharing
URR	Urea Reduction Ratio
USD	United States Dollars
USRDS	United States Renal Data System
US	United States
UTI	Urinary Tract Infection
VD	Valvular Disease
WHO	World Health Organization
WL	Weight Loss

1 INTRODUCTION

Chronic kidney disease (CKD) is defined as an estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m² or at least one marker of kidney damage (i.e., albuminuria, urinary sediment abnormality, electrolyte or other abnormality due to tubular disorder, abnormal histology, structural abnormalities detected by imaging, history of kidney transplantation [KTP]), or both, for at least 3 consecutive months in duration regardless of the underlying cause. (Webster, Nagler, Morton, & Masson, 2017) Progression of CKD is defined as a ≥25% decline in eGFR from baseline, thus, progressive loss of kidney function is tracked using the following stages: stage 3a (mild to moderate decrease in GFR; 45-59 mL/min per 1.73 m²), stage 3b (moderately to severely decreased GFR; 30-44 mL/min per 1.73 m²), stage 4 (severely decreased; 15-29 mL/min per 1.73 m²), and stage 5 (kidney failure also referred to as end-stage renal disease [ESRD]; <15 mL/min per 1.73 m²). (Webster et al., 2017) Age-adjusted rates and risks of cardiovascular events, all-cause hospitalization, and all-cause mortality have been found to substantially increase with progressively lower eGFR.(Go, Chertow, Fan, McCulloch, & Hsu, 2004) Therefore, ESRD is where the majority of the burden is recognized by all stakeholders (i.e., patients, caregivers, health care providers [HCP], and payers).

Autosomal dominant polycystic kidney disease (ADPKD) is a rare genetic condition that causes variable declines in kidney function to ESRD. It's important to understand the presence and burden of CKD and ESRD in the US, especially for the rare patient subgroups, such as ADPKD, for which healthcare access differs. Incidence and prevalence of ADPKD, as well as their estimated resource utilization and cost, in the US are controversial as they vary based on the data sources leveraged and criteria used to define

or classify ADPKD cases. For rare disease populations, like ADPKD, administrative encounters and claims data are a few data sources that enable a sufficiently large enough sample size for analyses, including incidence and prevalence estimation. (Jensen et al., 2015) This enables research that informs health care resource allocation and public health efforts for the prevention of comorbidity developments and disease progression to ESRD. (Jensen et al., 2015) As the case criteria for inclusion in the cohort becomes increasingly restrictive the estimated prevalence increases depending on the disease state and case definition for inclusion in the cohort. (Jensen et al., 2015) Requiring continuous benefit enrollment and observation longer periods have the greatest influence on prevalence estimates generated using administrative data sources. (Jensen et al., 2015) Patients with ADPKD are more likely to meet the more stringent definition for inclusion in study cohorts due to longer periods of continuous enrollment in direct medical and prescription drug benefits and because they utilize more health care that is observed in the data relative to source populations. (Jensen et al., 2015) However, the more stringent definition of an ADPKD cohort is a form of bias where overly restrictive cohort definitions may result in the selection of a study population that likely no longer represents the source population from which it was derived. (Jensen et al., 2015) Therefore, incidence and prevalence estimates provided in this introduction are subject to and limited by selection bias and should be interpreted accordingly.

1.1 Epidemiology of ADPKD

ADPKD is the most common hereditary cause of CKD, affecting approximately 1 in 400 per 1,000 live births in the US. (M.C. Hogan, Torres, Sandford, & Chapman, 2018; Martinez & Grantham, 1995; V.E. Torres & Harris, 2009) Approximately 600,000 Americans are impacted

by ADPKD and over 2,000 patients start renal replacement therapy (RRT) every year due to cystic kidney diseases.(M.C. Hogan et al., 2018) Early in the disease, there are generally no symptoms at all and many individuals experience delayed diagnosis because they have few or no symptoms. (Oberdhan et al., 2022) Initial signs and symptoms of ADPKD are high blood pressure (i.e., hypertension [HTN]), hematuria, urinary tract infections (UTI), kidney stones, and chronic pain.(C.M. Blanchette et al., 2015) However, these signs and symptoms are common in CKD patients with and without ADPKD, thus, they aren't enough to differentiate and diagnose ADPKD alone.

Patients living with ADPKD experience the development of fluid-filled cysts in the kidneys that increase in number, volume, and distribution per surface area of the kidney(s), which compress the normal kidney structure and intrarenal vasculature leading to interstitial fibrosis and tubular atrophy. (Baur & Meaney, 2014; C. M. Blanchette, C. Craver, et al., 2015; C. M. Blanchette, C. Liang, et al., 2015; C.M. Blanchette et al., 2015; Boucher & Sandford, 2004; A. B. Chapman, 2008; Arlene B. Chapman & Schrier, 1991; Davies et al., 1991; M.C. Hogan et al., 2018) The Modification of Diet in Renal Disease (MDRD) study found that patients living with ADPKD had the most rapid decline of kidney function compared to other causes of CKD.(M.C. Hogan et al., 2018) Delayed diagnosis of ADPKD and poor disease management leads to symptom exacerbation and progression to kidney failure (i.e., ESRD), compromised quality of life (QoL) for longer durations of life, excessive health care resource utilization (HCRU), and health care costs. (C. M. Blanchette, C. Craver, et al., 2015; C. M. Blanchette, C. Liang, et al., 2015; C.M. Blanchette et al., 2015; M.C. Hogan et al., 2018)

Variation in the timing of manifestations of the disease and presentation of patients in the healthcare setting leads to variations in the incidence and prevalence rates observed for the

ADPKD population. The evolution of the diagnostic criteria and disease education for HCPs, caregivers, and patients are also drivers of incidence and prevalence rates for ADPKD. All patients with polycystic kidney disease (PKD) mutations (i.e., PKD-1 and PKD-2) have CKD, it's a matter of when their symptoms manifest and whether the severity prompts patients to seek healthcare resources. Aung et al. (2021) conducted a retrospective cross-sectional analysis among members of the Kaiser Permanente Southern California (KPSC) health system between January 1, 2002 and December 31, 2018. Among this large racially and ethnically diverse US population, the prevalence of diagnosed ADPKD between 2002 and 2018 was 42.6 per 100,000 persons. (Aung et al., 2021) ADPKD prevalence (per 100,000) was observed higher in non-Hispanic White (63.2) and Black (73.0) patients compared with Hispanic (39.9) and Asian (48.9) patients. (Aung et al., 2021) These findings suggest that race may be a factor in the clinical presentation and diagnosis of patients living with ADPKD in the US. (Aung et al., 2021)

Suwabe et al. (2020) used the Rochester Epidemiology Project and the Mayo Clinic and Olmsted Medical Center radiology databases to obtain incidence and point prevalence estimates for definitive, likely, and possible ADPKD in Olmsted County, Minnesota. This study generated estimates using data from 1980-2016, which is an extension of the original analysis conducted using data from 1935-1980. The age- and sex-adjusted annual incidence of definitive and likely ADPKD in 1980-2016 (3.06 cases per 100,000 person-years) was twice the rate determined in 1935-1980 (1.38 cases per 100,000 person-years), which reflects increased sensitivity and specificity of newer diagnostic criteria and methodologies, technological advances in diagnostic testing, as well as improvements in disease education and awareness. (Garcia Iglesias et al., 1983; Suwabe et al., 2020) The point

prevalence of definitive and likely ADPKD on January 1, 2010, was 68 cases per 100,000 population. (Suwabe et al., 2020)

Data from 2013-2015 in the USRDS and the National Ambulatory Medical Care Survey (NAMCS) rendered an average annual prevalence of 4.3 diagnosed ADPKD cases per 10,000 persons in the US; age-adjusted prevalence increased between 2013 and 2015. (Willey, Kamat, Stellhorn, & Blais, 2019) Age and sex differences significantly impact the incidence and diagnosed prevalence of ADPKD in the US. Peak prevalence among commercial/Medicare Advantage patients occurs at an older age and is consistent with the typical age of ESRD diagnosis (3.29 cases per 10,000 aged 50-64 years old), but occurs at a younger age among Medicaid patients (3.8 cases per 10,000 aged 35-49 years old). (Willey et al., 2019) Prevalence is higher among females in the commercial/Medicare advantage (2.18 vs. 1.94 cases per 10,000) and Medicaid (1.56 vs. 1,22 cases per 10,000) populations. (Willey et al., 2019) At younger ages, the incidence rate in females is twice the rate determined in males (6.19 vs. 3.52 cases per 100,000 aged 20-34 years old) and is likely due to increased detection of ADPKD via ultrasonography conducted during childbearing years (Willey et al., 2019) Males are more likely to be diagnosed at older ages (18% and 80% higher incidence at 50-64 years old and 65+ years old, respectively), which indicates diagnosis in males occurs at more advanced stages of CKD and warrants earlier screening and management of progression. (Willey et al., 2019)

Updated annual prevalence (2017) and two-year prevalence (2016-2017) estimates for ADPKD have been reported for combined commercial and Medicare Advantage populations in the US. The annual prevalence of diagnosed ADPKD was 2.34 per 10,000 persons and the two-year prevalence was estimated at 3.61 cases per 10,000 persons.

(Willey et al., 2021) The annual and two-year prevalence estimates were consistently lower for the Western region compared to the Northeastern region of the US, indicating ADPKD is underdiagnosed in rural areas with minimized access to health care. (Willey et al., 2021) Furthermore, the annual prevalence of individuals with ADPKD at risk of rapid progression was 0.88 cases per 10,000 persons; the two-year prevalence estimate was 1.39 cases per 10,000 persons. (Willey et al., 2021) The proportion of individuals with ADPKD at risk of rapid progression was approximately 38% with the majority living in the Southern (42%) region of the US. (Willey et al., 2021) As a result, the proportion of patients with CKD stages 4 or 5 or living with KTP by the age of 55 years old was higher in the South (18%) compared to other regions (13%) and demonstrates a significant proportion of the ADPKD population would benefit from early treatment with medications intended to delay progression to ESRD. (Willey et al., 2021)

Annual incidence of ESRD due to ADPKD in the US has been reported higher among men than women (8.7 million vs. 6.9 million between 1998-2001) and age-adjusted sex comparisons suggest men experience a more progressive disease than women. (M.C. Hogan et al., 2018) ESRD due to ADPKD is less common among Black patients than White because their incidence of ESRD due to other causes is higher.(M.C. Hogan et al., 2018) Between 50 and 70% of the ADPKD population require RRT (i.e., dialysis and KTP) by their fourth to seventh decades of life, which exponentially increases the burden experienced by patients, caregivers, HCPs, and payers in the US. (Baur & Meaney, 2014; C. M. Blanchette, C. Craver, et al., 2015; C. M. Blanchette, C. Liang, et al., 2015; C.M. Blanchette et al., 2015; Boucher & Sandford, 2004; A. B. Chapman, 2008; Spithoven et al., 2014) ADPKD accounts for 10 to 15% of individuals receiving dialysis in the US. (Badani, Hemal, & Menon,

2004) Transplant waitlisting and KTP rates are higher among individuals with ADPKD and mortality rates are lower compared to matched ESRD controls without ADPKD. (Reule et al., 2014) Arteriovenous fistula as initial HD access (35.8%) and pre-emptive KTP (14.3%) are the initial RRT among individuals with ESRD due to ADPKD. (Reule et al., 2014) The rate of individuals with ADPKD beginning RRT due to ESRD is 7.5 cases per million per year; these individuals are more likely to be aged 40 to 64 years old, female, White, and non-Hispanic. (Reule et al., 2014) Health disparities exist and have a negative impact on ADPKD outcomes given Black and Hispanic patients with ADPKD reach ESRD earlier in life yet fewer of them receive KTP pre-emptively or after receiving dialysis compared to White patients with ADPKD.(Harrison et al., 2023; McGill, Saunders, Hayward, & Chapman, 2022)

2 LITERATURE REVIEW

This chapter takes a deeper dive into key literature characterizing the clinical and economic burden experienced by patients living with ADPKD. Literature is synthesized based on the etiology, diagnosis, and pathophysiology of ADPKD, as well as monitoring progression to ESRD/treatment, and HCRU/cost of illness.

2.1 Etiology of ADPKD

ADPKD is a rare disease characterized by the development of cysts in the kidneys that abnormally accumulate fluid derived from glomerular filtrate and predominately transepithelial fluid secretion of sodium chloride and water.(Martinez & Grantham, 1995) The fluid-filled cysts expand at an abnormally increased rate due to epithelial cell proliferation.(Martinez & Grantham, 1995) Cyst development is caused by genetic mutations PKD-1 and PKD-2, located on chromosomes 16 and 4, respectively.(Boucher & Sandford, 2004; Elles et al., 1994; Grantham, 2008a; Hateboer et al., 1999; M.C. Hogan et al., 2018; Martinez & Grantham, 1995; Vicente E. Torres, Harris, & Pirson, 2007) The majority of mutations in PKD-1 and PKD-2 genes are nonsense and frameshifting that result in truncated polycystin-1 and polycystin-2 protein products, which negatively impact kidney, cardiovascular, pancreatic, and skeletal tissue development.(Boucher & Sandford, 2004; Grantham, 2008a)

Spontaneous mutations in the PKD-1 or PKD-2 genes occur in up to 10% of all cases without a family history of ADPKD.(P.A. Gabow, 1993; Martinez & Grantham, 1995) PKD-1 accounts for approximately 85 to 90% of cases and 5 to 15% are due to PKD-2, but some cases have neither of these, indicating the presence of another gene (PKD-3) that has yet to be characterized.(Badani et al., 2004; Boucher & Sandford, 2004; Grantham, 2008a;

Hateboer et al., 1999; M.C. Hogan et al., 2018; Vicente E. Torres et al., 2007) The majority of ADPKD-related complications are present before diagnosis and/or filtration insufficiency (i.e., CKD stage 3a).(Knight et al., 2015; Taylor, Johnson, Tison, Fain, & Schrier, 2005) The cumulative probability of diagnosis is higher for individuals with PKD-1 mutation compared to PKD-2; the median age at diagnosis due to ADPKD-related symptoms is much younger for individuals with PKD-1 compared to those with PKD-2 (42 vs. 46 years old, respectively.(Hateboer et al., 1999)

2.2 Diagnosis of ADPKD

Variation exists in the age at which patients experience clinical symptoms (e.g., HTN, UTI, gross hematuria, pain) that prompt screening and suggest a diagnosis of ADPKD.(Boucher & Sandford, 2004; M.C. Hogan et al., 2018) Compared to those with PKD-1, individuals with PKD-2 are more likely to experience symptoms later in life once reaching advanced stages of CKD, which leads to an underestimation of the proportion of PKD-2 among those with ADPKD earlier in life.(Hateboer et al., 1999; V.E. Torres & Harris, 2009) Regular clinical screening consists of physical examination with blood pressure readings and blood work to assess serum electrolytes, blood urea nitrogen (BUN), creatinine, and fasting lipid profile, as well as urinalysis to assess increased urinary albumin excretion or proteinuria.(M.C. Hogan et al., 2018) Elevated lipids, urinary albumin excretion, or proteinuria are associated with a higher likelihood of progressive renal insufficiency; increased urinary albumin excretion is also correlated with a higher incidence of left ventricular hypertrophy (LVH) in patients with ADPKD.(M.C. Hogan et al., 2018)

The high cost of genetic testing and advanced diagnostic imaging limits screening for ADPKD among the general population.(Willey et al., 2019) Even though PKD-1 and PKD-

2 mutations exist at birth, screening via genetic testing or diagnostic imaging is not conducted in asymptomatic children and/or adults because no treatments are available for preventing cyst development and there are downstream implications for patients regarding insurance coverage and employment following an ADPKD diagnosis. (A. B. Chapman et al., 2015; Grantham, 2008a; M.C. Hogan et al., 2018) The Genetic Information Nondiscrimination Act (GINA) was passed into US law in 2008, preventing insurers from canceling, denying, refusing renewal, or changing coverage terms and premiums based on family history or genetic test results.(V.E. Torres & Harris, 2009) It also prevents employers from making employment-related decisions (i.e., hiring, firing, promoting) based on genetics.(V.E. Torres & Harris, 2009) However, GINA protects only individuals who are asymptomatic and does not prevent underwriting based on current health status.(V.E. Torres & Harris, 2009)

Genetic testing may be used to diagnose patients if imaging results are inconclusive, to confirm a presumed diagnosis if there is no family history of ADPKD, or when a definitive diagnosis is required in younger patients for living kidney donation screening.(M.C. Hogan et al., 2018) ADPKD diagnosis requires abdominal ultrasonography (i.e., the gold-standard approach), magnetic resonance imaging (MRI), or computed tomography (CT) scan to identify the presence of bilateral fluid-filled cysts, number and size of cysts, and total kidney volume (TKV) for a patient to receive a definitive ADPKD diagnosis without confirmation via genetic testing.(Gimpel et al., 2019; Grantham, 2008a; M.C. Hogan et al., 2018; Nicolau et al., 2000; Vicente E. Torres et al., 2007) A recent analysis of commercial claims data revealed that 41% of individuals with ADPKD did not receive any abdominal imaging scans and the majority of those that did received a CT scan: 25% received ≥1

ultrasonography, 46% received ≥1 CT scan, and 10% received ≥1 MRI.(Sanon Aigbogun, Stellhorn, Pao, & Seliger, 2021) The proportion of individuals with ADPKD undergoing ≥1 MRI or CT scan varied by stage and increased with disease severity: CKD stage 1 (37%), CKD stage 2 (42%), CKD stage 3 (48%), CKD stage 4 (56%), and CKD stage 5 (71%).(Sanon Aigbogun et al., 2021)

2.2.1 Genetic Testing

Genetic testing for mutations is done via linkage analysis or molecular analysis using direct deoxyribonucleic acid (DNA) sequencing.(M.C. Hogan et al., 2018; V.E. Torres & Harris, 2009; Vicente E. Torres et al., 2007) Linkage analysis leverages microsatellite markers flanking PKD-1 and PKD-2 mutations, but since it requires a sufficient number of affected family members with accurate diagnosis to consent for testing it is only suitable for <50% of families. (M.C. Hogan et al., 2018; V.E. Torres & Harris, 2009; Vicente E. Torres et al., 2007) The large size and complexity of the PKD-1 gene and allelic heterogeneity are constraints for direct DNA analysis. (M.C. Hogan et al., 2018; V.E. Torres & Harris, 2009; Vicente E. Torres et al., 2007) Mutation scanning via denaturing high-performance liquid chromatography (DHPLC) is associated with PKD-1 and PKD-2 mutation detection rates of 65 to 70%, but direct DNA sequencing has an even higher detection rate of 85 to 90% making it ideal for earlier diagnosis of asymptomatic individuals with positive family history of ADPKD.(V.E. Torres & Harris, 2009; Vicente E. Torres et al., 2007)

A family history may include a diagnosis of ADPKD, ESRD, intracranial aneurysms (ICA), hemorrhagic stroke, or subarachnoid hemorrhage.(M.C. Hogan et al., 2018) Approximately 60% of individuals with ADPKD report a family history of the disease and diagnostic imaging of parents has determined another 30% of cases have a family

history.(P.A. Gabow, 1993; Martinez & Grantham, 1995) However, 11 to 24% of PKD-1 gene carriers do not have kidney cysts that are detectable before the age of 30 years old.(P.A. Gabow, 1993) Nearly 62% of adults are reported to have been unaware they had ADPKD until the manifestation of the disease in their children prompted evaluation and diagnosis.(P.A. Gabow, 1993) A positive family history of ADPKD has led to a diagnosis of ADPKD in approximately 36 to 49% of cases compared to diagnoses resulting from patient-reported signs or symptoms (36%) or laboratory/physical exam abnormalities (i.e., HTN or asymptomatic microscopic hematuria) identified by physicians during office visits (15 to 35%).(Bajwa, Sial, Malik, & Steinman, 2004; Taylor et al., 2005) Only 5% of patients with a negative family history of ADPKD develop a new mutation.(M.C. Hogan et al., 2018) Genetic testing is offered to children with very early onset symptomatic disease independent of family history or to those with progressive disease and negative family history, but it could be beneficial for those with a positive family history and severe disease progression to identify relatives with potential for living kidney donation.(P.A. Gabow, 1993; Gimpel et al., 2019) Approximately two-thirds of adults diagnosed with ADPKD have a positive family history, but genetic testing is typically not offered to adults because of challenges in sequencing the PKD-1 gene and the high reliability of the established diagnostic imaging criteria.(Gimpel et al., 2019; Taylor et al., 2005) If genetic testing is conducted, next-generation sequencing panels are used because of significant genetic heterogeneity and phenotypic overlap between different cystic kidney diseases.(Gimpel et al., 2019)

2.2.2 Ultrasonography

Abdominal ultrasonography is the earliest method used, widely available, easily performed, and relatively inexpensive for diagnosis and monitoring the progression of ADPKD in symptomatic children and adults.(Boucher & Sandford, 2004; A. B. Chapman et al., 2015; Elles et al., 1994; P.A. Gabow, 1993; Grantham, 2008a; M.C. Hogan et al., 2018; O'Neill et al., 2005; Vicente E. Torres et al., 2007) Ultrasonography leverages the Ravine criteria to positively diagnose individuals with a 50% risk of ADPKD and imaging may be used to classify an individual's TKV into a broad range.(Boucher & Sandford, 2004; Grantham, 2008a; M.C. Hogan et al., 2018; Nicolau et al., 2000; O'Neill et al., 2005; Taylor et al., 2005; Vicente E. Torres et al., 2007) The following original Ravine criteria were developed via imaging studies among individuals with PKD-1, so it has 100% sensitivity among those that are ≥30 years old or younger with PKD-1 compared to only 67% among those with PKD-2 and <30 years old: the presence of ≥2 cysts (unilateral or bilateral) for individuals 15-29 years old, ≥2 cysts in each kidney for individuals aged 30-59 years old, and ≥4 cysts in each kidney for individuals aged ≥60 years old.(Boucher & Sandford, 2004; Grantham, 2008a; M.C. Hogan et al., 2018; Nicolau et al., 2000; Ravine et al., 1994; V.E. Torres & Harris, 2009; Vicente E. Torres et al., 2007)

The revised Ravine criteria were proposed to improve the diagnostic performance of ultrasonography in ADPKD with increased cyst requirements in the younger age groups: the presence of ≥3 cysts (either unilateral or bilateral) for individuals aged 15-39 years old, ≥2 cysts in each kidney for individuals aged 40-59 years old, and ≥4 cysts in each kidney for individuals aged ≥60 years old.(V.E. Torres & Harris, 2009) The requirement for ≥3 cysts (unilateral or bilateral) has a 100% sensitivity and minimizes false-positive diagnoses for

ADPKD in the younger age groups.(V.E. Torres & Harris, 2009) This requirement is intended for differentiation of those with ADPKD from the general population having simple kidney cysts without genetic mutations.(P.A. Gabow, 1993; Martinez & Grantham, 1995; V.E. Torres & Harris, 2009) Individuals with PKD-2 have fewer cysts that are harder to detect via ultrasonography and, thus, reduced sensitivity is observed when applying the revised Ravine criteria: 70% among those aged 15-29 years old, 95% among those aged 30-39 years old, and 89% among those aged 40-59 years old.(Pei et al., 2009; V.E. Torres & Harris, 2009) When considering individuals as potential living kidney donors, different ultrasonography criteria are used to exclude a diagnosis of ADPKD in at-risk individuals from a family with an unknown genotype: no cysts present among those aged 30-39 years old and ≤1 kidney cyst among those aged ≥40 years old.(V.E. Torres & Harris, 2009)

Ultrasonographic measurement of TKV in vivo has demonstrated inaccuracy and it lacks precision for measuring short-term disease progression in individuals with ADPKD.(A. B. Chapman et al., 2015; O'Neill et al., 2005) Application of the ellipsoid method has shown both overestimation and underestimation of TKV due to examination-specific factors across sonographers.(A. B. Chapman et al., 2015; O'Neill et al., 2005) Therefore, large intraobserver and interobserver variability exists in ultrasonography with errors ranging from 6 to 24% overestimation of TKV using the ellipsoid method.(O'Neill et al., 2005) The majority of the error is due to variability in transverse measurements of kidney width and depth as opposed to kidney length.(O'Neill et al., 2005) Nephromegaly (i.e., kidney length >13 cm) tends to precede ESRD and has been detected in 27% of individuals <30 years old and in 88% of those aged ≥30 years old.(Nicolau et al., 2000) However, kidney growth in

ADPKD is not proportional in all dimensions; therefore, kidney length is not useful in estimating TKV.(O'Neill et al., 2005)

2.2.3 MRI and CT Scan

Advanced diagnostic imaging, such as MRI and CT scan, are rarely utilized to diagnose ADPKD in the pediatric population because of a lack of established diagnostic criteria.(Gimpel et al., 2019; M.C. Hogan et al., 2018) MRI and CT scans are more costly compared to ultrasonography, but they are considered more sensitive in diagnosing ADPKD and are used to gain better resolution in obese individuals or obtain details surrounding kidney structure, function (e.g., renal blood flow), and progression of ADPKD with differentiation of cyst volumes from the TKV.(Boucher & Sandford, 2004; A. B. Chapman et al., 2015; A. B. Chapman et al., 2003; O'Neill et al., 2005) The use of MRI or CT scan to diagnose and monitor progression of ADPKD addresses the limitation of sonographer-dependent techniques and the original/revised Ravine criteria are not applicable as that would lead to false-positive results.(A. B. Chapman et al., 2003; M.C. Hogan et al., 2018; O'Neill et al., 2005; Vicente E. Torres et al., 2007) MRI with or without gadolinium contrast is more sensitive in measuring TKV compared to ultrasonography and it's as accurate as a CT scan in detecting small cysts (<1 cm) without exposure to ionizing radiation or iodinated contrast associated with CT scan; iodinated contrast poses an increased risk of further damaging the kidneys. (A. B. Chapman et al., 2015; A. B. Chapman et al., 2003; Grantham, 2008a; O'Neill et al., 2005; Sanon Aigbogun et al., 2021; Vicente E. Torres et al., 2007)

TKV is consistently overestimated when using the MRI ellipsoid formula compared to the MRI voxel method.(O'Neill et al., 2005) The MRI voxel method includes direct

measurement or tracing of the kidneys in sequential images with summation of voxels (i.e., the 3-dimensional equivalent of pixels) counted in cross-sectional areas of the kidney(s).(O'Neill et al., 2005) The MRI voxel method produces TKV measurements with less overestimation and variability (i.e., elimination of compounding error) observed in the application of the MRI ellipsoid formula.(O'Neill et al., 2005) Even though MRI and CT scans are superior in assessing TKV, greater variability occurs in the measurement of cyst volumes reflecting a persisting unmet need for improved techniques and technological advances that can minimize measurement variability for more accurate diagnosis of ADPKD.(O'Neill et al., 2005)

Suwabe et al. (2020) applied a hierarchy of diagnostic criteria to MRI and CT scan imaging reports for the classification of individuals as definite, likely, and possible ADPKD. Definite ADPKD diagnosis was defined as the presence of a family history of ADPKD or proven pathogenic PKD-1 or PKD-2 mutations.(Pei et al., 2009; Suwabe et al., 2020) Likely ADPKD diagnosis was defined as bilateral enlarged kidneys with innumerable cysts or more than 10 cysts (≥5 mm in size; excluding parapelvic cysts) in each kidney and the absence of CKD stages 4-5 (i.e., to eliminate acquired cystic kidney disease) or findings suggestive of other cystic kidney disease.(Garcia Iglesias et al., 1983; Suwabe et al., 2020) Possible ADPKD diagnosis was defined as normal size or mildly enlarged kidneys with the total number of cysts (≥5 mm in size; excluding parapelvic cysts) above 97.5th percentile of an age- and sex-matched control population and in the absence of CKD stages 4-5 or findings suggestive of other cystic kidney disease.(Rule et al., 2012; Suwabe et al., 2020) The 97.5th percentile values for the number of cysts ≥5 mm in size by age and sex are as follows: age ≤29 years old (males/females with ≥2 cysts), age 30-39 years old

(males/females with ≥3 cysts), age 40-49 years old (males with ≥4 cysts and females with ≥3 cysts), age 50-59 years old (males with ≥6 cysts and females with ≥4 cysts), age 60-69 years old (males with ≥11 cysts and females with ≥5 cysts), and age ≥70 years old (males having ≥11 cysts with ≥5 cysts in each kidney; females having ≥10 cysts with ≥5 cysts in each kidney).(Rule et al., 2012; Suwabe et al., 2020)

2.3 Pathophysiology of ADPKD

PKD-1 mutation is associated with more severe disease with the presence of more cysts at an earlier age, greater TKV, higher prevalence of HTN, and shorter mean survival to onset of ESRD or death compared to PKD-2 mutation.(Hateboer et al., 1999; Martinez & Grantham, 1995; Nicolau et al., 2000; Parfrey et al., 1990; V.E. Torres & Harris, 2009; Vicente E. Torres et al., 2007) The absolute changes in TKV are higher among those with PKD-1 compared to PKD-2 (74.9 mL/year vs. 32.2 mL/year, respectively), but the rate of TKV progression is not significantly different (5.68% per year vs. 4.82% per year, respectively) indicating there are other mechanisms driving kidney enlargement.(Vicente E. Torres et al., 2007) The majority of patients with PKD-1 have ESRD by 70 years old, whereas >50% of patients with PKD-2 have adequate kidney function at that age.(M.C. Hogan et al., 2018) The mean age at onset of ESRD is approximately 54 years old for those with PKD-1 compared to 74 years old among those with PKD-2.(M.C. Hogan et al., 2018) In addition, the median age at onset of ESRD or death is much younger among individuals with PKD-1 compared to those with PKD-2 and CKD controls (53 vs. 69 vs. 78 years old, respectively).(Boucher & Sandford, 2004; Grantham, 2008a; Hateboer et al., 1999) Furthermore, variation in manifestations of the disease and rate of progression to ESRD occurs even among those with the same gene mutation, such as ESRD onset almost 10 years earlier in Blacks than

Whites and a less aggressive course of disease observed in women compared to men.(P.A. Gabow, 1993; V.E. Torres & Harris, 2009) For PKD-1, there are no sex differences in the cumulative probabilities of survival to onset of ESRD or death, but women with PKD-2 mutation have significantly longer overall and kidney survival than men.(Hateboer et al., 1999)

The Consortium for Radiologic Imaging for the Study of Polycystic Kidney Disease (CRISP) study was conducted among individuals with early stages of ADPKD. The CRISP study found that kidney cysts account for 39% of TKV and the mean TKV is four-fold greater among individuals with ADPKD compared to the general population.(A. B. Chapman et al., 2003) TKV is highly correlated with total cyst volumes and tends to symmetrically increase at a steady rate in both kidneys.(Grantham, 2008a; Vicente E. Torres et al., 2007) Baseline TKV is a predictor of subsequent rates of increasing kidney volume and is associated with declines in eGFR if above 1,500 mL.(Grantham, 2008a; Vicente E. Torres et al., 2007) Mean total kidney, cystic, and non-cystic volumes have been reported greater among individuals with hypertensive ADPKD and age-adjusted TKV, cyst volume, and percent cyst volume are all inversely correlated with reductions in kidney function.(A. B. Chapman et al., 2003)

An increase in the number and volume of cysts, as well as the distribution of cysts per surface area of the kidney(s), is indicative of ADPKD progression, for which adults experience an average 5 to 6% annual increase in TKV up to a point of rapid annual declines in eGFR.(Grantham, 2008b; Grantham, Chapman, & Torres, 2006) Men have a higher rate of TKV progression compared to women.(Vicente E. Torres et al., 2007) Approximately 40% of individuals with ADPKD and aged <40 years old and 70% of those

with ADPKD and aged ≥40 years old have enlarged kidneys with preserved kidney function, but mean TKV remains significantly larger among those with comorbid ESRD in the same age groups.(Nicolau et al., 2000) Prognostic indicators for a more rapid decline in kidney function include male sex, Black race, severe proteinuria, younger age at diagnosis, gross or microscopic hematuria, PKD-1 gene mutation, reduced kidney blood flow, HTN, and increased left ventricular mass index (LVMI).(A. B. Chapman, 2008; A. B. Chapman et al., 2003; P.A. Gabow, 1993; Schrier, McFann, & Johnson, 2003; Taylor et al., 2005) Individuals with ADPKD have more recently been classified as rapid progressors if having one or more of the following risk factors: HTN at <35 years of age, hematuria at <30 years of age, albuminuria, CKD stage 2 at <30 years of age, CKD stage 3 at <50 years of age, CKD stages 4 or 5 or KTP at <55 years of age.(Willey et al., 2021)

Sections 2.3.1 through 2.3.7 summarize the primary manifestations of ADPKD (i.e., HTN, cardiovascular complications, gastrointestinal complications, proteinuria/albuminuria, anemia, and ESRD) that exacerbate the burden of disease experienced by patients at any age.

2.3.1 HTN

HTN (>140/90 mmHg) is the most commonly reported initial sign of ADPKD and it is the reason for an initial physician visit that prompts further evaluation that ultimately leads to a diagnosis of ADPKD.(Arlene B. Chapman & Schrier, 1991; M.C. Hogan et al., 2018; Taylor et al., 2005) HTN is an identified biomarker of comorbid cardiovascular disease (CVD) and when developed early it is a predictor of ADPKD severity, progression to ESRD, and mortality; individuals with PKD-1 are four times more likely to have HTN than those with PKD-2.(C. M. Blanchette, C. Craver, et al., 2015; C. M. Blanchette, C. Liang, et al., 2015; C.M.

Blanchette et al., 2015; A. B. Chapman, 2008; Ecder & Schrier, 2001; Fick, Johnson, Hammond, & Gabow, 1995; Hateboer et al., 1999; M. C. Hogan, Simmons, Ullman, Gondal, & Dahl, 2023; Ratnam & Nauli, 2010) Mean arterial pressure (MAP) tends to increase before declines in kidney function occur and it is likely due to increased plasma renin activity and aldosterone concentrations commonly observed among hypertensive adults with ADPKD.(A. B. Chapman, 2008; A.B. Chapman, Johnson, Gabow, & Shrier, 1990; Arlene B. Chapman & Schrier, 1991; M. C. Hogan et al., 2023; Nicolau et al., 2000; Schrier, 2009) Approximately 49 to 75% of individuals with ADPKD are hypertensive with preserved kidney function; some reports indicate 20 to 30% are <19 years old and 29% are <30 years old at diagnosis of HTN.(Boucher & Sandford, 2004; Arlene B. Chapman & Schrier, 1991; Ecder & Schrier, 2001; Gimpel et al., 2019; Grantham, 2008a; J. J. Grantham et al., 2006; Martinez & Grantham, 1995; Milutinovic et al., 1984; Vicente E. Torres et al., 2007) HTN tends to be more common in males with ADPKD compared to females and those with HTN have greater TKV compared to those without HTN.

Given that increased TKV predicts loss of kidney function in ADPKD, it's important to understand the association between TKV, reduced kidney blood flow, and HTN.(A. B. Chapman et al., 2003; Nicolau et al., 2000) Individuals with hypertensive ADPKD experience accelerated cyst growth that leads to significantly greater TKV compared to those without HTN. (Ecder & Schrier, 2001; Ratnam & Nauli, 2010) As TKV increases, enlarged cysts compress kidney arterioles causing increased vascular resistance and ischemia due to reduced kidney blood flow, which exacerbates HTN and significantly contributes to subsequent increases in TKV and the development of ESRD.(Ecder & Schrier, 2001; P.A. Gabow, 1993; Martinez & Grantham, 1995; Vicente E. Torres et al., 2007) Individuals with

hypertensive ADPKD show significant activation of the RAAS, but activation of the RAAS has also been observed among non-hypertensive patients with ADPKD.(A. B. Chapman, 2008; Ecder & Schrier, 2001; Martinez & Grantham, 1995; Schrier, 2009)

Individuals with hypertensive ADPKD have a more rapid loss of kidney function and an increased risk of cardiovascular death due to chronic stress from increased stimulation of the RAAS.(Ecder & Schrier, 2001; Schrier, 2009) Renin is an enzyme secreted by the kidneys in response to perceived low blood pressure in enlarged cystic kidneys.(Atlas, 2007; Martinez & Grantham, 1995) Renin converts angiotensinogen, a protein produced by the liver, into inactive angiotensin I hormone that is subsequently converted to angiotensin II via angiotensin-converting enzyme (ACE) in the lungs and kidneys.(Atlas, 2007) Angiotensin II is the active hormone of the RAAS that constricts small arteries and triggers the sympathetic stress response, release of aldosterone from the adrenal glands, and release of antidiuretic hormone (ADH) from the pituitary gland.(Atlas, 2007; Martinez & Grantham, 1995) Aldosterone and ADH hormones collectively increase sodium and water reabsorption by the kidneys to ultimately increase blood volume and pressure.(Atlas, 2007) These mechanisms create a vicious cycle of cyst growth, vascular compression, increased activity of angiotensin II, and further cyst growth.(Ecder & Schrier, 2001; Martinez & Grantham, 1995; Ratnam & Nauli, 2010) However, it is the cystogenesis, total number of cysts (i.e., total cyst volume), that impacts an individual's potential to develop HTN as a result of ADPKD with subsequent increases in TKV and declines in eGFR to ESRD.

Furthermore, there is a relationship between poor blood pressure control and progressive loss of kidney function, enlargement of the heart muscle (i.e., increase in the LVMI), and increased risk of stroke and other cardiovascular events among patients living with

ADPKD.(Grantham, 2008a; M. C. Hogan et al., 2023; Ratnam & Nauli, 2010; Vicente E. Torres et al., 2007) Those diagnosed with hypertensive ADPKD have a five-fold increased risk of progression to ESRD and 80 to 100% of those with diagnosed ESRD are hypertensive.(P.A. Gabow, 1993; Grantham, 2008a; Martinez & Grantham, 1995; Schrier et al., 2003) Up to 34% of adults with ADPKD do not know they are hypertensive and HTN persists in about 49% of adults with ADPKD despite the use of anti-hypertensive medications.(P. A. Gabow, Chapman, et al., 1990) Hypertensive adults with ADPKD are often treated with angiotensin-converting enzyme inhibitors (ACE-I), angiotensin II receptor blockers (ARB), or aldosterone antagonists.(Grantham, 2008a; Ratnam & Nauli, 2010; Vicente E. Torres et al., 2007) Rigorous blood pressure control, starting early in the disease, has been shown to slow cyst growth and, thus, progression of ADPKD to ESRD.(Ratnam & Nauli, 2010; Schrier et al., 2014) Uncontrolled HTN increases the individual's risk of developing proteinuria, and hematuria with declines in kidney function, as well as morbidity and mortality due to valvular heart disease and ICA.(Ratnam & Nauli, 2010; Vicente E. Torres et al., 2007)

2.3.2 Cardiovascular Complications

Chronic activation of the RAAS leading to HTN and the presence of polycystins in cardiac and vascular tissue put patients living with ADPKD at a higher risk of cardiovascular events or abnormalities.(Helal et al., 2012; M. C. Hogan et al., 2023; Taylor et al., 2005) There is an observed high prevalence of cardiovascular events (e.g., heart arrhythmias, peripheral vascular disease, heart valve abnormalities, LVH, stroke or cerebral bleeding, heart attack, and ICA) among patients living with ADPKD, which makes it the leading cause of mortality for all, particularly those that are older and diagnosed with ESRD.(Helal et al.,

2012) Cardiovascular abnormalities such as mitral valve prolapse, mitral and aortic regurgitation, LVH or increased LVMI, and ICA are key extra-renal manifestations of ADPKD.(Lumiaho et al., 2001; Martinez & Grantham, 1995) Patients with PKD-1 mutation have been found to have more heart valve abnormalities, such as mitral valve prolapse, regurgitation (mitral, tricuspid, or aortic valve), and LVH compared to healthy relatives and CKD controls.(M. C. Hogan et al., 2023; Lumiaho et al., 2001; Martinez & Grantham, 1995) Mitral valve abnormalities have been observed in 26 to 63% of patients with ADPKD.(Chauveau et al., 1994; P.A. Gabow, 1993; Gimpel et al., 2019; M. C. Hogan et al., 2023; Vicente E. Torres et al., 2007) A significant correlation exists between HTN and LVMI in children and adults with ADPKD.(Ecder & Schrier, 2001; Schrier, 2009) However, 23% of individuals with normotensive ADPKD have been found to have LVH indicating there are other mechanisms associated with higher LVMI among those with ADPKD.(Ecder & Schrier, 2001) Approximately 48% of patients with ADPKD have been reported to have LVH and it has been more common in men (46%) compared to women (37%).(Ecder & Schrier, 2001) Over the years, LVH has decreased among patients with ADPKD due to the increased use of ACE-I and ARB to manage HTN and downstream events.(M. C. Hogan et al., 2023)

ICA is the major vascular abnormality observed in 26 to 41% of individuals with ADPKD and it occurs more often among those with a family history of ICA (16 to 26%).(Bajwa, Gupta, Warfield, & Steinman, 2001; Chauveau et al., 1994; P.A. Gabow, 1993; Milutinovic et al., 1984; Pirson, Chauveau, & Torres, 2002; Vicente E. Torres et al., 2007) ICA has been linked to PKD-1 and PKD-2 modifications in the structural integrity of vascular smooth muscle and it's considered the most serious complication of ADPKD given the high likelihood of

rupture with subarachnoid, intraventricular, or intracerebral hemorrhaging.(Chauveau et al., 1994; M. C. Hogan et al., 2023; Martinez & Grantham, 1995; Pirson et al., 2002; Vicente E. Torres et al., 2007) However, there is broad intrafamilial variability in the occurrence and/or severity of ICA in ADPKD, meaning other factors influence the formation and likelihood of rupture.(Pirson et al., 2002)

The prevalence of asymptomatic ICA is three to five times higher among patients living with ADPKD (9 to 12%) compared to the general population (2 to 3%).(A. B. Chapman et al., 2015; M. C. Hogan et al., 2023; Martinez & Grantham, 1995; Pirson et al., 2002) A magnetic resonance (MR) angiographic study confirmed unruptured ICA in approximately 4% of young adults with ADPKD, but signs of unruptured aneurysms were detected among 16% of those with only CT scans.(A.B. Chapman et al., 1992) ICA rupture has been found to occur in 29% of normotensive individuals with ADPKD and among 50% with preserved kidney function at the time of rupture.(Chauveau et al., 1994; Pirson et al., 2002; Vicente E. Torres et al., 2007) However, those <50 years old and having poorly controlled HTN are more likely to experience ICA ruptures with a >50% 30-day mortality rate.(Martinez & Grantham, 1995; Pirson et al., 2002)

Incidence of rupture among individuals with ADPKD has been estimated at a five times higher rate than in the general population; it's eleven times higher among those with a family history of ICA or hemorrhagic stroke (23.5%) compared to those without a familial history of ICA or hemorrhagic stroke (11.6%).(M. C. Hogan et al., 2023; Pirson et al., 2002) Small ICA ruptures (i.e., <10 mm in diameter) are experienced by 52% of individuals with ADPKD and 6% are at risk of giant ICA (≥25 mm in diameter).(Pirson et al., 2002) Approximately 20 to 50% of individuals with ADPKD experience acute and transient

headaches within days or weeks of rupture, which is often overlooked, and 24 to 31% experience multiple ICA ruptures.(Pirson et al., 2002) Up to 25% of individuals with ADPKD experience ICA rupture that is complicated by cerebral ischemia within 2 weeks of hemorrhage.(Pirson et al., 2002) As a result, ICA ruptures impose a 35 to 55% risk of combined severe morbidity (i.e., neurocognitive impairment) and mortality among patients living with ADPKD; 3-month mortality rates are higher among those with comorbid ESRD (15%) compared to those without comorbid ESRD (6%).(Chauveau et al., 1994; Pirson et al., 2002; Vicente E. Torres et al., 2007) ICA ruptures have been reported to account for 4 to 7% of deaths among patients living with ADPKD.(M. C. Hogan et al., 2023)

2.3.3 Cystic Complications

Cystic complications including infections, hemorrhage, stones, fibrosis, and chronic pain impose a significant physiological burden on patients living with ADPKD and progressive CKD (i.e. stages 3a to 5).(C.M. Blanchette et al., 2015; Boucher & Sandford, 2004; J. J. Grantham et al., 2006; Vicente E. Torres et al., 2007) UTIs are infections typically caused by bacteria in the bladder (i.e. cystitis) and 50 to 75% of patients with ADPKD experience cystitis at some point in time with progression up the ureters into the kidneys if left untreated.(Grantham, 2008a; M.C. Hogan et al., 2018) There is an association between frequent UTI, worsening kidney function, and advancing age, but not with TKV.(Grantham, 2008a; Milutinovic et al., 1984; Multinovic et al., 1990) Approximately 41 to 46% of individuals with ADPKD report ≥1 episode of UTI with a frequency that is significantly higher in females than in males.(Bajwa et al., 2001; Milutinovic et al., 1984; Multinovic et al., 1990)

The incidence of acute infection of the kidney parenchyma (i.e., pyelonephritis) is two times higher among individuals with PKD-1 compared to PKD-2.(Hateboer et al., 1999) MRI and CT scans can be used to identify complicated cysts suspected of infection (i.e., pyocyst), but this can be challenging among those with many cysts and given imaging results are not specific for detection of infection.(Gimpel et al., 2019; Martinez & Grantham, 1995; Vicente E. Torres et al., 2007) Blood and urine cultures are used to confirm infection, but cultures may be negative, and laparoscopic or surgical aspiration of cysts is considered when imaging suggests the presence of a cyst infection; sclerosing agents may be injected to damage the epithelial lining of the cyst to prevent reaccumulating fluid or infection.(M.C. Hogan et al., 2018; Martinez & Grantham, 1995; Vicente E. Torres et al., 2007) The cultures may be negative because cysts do not communicate with the urinary tract for detection, which leads to a high failure rate in the treatment of cyst infections among patients living with ADPKD.(A. B. Chapman et al., 2015; Gimpel et al., 2019; M.C. Hogan et al., 2018) Cyst infections typically require long-term use (i.e., at least 6 weeks) of antibiotics and the infection is likely to recur if sclerosing agents are not used.(A. B. Chapman et al., 2015; Gimpel et al., 2019; M.C. Hogan et al., 2018)

Patients living with ADPKD are at an increased risk of kidney stones (i.e., nephrolithiasis), which occur 5 to 10 times more often for patients living with ADPKD compared to the general population; the prevalence of kidney stones is an estimated 8 to 36%.(M. C. Hogan et al., 2023) In ADPKD, kidney stones tend to occur bilaterally and are caused by reduced ammonia excretion, low urinary pH, low urinary citrate concentration, and urinary stasis secondary to structural abnormalities.(M. C. Hogan et al., 2023; Levine & Grantham, 1992; Martinez & Grantham, 1995; Milutinovic et al., 1984; Vicente E. Torres et al., 2007) Kidney

stones are most commonly caused by structural abnormalities because the enlarged cysts block the urinary tubules, thus, preventing normal drainage and causing crystal formation.(Grantham, 2008a) Incidence of kidney stones is associated with a prior history of UTI, acute pyelonephritis, cystitis, and flank pain; it has been observed higher among those with a higher number of cysts of larger size, greater TKV, and worse kidney function.(Bajwa et al., 2001; M. C. Hogan et al., 2023; Levine & Grantham, 1992) Potassium citrate causes three types of stones in ADPKD: uric acid stones, hypocitraturic calcium oxalate nephrolithiasis, and distal acidification defects.(M.C. Hogan et al., 2018) Uric acid (57%) or calcium oxalate (47%) stones are reported among 11 to 50% of adults with ADPKD who typically experience an average of 2 stones ranging from 3 to 20 mm in size.(Badani et al., 2004; Bajwa et al., 2001; Levine & Grantham, 1992; Martinez & Grantham, 1995) Hematuria occurs in approximately 45% of those with kidney stones and extracorporeal shock wave lithotripsy or surgical extraction (i.e., percutaneous nephrolithotomy) is required in about 20% of cases.(A. B. Chapman et al., 2015; M.C. Hogan et al., 2018; Levine & Grantham, 1992; Martinez & Grantham, 1995)

Hematuria is very common and it's an identified predictor of ADPKD progression to kidney failure.(C. M. Blanchette, C. Craver, et al., 2015; C. M. Blanchette, C. Liang, et al., 2015; C.M. Blanchette et al., 2015; Boucher & Sandford, 2004; A. B. Chapman, 2008; J. J. Grantham et al., 2006; M.C. Hogan et al., 2018) More than half of patients with ADPKD experience hematuria at some point in their journey, but it is more common among those with higher TKV and HTN.(Grantham, 2008a) Causes of hematuria include rupture of cysts or small blood vessels around cysts, kidney or bladder infections, and kidney stones.(Grantham, 2008a) Approximately 43 to 90% of patients living with ADPKD experience cyst bleeding

and microscopic or gross hematuria.(Badani et al., 2004; Bajwa et al., 2001; Grantham, 2008a; Vicente E. Torres et al., 2007)

Gross hematuria prompts 19 to 35% of patients living with ADPKD to seek medical care and those with PKD-1 experience significantly more episodes of gross hematuria compared to those with PKD-2.(Badani et al., 2004; P.A. Gabow, 1993; Hateboer et al., 1999) Initial episodes of gross hematuria tend to occur at a mean age of 30 years old and incidence before the age of 30 to 35 years old is associated with reduced kidney survival.(Bajwa et al., 2001; P. A. Gabow, Duley, & Johnson, 1992; Gimpel et al., 2019) Gross hematuria is reported in approximately 5 to 15% of children with ADPKD and 10% report an initial episode before the age of 16 years old.(P. A. Gabow et al., 1992; Gimpel et al., 2019) Approximately 39 to 42% of adults with ADPKD experience ≥1 episode(s) of gross hematuria with frequency primarily driven by age, presence of HTN, and TKV.(Bajwa et al., 2001; P.A. Gabow, 1993; P. A. Gabow et al., 1992; Martinez & Grantham, 1995; Milutinovic et al., 1984) Gross hematuria tends to last 2 to 7 days and is rarely massive enough to require a blood transfusion.(Bajwa et al., 2001; A. B. Chapman et al., 2015; P. A. Gabow et al., 1992; Martinez & Grantham, 1995; Milutinovic et al., 1984) Approximately 62% of patients with ADPKD report gross hematuria following precipitating events, such as UTI, kidney stones, cyst ruptures, strenuous physical activity, or injury.(P.A. Gabow, 1993; P. A. Gabow et al., 1992; Martinez & Grantham, 1995; Milutinovic et al., 1984)

Chronic flank and abdominal pain persisting for more than 4 to 6 weeks is also a common reason patients present to the doctor for care; patients living with ADPKD and experiencing flank pain have reported reduced health-related quality of life (HRQoL) with reduced physical functioning and sleep.(Casteleijn et al., 2014; M. C. Hogan et al., 2023; M.C. Hogan

et al., 2018; Winterbottom et al., 2022) The majority of patients living with ADPKD (70%) experience more than one source of pain compared to only 18% reporting one focus of pain.(Bajwa et al., 2004) Approximately 50 to 60% of adults with ADPKD frequently report back, flank, or abdominal pain that can be mild to moderate, but may be severe and disabling depending on the underlying cause (i.e., cyst infection or rupture vs. kidney stones).(Bajwa et al., 2001; Casteleijn et al., 2014; P.A. Gabow, 1993; Martinez & Grantham, 1995; Milutinovic et al., 1984; Taylor et al., 2005; Vicente E. Torres et al., 2007) Acute pain can occur among individuals with ADPKD due to UTI (i.e., pyelonephritis or cystitis), cyst hemorrhage, cyst abscess caused by infection, cyst ruptures, and passage of kidney stones or urinary obstruction.(Badani et al., 2004; Bajwa et al., 2001; Casteleijn et al., 2014; P.A. Gabow, 1993; Vicente E. Torres et al., 2007) Abdominal pain is reported in 10 to 20% of children with ADPKD.(Gimpel et al., 2019; Taylor et al., 2005) Furthermore, back or abdominal pain has been reported to occur among 32% of patients living with ADPKD and also experiencing hematuria.(Bajwa et al., 2004)

Chronic flank pain is associated with advancing age and progressive TKV, but not the level of kidney function given severe pain has been observed across all CKD stages. (Bajwa et al., 2001; Milutinovic et al., 1984; Taylor et al., 2005; Vicente E. Torres et al., 2007) Pain is a persisting issue for patients living with ADPKD and it's a reminder of their physical health status as the disease progresses and even following RRT; 59% of patients with ADPKD who have received dialysis and 44% of patients with ADPKD who have received a KTP report pain.(M. C. Hogan et al., 2023) Pain imposes a mental burden that may lead to depression as observed in 22 to 60% of patients living with ADPKD.(Casteleijn et al., 2014; M. C. Hogan et al., 2023) Whether acute or chronic, the pain can be intermittent and mild

requiring occasional over-the-counter pain medication like acetaminophen or it can be constant and severe in some patients with progressive disease requiring prescription medications, cyst aspiration, or surgical nephrectomy of one the native polycystic kidneys.(Casteleijn et al., 2014; M.C. Hogan et al., 2018; Vicente E. Torres et al., 2007)

Bed rest and a stepwise approach in the use of analgesic therapies (i.e., acetaminophen, non-steroidal anti-inflammatory drugs [NSAIDs], and opioids) are recommended for patients with acute and severe pain.(Casteleijn et al., 2014; M.C. Hogan et al., 2018) Chronic and high-dose use of NSAIDs should be avoided in the treatment approach for managing pain symptoms among patients living with ADPKD due to the potential adverse effects on the kidneys.(Casteleijn et al., 2014; Gimpel et al., 2019; M.C. Hogan et al., 2018) Chronic and high-dose opioids should also be avoided because of an increased risk of opioid dependence or abuse.(Casteleijn et al., 2014; Martinez & Grantham, 1995) Increased cyst volume or TKV has been validated as the primary cause of severe pain, but 80% and 62% of individuals having surgical decompression or aspiration of cysts are pain-free within one year and two years of the procedure, respectively.(Casteleijn et al., 2014; P.A. Gabow, 1993; M. C. Hogan et al., 2023; Martinez & Grantham, 1995) If sclerosing agents are not used to eliminate the epithelial lining of the drained cysts, the pain is often likely to recur as the cysts reaccumulate fluid. (Casteleijn et al., 2014; P.A. Gabow, 1993; M. C. Hogan et al., 2023; Martinez & Grantham, 1995; Vicente E. Torres et al., 2007) Furthermore, increased abdominal girth due to enlarged cysts causes increased lumbar lordosis and/or pelvic shifts over time, which lead to hypertrophy of the lumbodorsal muscles and degenerative spine/disc diseases causing more pain for patients living with ADPKD.(Bajwa et al., 2001)

Surgical native nephrectomy (NN) before KTP is generally not performed unless the patient has a history of persistent or recurrent cyst infections, severe gross hematuria, cancer, the cystic kidneys are too large for a new graft to be transplanted, and/or the cystic kidneys are causing excessive pain due to their size.(Alam & Perrone, 2010; A. B. Chapman et al., 2015; M.C. Hogan et al., 2018; Martinez & Grantham, 1995; Polycystic Kidney Disease Foundation, 2018) Patients with ADPKD and receiving NN before KTP is associated with significant morbidity and mortality, so it is only done in cases where the risk of leaving polycystic kidneys in place outweighs the benefits.(A. B. Chapman et al., 2015) Simultaneous NN and KTP or staged NN following KTP have also been reported, but there is no evidence of better outcomes in terms of the timing of the NN and incidence of complications of either the native kidneys or the transplanted graft.(Alam & Perrone, 2010; A. B. Chapman et al., 2015; Maxeiner et al., 2019) However, there is evidence showing a 9 to 24% decrease in TKV of native polycystic kidneys following KTP, so complications of the native kidneys may be reduced and NN may not be necessary in most cases.(Alam & Perrone, 2010; Kanaan, Devuyst, & Pirson, 2014)

2.3.4 Gastrointestinal Complications

Hepatic cysts have been estimated to occur in 60 to 83% of individuals diagnosed with ADPKD, affecting more females (85%) than males (79%) and older adults (94% >35, 40% 50 to 59, and 57 to 75% ≥60 years old).(Bae et al., 2006; Boucher & Sandford, 2004; Chauveau et al., 1994; P.A. Gabow, 1993; M. C. Hogan et al., 2023; Multinovic et al., 1990; Nicolau et al., 2000) The prevalence of hepatic cysts has been determined directly related to TKV and kidney cyst volume.(Bae et al., 2006; Boucher & Sandford, 2004; P. A. Gabow, Johnson, et al., 1990; M. C. Hogan et al., 2023; Nicolau et al., 2000) The number and size of hepatic cysts is

associated with the age and severity of kidney disease, particularly ESRD.(Boucher & Sandford, 2004; Martinez & Grantham, 1995; Multinovic et al., 1990) Approximately 92% of individuals with ADPKD and comorbid ESRD and/or receiving RRT have hepatic cysts compared to only 48% of those with normal kidney function.(Nicolau et al., 2000) The majority of patients with ADPKD and comorbid polycystic liver disease (PLD) are asymptomatic and do not require treatment, but those with severe PLD typically present to the doctor with heartburn, reflux, nausea, dyspnea, early satiety, and/or increased abdominal girth.(M. C. Hogan et al., 2023; M.C. Hogan et al., 2018)

Hepatic cysts are associated with pregnancy among females with ADPKD; 90% with hepatic cysts report pregnancy compared to 63% without hepatic cysts.(A. B. Chapman et al., 2015; P.A. Gabow, 1993; P. A. Gabow, Johnson, et al., 1990; M. C. Hogan et al., 2023; Martinez & Grantham, 1995) Females with ADPKD who report multiple pregnancies or the use of oral contraceptive drugs or estrogen replacement therapies have more hepatic cysts of larger size.(A. B. Chapman et al., 2015; P.A. Gabow, 1993; P. A. Gabow, Johnson, et al., 1990; M. C. Hogan et al., 2023; Martinez & Grantham, 1995; Vicente E. Torres et al., 2007) Pancreatic cysts have been found to occur in 15 to 23% of individuals diagnosed with ADPKD and prevalence is higher among females.(Boucher & Sandford, 2004; M. C. Hogan et al., 2023; Nicolau et al., 2000; Vicente E. Torres et al., 2007) However, no relationship has been found between TKV and the size of pancreatic cysts.(Nicolau et al., 2000)

2.3.5 Proteinuria and Albuminuria

Proteinuria is a biomarker of CKD progression that occurs in patients living with ADPKD and advanced stages of CKD; 14 to 20% of children, 18 to 34% of adults, and 70 to 80% with progressive disease.(A. B. Chapman et al., 2015; A.B. Chapman, Johnson, Gabow, &

Schrier, 1994; P.A. Gabow, 1993; Gimpel et al., 2019) The mean (standard deviation [SD]) 24-hour urinary protein excretion rate has been reported as 259 (22) mg/day, ranging from 7 to 2,049 mg/day, among patients living with ADPKD and even 82% of normotensive individuals with preserved kidney function have <300 mg/day of proteinuria.(A.B. Chapman et al., 1994) Men with ADPKD tend to have higher levels of proteinuria compared to women and other key factors significantly associated with proteinuria include reduced creatinine clearance, higher MAP, higher kidney volume corrected for body surface area, presence of hematuria, and older age.(A. B. Chapman et al., 2015; A.B. Chapman et al., 1994) Proteinuria is also an indicator of end-organ damage other than ESRD, including arteriosclerosis and LVH, thus, it's significantly associated with an increased risk of cardiovascular mortality among patients living with ADPKD.(A.B. Chapman et al., 1994; Martinez & Grantham, 1995; Masoumi, Reed-Gitomer, Kelleher, Bekheirnia, & Schrier, 2008) Albuminuria is a measure of urinary albumin excretion that serves as a prognostic indicator of future loss of kidney function and an indicator of an increased risk of cardiovascular mortality among patients living with ADPKD.(A.B. Chapman et al., 1994; Testa & Magistroni, 2020) Approximately 41% of individuals with hypertensive ADPKD and LVH experience albuminuria, which is consistent with the incidence observed among individuals with essential HTN with or without LVH (30 to 45%).(A.B. Chapman et al., 1994) Individuals with hypertensive ADPKD and albuminuria have higher MAP, TKV, and filtration fractions compared to those without albuminuria.(A.B. Chapman et al., 1994)

2.3.6 Anemia Due to Chronic Kidney Disease

The World Health Organization (WHO) defines anemia among adults as <12 g/dL for non-pregnant women and <13 g/dL in men.(Palaka, Grandy, van Haalen, McEwan, & Darlington,

2020) Anemia is a common complication of CKD with increased prevalence as eGFR declines.(Stauffer & Fan, 2014; Webster, Nagler, Morton, & Masson, 2017; Wong et al., 2020) The kidney's ability to produce erythropoietin (EPO) is compromised with progressing kidney damage, which results in reduced red blood cell (RBC) production and hemoglobin (Hgb) concentration.(Webster et al., 2017) The GBD study determined that 8% of the CKD population were anemic, but it has been found as high as 15% among CKD patients in the US.(G. B. D. Chronic Kidney Disease Collaboration, 2020; Stauffer & Fan, 2014) In 2020, the USRDS reported approximately 63% of all ESRD beneficiaries receiving dialysis (87% HD and 80% PD) had anemia with Hgb concentrations ≤11.9 g/dL.(United States Renal Data System, 2022a) RBC transfusions occurred in 23% of all dialysis beneficiaries with nearly 9% having ≥2 transfusion events a year.(United States Renal Data System, 2022a) Individuals with anemia due to CKD experience reduced QoL, increased incidence of cardiovascular events, higher rates of hospitalization, cognitive impairment, and mortality.(Babitt & Lin, 2010; Webster et al., 2017)

Anemia due to CKD is treated using oral or intravenous (IV) iron, recombinant EPO, and synthetic derivatives called erythropoietin stimulating agents (ESA) (i.e., epoetin alfa, epoetin beta, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta).(Webster et al., 2017) Collectively, these treatments reduce the need for RBC transfusion.(Webster et al., 2017) The use of ESA to target high Hgb levels (12.0 – 15.0 g/dL) is associated with an increased risk of stroke, HTN, and vascular access thrombosis compared to lower Hgb targets (9.5 – 11.5 g/dL).(Webster et al., 2017) Iron deficiency limits response to ESA, so IV iron is used to reduce ESA requirement and achieve a greater increase in Hgb concentration without an increased risk of all-cause death.(Webster et al., 2017)

Approximately 75% of all beneficiaries receiving dialysis (77% HD and 59% PD) received an ESA (i.e., epoetin alfa, darbepoetin alfa, pegylated epoetin beta) each month.(United States Renal Data System, 2021) Approximately 61% of all beneficiaries receiving dialysis (64% HD and 39% PD) received oral or IV iron each month, but IV iron is the preferred route of administration (RoA) in dialysis patients.(United States Renal Data System, 2021) Patients with ADPKD and ESRD have been found to have higher Hgb levels compared to non-ADPKD controls.(Alam & Perrone, 2010; A. B. Chapman et al., 2015) This is because patients with ADPKD have higher endogenous EPO levels produced by interstitial cells of the cyst wall, which have been detected in the renal cyst fluid of nephrectomized polycystic kidneys and it may explain their improvement in cardiovascular outcomes throughout ESRD compared to controls.(Alam & Perrone, 2010) Patients with ADPKD and experiencing gross hematuria are likely to develop anemia and require RBC transfusion, which leads to sensitization that may impact their candidacy for a KTP.(Alam & Perrone, 2010) Approximately 16% of beneficiaries diagnosed with cystic kidney disease have been reported as treated with an ESA, but this estimate was not exclusively representative of ADPKD.(United States Renal Data System, 2021)

2.3.7 ESRD

ADPKD accounts for approximately 5 to 10% of patients diagnosed with ESRD in the US and Europe.(Alam & Perrone, 2010; Amro & Perrone, 2015; K. Rangan et al., 2020) The one-year mortality rate is much lower for patients living with ADPKD and ESRD compared to the general non-diabetic ESRD population (6% vs. 24%, respectively) in the US.(Alam & Perrone, 2010; Amro & Perrone, 2015) The lower one-year mortality rate is likely due to patients with ADPKD and receiving dialysis having a higher KTP rate within the first year

of initiating dialysis compared to the total incident ESRD population (25% vs. 5%, respectively) in the US.(Alam & Perrone, 2010) Additional details on the progression of ADPKD to ESRD, the dialysis and KTP processes, and associated outcomes among patients living with ADPKD can be found in Section 2.4 below.

2.4 Monitoring Progression to ESRD and Standards of Care

The rate of ADPKD progression is widely variable and dependent on genetic (i.e., PKD-1 vs. PKD-2) and non-genetic treatable factors (i.e., HTN, kidney stones, proteinuria) previously discussed in the etiology and pathophysiology review sections of this dissertation.(Grantham & Torres, 2016; Ozkok et al., 2013) TKV and age are the most commonly reported prognostic indicators of a faster rate of ADPKD progression to ESRD; kidney enlargement over time is a surrogate marker for ADPKD progression considering total cyst volume, per kidney volume, and TKV.(Woon, Bielinski-Bradbury, O'Reilly, & Robinson, 2015) Adult patients with ADPKD experience an average 5 to 6% increase in TKV per year.(A. B. Chapman et al., 2015) Substantial kidney enlargement and reductions in renal blood flow may occur among ADPKD patients before a decline in kidney function (i.e., eGFR) is observed.(A. B. Chapman, 2008; A. B. Chapman et al., 2015; Grantham, 2015; Woon et al., 2015) Once a decline in kidney function occurs, a universal rapid decline in kidney function of approximately 5.9 ml/min/year is observed among patients with ADPKD.(A. B. Chapman, 2008)

Analysis of the CRISP cohort and pooled registry data identifies height-adjusted TKV (htTKV) as a predictor of eGFR decline and ADPKD progression to ESRD; the rate of change in htTKV was found negatively correlated with the slope of the eGFR.(A. B. Chapman et al., 2003; Shukoor et al., 2021; Yu et al., 2018) Specifically, the CRISP cohort

study qualified htTKV as a prognostic biomarker of disease progression among patients with ADPKD with a baseline htTKV of at least 600 cc/m being associated with the development of renal insufficiency (i.e., CKD stage 3 [eGFR of <60 ml/min]) within 8 years of follow-up.(A. B. Chapman et al., 2012; A. B. Chapman et al., 2003; Grantham, 2015) In combination with age and eGFR, baseline htTKV is a strong prognostic biomarker where larger baseline htTKV among younger patients with preserved eGFR at diagnosis is associated with worse outcomes, such as more rapid increases in htTKV and declines in kidney function to ESRD.(A. B. Chapman et al., 2012; A. B. Chapman et al., 2003; J.J. Grantham et al., 2006; Perrone et al., 2017)

Differences in htTKV and development of ESRD among patients with PKD-1 vs. PKD-2 are best explained by cystogenesis, the total number of cysts developed, rather than the moderate rate of cyst expansion that is typically observed.(A. B. Chapman, 2008; Grantham, 2015) The PKD-1 mutation, male sex, presence of HTN, and reduced renal blood flow are strongly associated with rapid cyst growth and eGFR decline because more cysts develop (i.e., higher total cyst number) at any given age and earlier in the course of the disease, so their htTKV is larger at any given point in time.(Bae et al., 2019; A. B. Chapman, 2008; Fick-Brosnahan, Belz, McFann, Johnson, & Schrier, 2002; J.J. Grantham et al., 2006; Harris et al., 2006; Perrone et al., 2017; Shukoor et al., 2021; Woon et al., 2015) Shukoor et al. (2021) conducted a cross-sectional analysis of patients with ADPKD and found htTKV at the time of ESRD is negatively correlated with age and highly impacted by sex as determined by smaller htTKV observed among those of older age (i.e., 12.3% smaller with each decade of age) and female. Macrovascular disease was also found associated with smaller htTKV among females at ESRD diagnosis; the slower cyst growth indicates other age-related factors, such

as renal vascular remodeling, may have contributed to their progression as they aged.(Shukoor et al., 2021)

Reductions in TKV and eGFR declines are also leveraged as indicators of treatment efficacy for existing standards of care (SoC). Existing SoC are summarized below and include anti-hypertensives for rigorous blood pressure control and JYNARQUE® (tolvaptan) for reducing or maintaining TKV in the prevention of ADPKD progression to ESRD. There are several emerging treatments, including at least eight small molecule drugs (i.e., lixivaptan, tesevatinib, venglustat, bardoxolone, pravastatin, hydralazine, pioglitazone, metformin), currently under investigation for their impact on ADPKD progression to ESRD; a detailed review of these alternatives was not conducted.(K. Rangan et al., 2020) RRT (i.e., dialysis and KTP) becomes part of the SoC once patients with ADPKD approach ESRD diagnosis. A detailed review of the RRT processes and outcomes is provided below in Section 2.4.3 Dialysis and Section 2.4.4 KTP.

2.4.1 Blood Pressure Control

Partial inhibition of the RAAS via ACE-I and ARB has been shown to reduce proteinuria and significantly improve kidney survival among patients with CKD.(Gimpel et al., 2019) Improved disease awareness and significant increases in the use of ACE-I among patients with ADPKD and HTN has resulted in lower diastolic pressure and MAP for longer mean and median survival times for ESRD. (Schrier et al., 2003) Short-term management of HTN using ACE-I among patients with ADPKD has shown to relatively improve renal blood flow compared to patients with essential HTN, thus, RAAS inhibition using ACE-I plays a reno-protective role in ADPKD.(A. B. Chapman, 2008) Treatment of HTN among patients with ADPKD aims to achieve a blood pressure target of 110/75 for high-risk patients with

preserved kidney function and 120/80 for patients with kidney decline.(M. C. Hogan et al., 2023)

The Halt Progression of Polycystic Kidney Disease (HALT-PKD) trial compared rigorous and standard blood pressure control in patients with early ADPKD and found the annual percentage increase in TKV and risk of cardiovascular complications were lower among those with rigorous blood pressure control (i.e., higher dosage and frequency of medication).(M.C. Hogan et al., 2018; Schrier et al., 2014; V. E. Torres et al., 2014) The rate of TKV growth was slowed and the rate of eGFR decline marginally diminished for those receiving rigorous blood pressure control (i.e., blood pressure target of 95/60 mmHg to 110/75 mmHg) compared to those receiving standard blood-pressure control (i.e., blood pressure target of 120/70 mm Hg to 130/80 mm Hg) and it was independent of whether ACE-I or ARB were used.(A. B. Chapman et al., 2015; Grantham & Torres, 2016; Schrier et al., 2014; V. E. Torres et al., 2014) While the RAAS was previously discussed as one of the mechanisms driving the progression of TKV and subsequent declines in eGFR among patients diagnosed with ADPKD, the rates of change in eGFR for patients with standard vs. rigorous blood pressure control were similar.(A. B. Chapman et al., 2010; M.C. Hogan et al., 2018; Schrier et al., 2014) Rigorous inhibition of the RAAS was also found to decrease albuminuria and LVMI among patients with early ADPKD.(A. B. Chapman et al., 2015; Schrier et al., 2014) The HALT-PKD trial among patients with late ADPKD confirmed ACE-I monotherapy as an effective first-line approach in controlling blood pressure for those with advanced disease; combination therapy with ACE-I and ARB was found to have no impact on the decline in eGFR.(A. B. Chapman et al., 2015; M.C. Hogan et al., 2018; V. E. Torres et al., 2014) While the HALT-PKD trials emphasized the need for early detection

and management of HTN among patients living with ADPKD to achieve better long-term renal outcomes, novel treatments with different mechanisms of action are also needed to slow their rate of TKV expansion and rate of eGFR decline to ESRD.(A. B. Chapman et al., 2015)

2.4.2 Reduce or Maintain TKV

Animal models have demonstrated cyst growth occurs due to arginine vasopressin via its second cyclic adenosine monophosphate (cAMP) messenger, a proliferative stimulus causing secretion of fluid into the cyst by the cystic fibrosis transmembrane conductance regulator chloride channel.(Grantham, 2015; Testa & Magistroni, 2020) In 2018, JYNARQUE® (tolvaptan) was approved for the treatment of patients living with ADPKD in the US; it is a vasopressin V_2 receptor antagonist that lowers cAMP concentrations in the distal nephrons and collecting ducts of the kidneys, the major site of cyst development in ADPKD.(Grantham, 2015; M.C. Hogan et al., 2018; K. Rangan et al., 2020) Tolvaptan is indicated for use in adults at risk of rapidly progressing ADPKD (i.e., PKD-1 mutation) to delay the time to ESRD and reduce ADPKD-related pain.(Gimpel et al., 2019; Otsuka America Pharmaceuticals, 2024)

Several trials have assessed the efficacy and safety of tolvaptan in delaying the progression of TKV and eGFR to ESRD among patients with early and late ADPKD. In Tolvaptan Efficacy and Safety in Management of ADPKD and Its Outcomes (TEMPO) 3:4 trial, tolvaptan slowed the rise in TKV by up to 50% and decline in kidney function by up to 31% over 3 years in patients with ADPKD CKD stages 1-3 compared to placebo, but it was associated with a higher discontinuation rate due to adverse events.(Baur & Meaney, 2014; Blair & Keating, 2015; A. B. Chapman et al., 2015; Grantham, 2015; Grantham & Torres,

2016; M.C. Hogan et al., 2018; Mahnensmith, 2014; Testa & Magistroni, 2020; V. E. Torres et al., 2012) Post-hoc analyses of TEMPO 3:4 patients showed that tolvaptan prevents increases in TKV for patients with ADPKD across all stages of CKD; the largest reductions in TKV were observed within the first year of treatment followed by subsequent significant reductions at years three and five of treatment.(Testa & Magistroni, 2020; Zhou et al., 2022) The TEMPO 4:4 trial provided an additional 2 years of data on the long-term safety and efficacy of tolvaptan in subjects completing TEMPO 3:4 and it showed the disease-modifying effect that tolvaptan has on eGFR.(K. Rangan et al., 2020; V. E. Torres et al., 2018) A longitudinal matched analysis confirmed the long-term treatment effect of tolvaptan on the decline in kidney function; tolvaptan slowed annualized eGFR decline by 1.01 ml/min per 1.73 m^2 compared to SoC across 5.5 years.(Zhou et al., 2022) Furthermore, the Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) trial was an exploration of the safety and efficacy of tolvaptan in patients with later-stage ADPKD (i.e. CKD stage 3-4), which found tolvaptan resulted in slower annual decline in eGFR compared to placebo, but it was found less effective among older patients.(Testa & Magistroni, 2020; V. E. Torres et al., 2017)

Collectively, these trials and follow-up analyses demonstrate the reliability of tolvaptan in reducing the burden of ADPKD by delaying the progression of ADPKD to comorbid ESRD. However, there are disadvantages in the use of tolvaptan, including liver toxicity or acute liver failure observed via elevation in liver enzymes (i.e., alanine aminotransferase [ALT]) and polyuria that affects patients activities of daily living and sleep routines.(Gimpel et al., 2019; M.C. Hogan et al., 2018; Testa & Magistroni, 2020; Watkins et al., 2015) Therefore, tolvaptan is only available to patients through the JYNARQUE® Risk

Evaluation and Mitigation Strategy (REMS) Program.(Otsuka America Pharmaceuticals, 2024) Blood work is assessed before beginning tolvaptan, within 2-4 weeks after initiating, and then once a month to every three months when taking the medication for 18 months or longer; patients are taken off treatment if liver toxicity becomes a complication of treatment.(Otsuka America Pharmaceuticals, 2024; Watkins et al., 2015)

The ADPKD Outcomes Model (ADPKD-OM) found greater long-term effectiveness of tolvaptan in delaying ADPKD progression to ESRD among those with early CKD (i.e., stages 1-3) and evidence of rapid progression, which aligns with results from the TEMPO 3:4 trial.(Bennett, McEwan, Hamilton, & O'Reilly, 2019) However, it means not all patients living with ADPKD are candidates for tolvaptan treatment, thus, the unmet need for innovate treatments that prevent ADPKD progression to ESRD persists.

2.4.3 Dialysis for ESRD

Dialysis is the clinical process of blood purification as a substitute for normal kidney function that aims to remove harmful, excess cellular waste, salt, and fluids from the body.(Bernard, 2021; Centers for Medicare and Medicaid Services, 2017) There are two types of dialysis available for patients diagnosed with ESRD, including hemodialysis (HD) and peritoneal dialysis (PD).(Bernard, 2021; Centers for Medicare and Medicaid Services, 2017) There are two metrics HCPs use to monitor dialysis effectiveness, the urea reduction ratio (URR) and (Kt/V) urea. The URR is the quantity of BUN removed during a dialysis session and Kt/V is the volume of urea completely cleared within a dialysis session per the total body water.(Bernard, 2021; Centers for Medicare and Medicaid Services, 2017) Dialysis prescription/modality may be changed if the minimum URR of 65% and a Kt/V of 1.2 are

not being met for adequate dialysis.(Bernard, 2021; Centers for Medicare and Medicaid Services, 2017)

HD is a 3 to 4-hour process that leverages a special filter, called a dialyzer, connected to a machine to remove cellular waste, excess salts, and liquids from the blood at least 3 to 4 days a week; the blood flows through tubes into the dialyzer and then cleansed blood flows through another set of tubes back into the body.(Bernard, 2021; Centers for Medicare and Medicaid Services, 2017) The entry point of blood removal and return to the body is either an arteriovenous (AV) fistula, AV graft, or a central venous catheter (CVC).(Bernard, 2021) An AV fistula joins a vein to an artery in the forearm to create a strong site for HD treatment, but it requires a few months to mature into a useful site for HD.(Bernard, 2021) An AV graft is done for patients whose veins are too small and likely won't mature into a working fistula, so a synthetic, durable tube is implanted to provide a useful site for HD.(Bernard, 2021) CVCs are used in urgent cases or when an AV fistula or graft is not possible; it is implanted into a large vein in either the neck, chest, or groin.(Bernard, 2021) CVC imposes a greater risk of infection, but it has a shorter time to maturation (i.e., one week) compared to months of maturation needed for AV fistula/graft.(Bernard, 2021) The CVC is capped with an antibacterial solution between dialysis sessions to lower the patient's risk of developing sepsis.(Alam & Perrone, 2010; Amro & Perrone, 2015; Bernard, 2021; M.C. Hogan et al., 2018) HD imposes vascular access challenges, risk of sepsis, hypotension, and cardiac complications, as well as requiring frequent transportation or travel to dialysis centers.(Bernard, 2021) HD causes fluctuations in blood pressure and volume, which is harder on the patient's heart and, thus, they are at increased risk of cardiovascular mortality because of HD treatment.(Bernard, 2021)

Dialysate is a special solution used in PD to extract waste from the blood and it can be changed to adjust filtration; a more dilute dialysate pulls out more waste while a richer dialysate pulls out less waste.(Bernard, 2021; Centers for Medicare and Medicaid Services, 2017) PD is a process in which the dialysate is infused through a permanent peritoneal catheter placed into the peritoneum, through the skin of the abdomen beneath the umbilicus and extending down into the pubic floor of the abdominal cavity, for uptake of cellular waste, excess salts, and fluids across the peritoneal membrane.(Bernard, 2021; Centers for Medicare and Medicaid Services, 2017) There are two types of PD, including continuous ambulatory and automated. Continuous ambulatory PD is not common because it is round the clock (24/7) treatment, but it is leveraged in cases where the patient has kidney failure in the hospital and they are not a good candidate for HD because of pre-existing cardiovascular morbidity and/or complications.(Bernard, 2021) Automated PD is more common because it's done at home via 3 to 4 nightly cycles (45 minutes to 2 hours apart) and minimizes interruption in the patients' daytime schedules.(Bernard, 2021) PD patients aren't required to travel to dialysis centers because the treatment is conveniently administered at home or while traveling, but there is a risk of peritonitis and the potential for social isolation if at home.(Bernard, 2021) PD is also easier on the patient's body systemically, it provides better blood pressure control, reduces the risk of anemia, and preserves kidney function.(Bernard, 2021) While nurse or caregiver oversight is not required for PD, patients/caregivers are required to complete training before undergoing home PD treatment and that may be a challenge for some.(Bernard, 2021)

HD is more commonly elected and most patients elect to undergo in-center HD as opposed to home HD given the added benefit of nursing oversight in case there are

complications.(Bernard, 2021) HD is preferred over PD in patients with ADPKD because large kidney sizes do not permit adequate volumes of dialysis fluid instills and the risk of peritonitis and inguinal or umbilical hernias is increased.(Alam & Perrone, 2010; Amro & Perrone, 2015; M.C. Hogan et al., 2018) Analyses of ADPKD patients receiving PD have revealed no difference in patient survival, risk of PD technique failure, or rates of peritonitis compared to non-ADPKD patients receiving PD.(Alam & Perrone, 2010; Boonpheng et al., 2019; Zhang, Dou, Wang, Li, & Cao, 2018) The United States Renal Data System (USRDS) data revealed a higher adjusted risk of mortality among patients with ADPKD and receiving HD as compared to those receiving PD, but recent evidence suggests there is no difference in all-cause mortality between ADPKD patients receiving HD vs. PD.(Alam & Perrone, 2010; Zhang et al., 2018) Therefore, there is value in more patients with ADPKD electing to undergo PD.

2.4.4 KTP for ESRD

While dialysis prolongs life for those with ESRD, KTP surgery is the preferred therapeutic option for all patients. (Centers for Medicare and Medicaid Services, 2017; Spithoven et al., 2014) However, there are challenges in terms of donor organ availability (living vs. deceased kidney donors) and donor-recipient matching that delay or prevent KTP regardless of the underlying cause of the ESRD. Patients with ADPKD tend to have better outcomes following KTP compared to the general KTP population.(Alam & Perrone, 2010) Patients with ADPKD typically consider KTP as their GFR approaches 20 (i.e., CKD stage 4), but KTP wait time doesn't begin accumulating until GFR is ≤20 mL/min.(Polycystic Kidney Disease Foundation, 2018) Early transplant listing before dialysis, also known as pre-emptive KTP, through living kidney donation is ideal for patients living with ADPKD due

to the progressive nature of the disease and the complex manner in which kidneys are evaluated and then allocated among those in need.(Alam & Perrone, 2010; A. B. Chapman et al., 2015; Polycystic Kidney Disease Foundation, 2018; The American Association of Kidney Patients, 2018) The KTP process is complex and includes the following: physical evaluation for KTP by the transplant center medical team, registration on the national organ transplant waiting list at a single or multiple transplant center(s) (if accepted as a KTP candidate by the transplant center[s]), organizing a support team (i.e., family and friends) and developing a financial strategy, the waiting period with monthly blood testing and healthy lifestyle habits, undergoing the KTP surgery, and post-KTP care managed by the medical team.(Polycystic Kidney Disease Foundation, 2018; The American Association of Kidney Patients, 2018)

Patients' medical and social history is evaluated along with physical and mental health examinations to identify potential health issues (i.e., heart disease, obesity, and diabetes) or sociodemographic challenges (i.e., history of drug or alcohol abuse, transportation, and housing, level of family and financial support) that interfere with an individual's KTP eligibility or candidacy; social workers or transplant coordinators discuss and help manage logistics concerning physical evaluations, the KTP surgery, and post-surgical care.(Polycystic Kidney Disease Foundation, 2018; The American Association of Kidney Patients, 2018) Several screenings are conducted such as urine and blood tests, imaging tests of chest and abdomen, cancer, and gynecological examinations.(Polycystic Kidney Disease Foundation, 2018) Blood and tissue typing are required to match transplant candidates to a living or deceased donor kidney.(Centers for Medicare and Medicaid Services, 2017; Polycystic Kidney Disease Foundation, 2018) Blood typing is done to assess compatibility: if the

recipient is type A then the donor must be A or O, type B then the donor must be B or O, type AB then the donor can be any blood type (i.e., universal recipient - A, B, AB, or O), or type O then the donor must be O (i.e., universal donor).(Polycystic Kidney Disease Foundation, 2018) Tissue typing is done via human leukocyte antigen (HLA) determination; HLA is a marker on most cells that communicates to the immune system which cells belong to the body and which cells do not.(Polycystic Kidney Disease Foundation, 2018) Crossmatch testing is performed to assess what antibodies are present in the body; antibodies are produced when the immune system attacks foreign substances, such as a kidney graft, detected in the body due to the presence of infection, pregnancy, RBC transfusions, or KTP.(Polycystic Kidney Disease Foundation, 2018) If an individual has antibodies to the donor kidney graft then graft rejection and/or failure are potential outcomes following KTP.(Polycystic Kidney Disease Foundation, 2018)

Once evaluations are completed and the individual is accepted by the transplant center(s) as a KTP candidate, they are registered on the national organ transplant waitlist.(Polycystic Kidney Disease Foundation, 2018; The American Association of Kidney Patients, 2018) There are 200+ transplant centers in the US and patients are encouraged to select one or multiple hospitals based on their needs, including insurance coverage, geographical location, average wait time per center, finances, and support group availability.(Polycystic Kidney Disease Foundation, 2018) Candidates may elect living donor KTP at the time of listing and if a living kidney donor is identified as a match, then evaluations previously mentioned must also be completed by the donor.(Polycystic Kidney Disease Foundation, 2018) Approximately 6,000 organ transplants are completed per year due to living donation and the kidney is the most commonly transplanted organ from living donors.(Polycystic Kidney

Disease Foundation, 2018) There are 3 types of living donor transplantations: directed, non-directed/altruistic, and paired exchange. Directed donation is the most common and is when the donor names a specific person to receive the donated kidney.(Polycystic Kidney Disease Foundation, 2018; The American Association of Kidney Patients, 2018) Altruistic donation is when a specific recipient is not named, but physical compatibility is determined per the blood and tissue typing.(Polycystic Kidney Disease Foundation, 2018; The American Association of Kidney Patients, 2018) Paired exchanged donation involves 2 or more pairs of living kidney donors and transplant candidates without matching blood types; the candidates trade donors for increased compatibility.(Polycystic Kidney Disease Foundation, 2018; The American Association of Kidney Patients, 2018) More KTPs are made possible via paired exchange occurring across different hospitals and geographical locations in the US.(Polycystic Kidney Disease Foundation, 2018)

HCPs take the Hippocratic oath when entering into clinical practice, which essentially is a pledge to "do no harm" to patients in their care. While most KTP come from deceased kidney donors, it is an interesting dynamic in living organ donation, where to save a life surgeons endanger the life of an otherwise healthy individual undergoing surgical nephrectomy for no other reason than kidney donation. The lifetime general population risk of kidney failure is 3%, where 90% of cases were over 44 years old and 50% were over 64 years old.(Steiner, 2016) The risk of kidney failure in the remaining kidney among living kidney donors post-surgery is minimal due to the pre-KTP screening process and the benefits of saving a life are viewed to outweigh the minimal risk to the donor.(Steiner, 2016) However, there is evidence suggesting the incidence of ESRD among living donors in the US is eight times that of nondonor controls, but there is methodological debate regarding

the validity of this predicted risk.(Steiner, 2016) Furthermore, living donation provides advantages to the recipient that deceased donation does not, including the following: optimal timing, better genetic matches that decrease the risk of organ rejection, living donor grafts tend to function immediately after transplantation, and it eliminates or decreases dialysis time and/or years of waiting to find a matched deceased donor kidney.(Polycystic Kidney Disease Foundation, 2018; The American Association of Kidney Patients, 2018)

The process for deceased donation is different and deceased donor kidneys are matched to waiting recipients using a national registry, the Organ Procurement and Transplantation Network (OPTN), that is operated by the United Network for Organ Sharing (UNOS) in the US.(Polycystic Kidney Disease Foundation, 2018) In December 2014, the Kidney Allocation System (KAS) was implemented to give recipients longer function with their transplanted kidney by matching the donated deceased kidney with the longest potential life to the recipient who has the longest potential life with that deceased kidney.(Polycystic Kidney Disease Foundation, 2018) Deceased donor kidneys are allocated using two metrics, the estimated post-transplant survival (EPTS) score for transplant candidates and the kidney donor profile index (KDPI) score for the deceased donor kidney.(Polycystic Kidney Disease Foundation, 2018)

Transplant candidates are assigned an EPTS score, a percentile score of 0 to 100, that is based on how long the candidate will need a functioning kidney compared to others on the waitlist.(Polycystic Kidney Disease Foundation, 2018) The EPTS is determined using a mathematical formula that accounts for diabetes status, current age, dialysis status and duration of dialysis, and prior transplantation (any organ).(Polycystic Kidney Disease Foundation, 2018) Low EPTS scores, such as 20, mean the candidate will need a kidney

longer than 80% of all other candidates on the waitlist and will likely be given priority.(Polycystic Kidney Disease Foundation, 2018) Each deceased kidney is assigned a KDPI score, a percentile score of 0 to 100, that is associated with how long the kidney is likely to function compared to other deceased donor kidneys.(Polycystic Kidney Disease Foundation, 2018) The KDPI score is derived using donor factors, such as age, height, weight, ethnicity, cause of death, HTN status, diabetes status, exposure to hepatitis C, and renal function via serum creatinine levels.(Polycystic Kidney Disease Foundation, 2018) High KDPI scores mean the deceased donor kidney is expected to function for a shorter time compared to other deceased donor kidneys, but these kidneys are best suited for recipients less able to stay on dialysis long-term and need a KTP as soon as possible.(Polycystic Kidney Disease Foundation, 2018)

In deceased kidney donation, geographical location and time to the transplant center(s) are critical. The less time a kidney graft remains outside the deceased donor's body means better functional outcomes for the transplanted graft.(Polycystic Kidney Disease Foundation, 2018; The American Association of Kidney Patients, 2018) An available organ is first offered to the transplant candidate within the local Organ Procurement Organization (OPO) and if the local OPO doesn't find a match, available organs are first offered at transplant centers in a wider area within one of eleven US regions.(Polycystic Kidney Disease Foundation, 2018) If there are no local or regional matches identified, deceased donor kidneys may be offered nationwide to any candidate in the US who is a potential match.(Polycystic Kidney Disease Foundation, 2018) Most patients are listed at a single transplant center, but multiple listings can increase the chances of receiving a deceased donor kidney even if it doesn't ensure a

shorter wait time for candidates.(Polycystic Kidney Disease Foundation, 2018; The American Association of Kidney Patients, 2018)

Once living vs. deceased donation is elected and candidates are registered on the national transplant waitlist, candidates typically organize their social support group, consider financial strategies, and continue routine bloodwork and health lifestyle behaviors to maximize health status while they are waiting out the matching process to receive a new kidney.(Polycystic Kidney Disease Foundation, 2018; The American Association of Kidney Patients, 2018) When a living or deceased donor match is found for the transplant candidate, the KTP is scheduled. The KTP is a major surgery with administration of general and pain-blocking anesthesia and it comes with the risk of post-surgical complications.(Polycystic Kidney Disease Foundation, 2018; The American Association of Kidney Patients, 2018) Post-surgical complications following KTP surgery are monitored and include the following: new onset diabetes after transplant (NODAT), adverse cardiovascular events (e.g., HTN, myocardial infarction [MI]), thromboembolic events (e.g., deep vein thrombosis [DVT], pulmonary embolism), cerebrovascular events (e.g., ischemic or hemorrhagic stroke and ICA), erythrocytosis, neoplasms (i.e., skin tumors) or renal cell carcinoma [RCC]), and sepsis.(A. B. Chapman et al., 2015; Jacquet et al., 2011; Kanaan et al., 2014; Stiasny, Ziebell, Graf, Hauser, & Schulze, 2002) Even though cardiovascular complications are the most common cause of mortality among patients with ADPKD following KTP, cardiovascular-related mortality rates are comparable among KTP patients with and without ADPKD.(Alam & Perrone, 2010; A. B. Chapman et al., 2015; Fick et al., 1995; Goncalves et al., 2009; Jacquet et al., 2011; Johnston et al., 2009; Kanaan et al., 2014)

The KTP surgery may be an open or laparoscopic procedure, where the surgeon makes an incision in the lower abdomen of the recipient, where the kidney graft is inserted in the pelvic region and connected to the abdominal aorta, central vena cava, and bladder via the renal artery, vein, and ureter.(Polycystic Kidney Disease Foundation, 2018; The American Association of Kidney Patients, 2018) The kidney graft typically functions immediately if a living donor kidney is transplanted, but there are some cases in transplantation of deceased donor kidneys when dialysis is needed 1 to 3 weeks post-surgery to support the graft until it's fully functional.(Polycystic Kidney Disease Foundation, 2018; The American Association of Kidney Patients, 2018) Transplant recipients may remain in the hospital between 2 to 7 days after KTP surgery; the transplant surgeon and nephrologist monitor the recipient's recovery progress during this period.(Polycystic Kidney Disease Foundation, 2018; The American Association of Kidney Patients, 2018)

Once discharged from the hospitalization for KTP surgery, post-surgical follow-up care is typically required for up to one year and is provided by the hospital and primary care physician (internist or nephrologist); follow-up care consists of routine blood testing to monitor kidney function, immunosuppression levels, and signs of infection or graft rejection.(Polycystic Kidney Disease Foundation, 2018; The American Association of Kidney Patients, 2018) Immunosuppressant medications are typically required by transplant recipients for the rest of life; the drug regimen can vary given several factors and over-suppression of the recipients' immune function puts them at an increased risk of infection and cardiovascular events.(Bamoulid et al., 2015; Centers for Medicare and Medicaid Services, 2017; Polycystic Kidney Disease Foundation, 2018; The American Association of Kidney Patients, 2018) Failure to adhere to the immunosuppressant therapy may result in graft rejection

and/or failure, but the immunosuppressant combinations currently used have resulted in reduced TKV for the native polycystic kidneys, as well as provided longer graft survival rates among KTP recipients.(Alam & Perrone, 2010; Bamoulid et al., 2015; Centers for Medicare and Medicaid Services, 2017; Polycystic Kidney Disease Foundation, 2018; The American Association of Kidney Patients, 2018)

Several studies have been conducted to assess post-KTP outcomes, such as post-KTP complications, graft rejection and survival, and patient survival rates in the US, Europe, and Asia. A 20-year study of the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) registry across 12 European countries showed an increase in the prevalence of patients with ADPKD using RRT (HD, PD, and/or KTP) and there were improvements in survival rates.(Spithoven et al., 2014) Specifically, the two-year survival of patients with ADPKD and receiving RRT increased (89 to 93%) and was significantly higher than non-diabetic controls after adjustment for age, sex, and country.(Spithoven et al., 2014) This may have been due to the observed decrease in cardiovascular mortality among patients with ADPKD and receiving RRT compared to non-diabetic controls.(Spithoven et al., 2014) Another 20-year post-KTP follow-up study revealed a lower risk of death-censored graft failure (DCGF) and mortality among patients with ADPKD compared to non-diabetic controls after adjustment for demographics, dialysis, comorbidities, as well as surgical, and immunologic variables.(Bhutani et al., 2021) The presence of coronary artery disease (CAD) and higher body mass index (BMI) were found associated with an increased risk of acute rejection, DCGF, and mortality among patients with ADPKD and non-diabetic controls.(Bhutani et al., 2021) HLA mismatch was found associated with an increased risk of DCGF, while immunosuppression via

calcineurin inhibitors (CNI) was found associated with a reduced risk of DCGF.(Bhutani et al., 2021)

Patients with ADPKD and receiving their first KTP have been reported older compared to non-diabetic controls.(Bhutani et al., 2021; Goncalves et al., 2009; Johnston et al., 2009; Tsai, Chen, Wu, & Tsai, 2022) A post-KTP follow-up study conducted among patients with ADPKD at a single center in Portugal found no significant differences regarding immediate graft function, as well as graft or patient survival compared to non-diabetic controls.(Goncalves et al., 2009) However, there was a lower incidence of proteinuria and a higher incidence of acute rejections, erythrocytosis, and NODAT observed among patients with ADPKD following KTP.(Goncalves et al., 2009) In addition, a KTP follow-up study conducted in Germany found similar KTP and patient survival rates at one, five, and ten years after transplantation among patients with ADPKD and non-diabetic controls; patient and KTP survival rates were higher among female than male recipients with ADPKD.(Stiasny et al., 2002) Cardiovascular event rates were also similar, but patients with ADPKD were observed to have a higher rate of sepsis and UTI complications compared to non-diabetic controls.(Stiasny et al., 2002)

A trending increase in one-year graft survival rate was observed among patients with ADPKD who received their KTP in 2000-2007 vs. 2007-2012 at a single center in the US that was likely due to consistent post-KTP clinical care given there were no significant differences in inter-operative complications, the need for reoperation, 30-day readmissions, delayed graft function, and mortality among patients with ADPKD between the two time periods.(Patel, Kandula, Wojciechowski, Markmann, & Vagefi, 2014) In Ireland, a 6% increase in the age-adjusted five-year graft survival rate was observed among patients with ADPKD

and it was higher than non-diabetic controls (79% vs. 68%, respectively).(Johnston et al., 2009) A 15-year follow-up analysis of the Données Informatisées et VAlidées en Transplantation (DIVAT) data in France revealed patients with ADPKD and KTP had better graft survival compared to non-diabetic controls but with higher incidences of thromboembolic complications, metabolic complications, and HTN.(Jacquet et al., 2011) However, a 35-year follow-up study in Taiwan determined patients with ADPKD and KTP experience higher rates of cell-mediated and antibody graft rejection, malignancy, NODAT, and, thus, worse long-term graft survival compared to non-diabetic controls.(Tsai et al., 2022)

2.5 Economic Burden Associated with ADPKD

The economic burden of CKD, ESRD, and ADPKD shifts to different stakeholders depending on the patient's age, income level, employment or disability status, and/or receipt of ESRD diagnosis. Explicit evidence of the HCRU and economic burden occurring among patients living with ADPKD in the US is limited and there is no standardization in terms of cohort definition nor timeframes for which existing estimates were derived. Therefore, estimates of HCRU and cost of health care among patients living with ADPKD provided in Section 2.5.1 below are limited in terms of generalizability.

2.5.1 HCRU and Cost Outcomes

Patients diagnosed with CKD stages 2 to 4 have been reported to utilize 1.9 to 2.5 times more prescriptions, 1.3 to 1.9 times more outpatient visits, and 1.8 to 4.2 times more hospital admissions than age- and gender-matched controls.(Go et al., 2004) This association between kidney dysfunction and increased risk of adverse outcomes, including cardiovascular events, hospital admissions, outpatient visits, and mortality has also been

observed among patients living with ADPKD in the US.(Blanchette et al., 2014; Go et al., 2004) In terms of societal burden, the total annual cost (i.e., direct health care, direct non-health care, and indirect costs) of ADPKD has been estimated to range from $7.3 to $9.6 billion, which is approximately $51,970 to $68,091 per patient living with ADPKD in the US.(Cloutier et al., 2020) Direct health care cost accounts for approximately 79% of the total annual cost and is primarily driven by the need for RRT.(Cloutier et al., 2020) Indirect cost accounts for approximately 20% of total annual cost and is primarily driven by financial losses due to unemployment and reduced work productivity (i.e., presenteeism).(Cloutier et al., 2020) Economic analyses showcasing the direct healthcare burden of ADPKD in the US are limited, but those that do exist tend to leverage different real-world datasets (i.e., electronic medical records or insurance claims data) and a variety of methodologies to generate estimates of the burden to US payers (i.e., commercially insurers vs. Medicare). Therefore, direct HCRU and cost estimates differ across retrospective studies described below, but it generally increases as patients' disease progresses to ESRD and the need for RRT arises.

A retrospective analysis of commercial claims data (2003-2006) showed patients diagnosed with ADPKD or PKD-U with CKD stage 5 have five-fold higher direct medical costs than those diagnosed with CKD stage 1 ($134,784 vs. $24,427, respectively).(C.M. Blanchette et al., 2015; Lentine, Xiao, Machnicki, Gheorghian, & Schnitzler, 2010) Mean annual direct medical charges were found higher for dialysis-related services than hospitalization for KTP ($131,890 vs. $119,931, respectively), and, collectively, dialysis and KTP services comprised 71% of the total direct medical charges observed.(Lentine et al., 2010) Each <30 mL/min decline in the eGFR was found associated with higher annual charges ($5,435),

which indicates prevention of kidney decline to <30 mL/min may significantly reduce economic burden.(C.M. Blanchette et al., 2015; Lentine et al., 2010)

A retrospective analysis of commercially insured and Medicare Advantage patients diagnosed with ADPKD or PKD-U in the Optum Research Database and Impact National Benchmarking Database (2006-2012) confirmed that irrespective of payer, total direct medical HCRU and costs increased significantly with each stage of eGFR decline and it was primarily driven by ADPKD management and dialysis-related services occurring for those progressing from CKD stage 3 to stages 4 and 5 ($42,686 at stage 3 to $148,402 at stage 4 and $207,548 at stage 5).(Blanchette et al., 2014) Retrospective analysis of Truven MarketScan claims data (2005-2010) revealed significant economic burden exists for ADPKD patients with and without ESRD per an observed increase in the proportion of patients with ADPKD having at least one hospitalization per advancing CKD stage and RRT exposure (12 to >40% CKD stage 2 to 5, dialysis, or post-KTP).(Knight et al., 2015) Further analysis of Truven MarketScan claims (2015-2017) has shown patients with ADPKD accrue significantly higher total annual healthcare costs than controls (mean cost difference of $22,879 PPPY) with significant cost differences observed among those with HTN and/or rapid progression to ESRD and RRT.(Gagnon-Sanschagrin et al., 2021)

Iyer et al. (2018) also conducted a retrospective analysis of insurance claims data (2011-2012) confirmed significant incremental burden exists before and following ESRD diagnosis among patients living with ADPKD in the US. With adjustment for risk factors previously mentioned in this literature review, ADPKD was found associated with incremental mean (standard error [SE]) resource use of 0.68 (0.090) hospital days, equal to 68 additional hospital days per 100 ADPKD patients, and 6.9 (0.28) outpatient visits,

equal to 690 additional visits per 100 ADPKD patients.(Iyer et al., 2018) The mean (SE) incremental total expenditures associated with ADPKD were $8,639 ($470) and were highest for outpatient visits ($4,918 [$198]) followed by hospitalizations ($2,603 [$263]) and medications ($1,589 [$77]).(Iyer et al., 2018)

Patients with ADPKD, and ESRD, and receiving dialysis at a single large dialysis organization (2007-2009) were found to have high total direct medical costs at $51,048 per patient-year (PPY), but it was observed lower compared to controls.(Brunelli et al., 2015) Patients with ADPKD had an overall mean rate of 8.6 hospitalizations per 100 patient-years; the hospitalization rate was highest within months 0-2 of dialysis treatment and it was a driver of the economic burden occurring within that timeframe.(Brunelli et al., 2015) Patients living with ADPKD, ESRD, and receiving dialysis in this study were younger and healthier as evidenced by a lower Charlson Comorbidity Index (CCI) score and comorbidity rates, which may have contributed to the lower overall total direct medical costs compared to controls.(Brunelli et al., 2015) A cohort analysis of ESRD patients with and without ADPKD and receiving dialysis was conducted using the 2013-2018 all-payer Nationwide Readmissions Database (NRD).(Saha, Ericksen, Liriano Cepin, Nadkarni, & Chan, 2022) Patients with ADPKD, ESRD, and dialysis were observed to have fewer 30-day unplanned hospital readmissions than patients without ADPKD, but the cost of index hospitalizations ($15,093 vs. $12,394) and readmissions ($17,391 vs. $16,455) was higher among those with ADPKD compared to those without ADPKD.(Saha et al., 2022)

In 2020, the average cost of KTP in the US was $442,500 with charges for the transplant admission (i.e., the KTP surgery) accounting for the largest portion (34%) of the total cost.(Wang & Hart, 2021) Between 2016 and 2019, the all-cause one-year post-KTP rate of

hospitalization among Medicare beneficiaries (not explicitly ADPKD) was 1.48 hospitalizations per person-year; hospitalizations due to infections were three-fold compared to those for cardiovascular events.(United States Renal Data System, 2022b) While these estimates exist for patients receiving KTP regardless of the cause of their ESRD, there are limited explicit real-world estimates of the cost of KTP surgery and 30-day all-cause readmissions following KTP among patients living with ADPKD in the US.

2.6 Summary

A review of the clinical literature among patients living with ADPKD in the US revealed evidence of a higher physiological burden among those diagnosed with advanced CKD stages 4 and 5, as well as those with ESRD and relying on RRT to extend their life. Thus, the importance of treatments intended to delay the progression of ADPKD to ESRD, such as ACE-I and tolvaptan, to reduce the subsequent HCRU and economic burden to all stakeholders over time. A review of the economic literature indicates that HCRU and cost of care among patients living with ADPKD is significant across CKD stages, but it is much higher among those with advanced kidney disease (i.e., CKD stages 4-5, ESRD) and is primarily driven by unplanned hospitalizations for management of ADPKD or complications due to RRT.

Even though KTP is the ideal therapeutic option for patients living with ADPKD and approaching ESRD, there is limited evidence of the HCRU and cost outcomes of KTP (i.e., cost of KTP surgery and 30-day all-cause readmissions) among patients living with ADPKD in the US. While TKV of the native polycystic kidneys and HTN tend to decrease among patients with ADPKD who receive KTP, patients are also at risk of complications (i.e., cyst ruptures/infections, UTI, kidney stones) in the retained native kidneys that

prompt HCRU and cost following KTP. Even though the literature states graft and patient survival rates are better for those with ADPKD compared to ESRD due to other causes, post-KTP complications (i.e., graft infection, rejection, or failure) are still observed and may also be significant drivers of all-cause hospitalizations occurring post-KTP surgery. There is currently no standardized approach to quantify HCRU and cost outcomes among patients living with ADPKD in the US, and comparison of existing real-world estimates levering large administrative databases is challenging. Analyses tend to assess HCRU and cost as associated with ADPKD diagnosis vs. ESRD diagnosis and receipt of RRT collectively. The KTP process is complex, as previously described, and the profile of patients receiving KTP is different from those not receiving KTP in the US. Furthermore, the profile of patients living with a rare disease, like ADPKD, is also different from the profile of patients with ESRD and receiving KTP due to other etiologies of disease. Therefore, outcomes of KTP should be assessed explicitly for patients living with ADPKD. The goal of this dissertation was to leverage a large, all-payer hospital database to generate real-world estimates of inpatient readmission, resource use, total patient cost, and mortality outcomes among patients with vs. without ADPKD at index hospitalization for KTP surgery and 30-day all-cause readmissions post-KTP.

3 METHODS

3.1 Preliminary Research

Preliminary research was conducted using various retrospective databases to further characterize HCRU and charge/cost outcomes among samples of patients with ADPKD in the US. The databases included Health Care Cost and Utilization Project (HCUP) National Inpatient Sample (NIS) KID 2012, HCUP Nationwide Emergency Department Sample (NEDS) 2010, and 5% Medicare Limited Dataset (LDS) 2011-2014.

HCUP inpatient data are based on administrative data (i.e., discharge abstracts) created by hospitals for billing purposes. (The Agency for Healthcare Research and Quality, 2015a) The NIS-KID is the largest publicly available all-payer pediatric inpatient care database in the US, containing data from approximately 3 million (unweighted) to 7 million (weighted) discharges each year in patients younger than 21 years of age. (The Agency for Healthcare Research and Quality, 2015a) The large sample size in NIS-KID enables analysis of rare conditions, such as ADPKD, from community hospitals (i.e., short-term, non-federal, general, and specialty) in the US. (The Agency for Healthcare Research and Quality, 2015a) The NIS-KID was selected to characterize a subset of the ADPKD population, including hospitalized children who are diagnosed with ADPKD at an early age and/or are rapid progressors with comorbid ESRD. The NEDS provides a large sample of nationally representative estimates of hospital-owned emergency department (ED) visits in the US, regardless of whether they result in hospital admissions. (The Agency for Healthcare Research and Quality, 2015b) The NEDS contains all-payer data from approximately 28 million (unweighted) to 123 million (weighted) ED visits each year in the US. (The Agency for Healthcare Research and Quality, 2015b) The NEDS enables analysis across hospital types

and in rare conditions, such as ADPKD. (The Agency for Healthcare Research and Quality, 2015b) NEDS was selected to characterize primary diagnoses and procedures as the reasons a subset of the symptomatic ADPKD population seeks care at an ED in the US.

The 5% Medicare LDS is a de-identified, longitudinal administrative database of inpatient and outpatient FFS claims paid directly by the Centers for Medicare and Medicaid (CMS) for Medicare beneficiaries living in the US. (CMS, 2023) As previously discussed in Chapter 2, Medicare Part A coverage extends to final action FFS claims submitted by inpatient hospital providers (e.g., community hospitals, critical access hospitals, short-term SNFs, hospice care, and some home health care) for reimbursement of facility costs. (CMS, 2023) Medicare Part B coverage extends to final action FFS claims submitted by non-institutional providers (e.g., physicians, physician assistants, physical and occupational therapists, clinical social workers, nurse practitioners) or outpatient facilities (e.g., independent clinical laboratories, ambulatory transportation, surgical centers) and home health agencies for reimbursement of services rendered. (CMS, 2023) The 5% Medicare LDS was selected to characterize direct medical HCRU and cost outcomes among subsets of the ADPKD population who were either ≥65 years of age, < 65 years of age with certain disabilities, or all ages with ESRD requiring dialysis or KTP.

3.1.1 Characteristics of Hospitalized Children with ADPKD and HTN in the US

The objective of this cross-sectional analysis was to assess the inpatient resource utilization outcomes of hospitalized children diagnosed with ADPKD and HTN in the US using the 2012 HCUP NIS-KID database. The sample included encounters for inpatients >5 to 21 years of age with a diagnosis of ADPKD (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM]: 753.13) and/or >15 to 21 years with a

diagnosis of PKD-Unspecified (PKD-U) (ICD-9-CM: 753.12). These age constraints were applied to control for the inclusion of infants or children diagnosed with Autosomal Recessive Polycystic Kidney Disease (ARPKD). The sample was stratified by the presence of HTN (ICD-9-CM 401.xx – 405.xx). Specifically, HTN was defined as essential HTN, hypertensive heart disease, hypertensive CKD, hypertensive heart disease and CKD, and/or secondary HTN. Inpatients with primary pregnancy-related diagnoses (ICD-9-CM: 630.xx– 679.xx) were excluded to control for potential pregnancy-induced HTN. Demographic and clinical characteristics included sex, age, CCI score, Charlson comorbidities, and related medical procedures. HCRU outcomes included length of stay (LOS), inpatient charges, inpatient mortality, and discharge location. Demographics, comorbidities, LOS, and inpatient charges were compared using descriptive statistics, chi-square, and Student's t-tests. Frequencies (n) and percentages (%) were used to represent all binary/categorical demographic and clinical characteristics, with the means and SDs used to represent continuous CCI scores and HCRU outcomes. All analyses were done using the Statistical Analysis Software (SAS) package 9.3 (Cary, NC). The alpha level was set at 0.05.

3.1.2 Characteristics of Hospitalized Children with ADPKD and Kidney-Related Complications in the US

The objective of this cross-sectional analysis was to assess the inpatient resource utilization outcomes of hospitalized children diagnosed with ADPKD and kidney-related complications in the US using the 2012 HCUP NIS-KIDS database. The sample included encounters for inpatients >5 to 21 years of age with diagnosis of ADPKD (ICD-9-CM: 753.13) and/or >15 to 21 years with a diagnosis of PKD-U (ICD-9-CM: 753.12). These age constraints were applied to control for the inclusion of infants or children diagnosed

with ARPKD. The sample was stratified by the presence of kidney-related complications (ICD-9-CM 580-588.xx, 590-593.xx, 595.xx, 599.xx).

Specifically, kidney-related complications were defined as the following: acute glomerulonephritis, nephrotic syndrome, chronic glomerulonephritis, nephritis and nephropathy not specified as acute or chronic, acute kidney failure (AKF), CKD, unspecified kidney failure, unspecified kidney sclerosis, disorders resulting from impaired kidney function, infections of the kidney (i.e., acute and chronic pyelonephritis, kidney and perinephric abscess, pyeloureteritis cystica, pyelonephritis unspecified, pyelonephritis or pyelonephritis in diseases classified elsewhere, and infection of kidney unspecified), hydronephrosis, calculus of kidney and ureter, and other disorders of kidney and ureter (i.e., nephroptosis, hypertrophy of kidney, acquired cyst of kidney, stricture or kinking of ureter, other ureteric obstruction, hydroureter, postural proteinuria, vesicoureteral reflux, vascular disorders of kidney, ureteral fistula, other specified disorders of kidney and ureter, unspecified disorder of kidney and ureter), cystitis, and other disorders of urethra, and urinary tract (i.e., UTI, urethral fistula, urethral diverticulum, urethral caruncle, urethral false passage, prolapsed urethral mucosa, urinary obstruction, hematuria, urethral hypermobility, intrinsic urethral sphincter deficiency, urethral instability, other specified disorders of urethra and urinary tract, unspecified disorder of urethra and urinary tract).

Inpatients with primary pregnancy-related diagnoses (ICD-9-CM: 630.xx– 679.xx) were excluded to control for potential pregnancy-induced HTN. Demographic and clinical characteristics included sex, age, CCI score, Charlson comorbidities, and related medical procedures. HCRU outcomes included LOS, inpatient charges, inpatient mortality, and discharge location. Demographics, comorbidities, LOS, and inpatient charges were

compared using descriptive statistics, chi-square, and Student's t-tests. Frequencies (n) and percentages (%) were used to represent all binary/categorical demographic and clinical characteristics with means, and SDs used to represent continuous CCI scores and HCRU outcomes. All analyses were done using the SAS package 9.3 (Cary, NC). The alpha level was set at 0.05.

3.1.3 ED Use Among Patients Diagnosed with ADPKD in the US

The objective of this cross-sectional analysis was to leverage the 2010 HCUP NEDS to evaluate the reasons individuals living with ADPKD in the US seek ED services for symptom management. The cohort included ED encounters with a diagnosis of ADPKD (ICD-9-CM: 753.13) and/or PKD-U (ICD-9-CM: 753.12). ED encounters with a diagnosis of ARPKD (ICD-9-CM: 753.14) were excluded from the sample to control for the inclusion of individuals diagnosed with the recessive form of the disease. ARPKD is more commonly observed among infants and children, but improvements in disease awareness, education, and management of the disease have increased the likelihood of observing adults with ARPKD diagnoses in NEDS. ED encounters were stratified for comparison by disposition from ED status, hospitalized or discharged, to characterize the outcome of ED services used. ED encounters were classified as hospitalized if they were transferred to a short-term hospital and/or admitted as an inpatient from the ED.

The frequency (n) of procedural services utilized during ED visits was assessed using Current Procedural Terminology (CPT) and Healthcare Common Procedure Coding System (HCPCS) codes on the ED encounters. Frequency (n) of primary diagnoses and procedures during ED visits were assessed using ICD-9-CM diagnosis and procedure codes on the ED encounters. Descriptive statistics, chi-square, and Student's t-tests were used to

identify and summarize patterns in demographics, ED service utilization, and charges by disposition from ED status. Frequencies (n) and percentages (%) were used to represent all binary/categorical demographic and clinical characteristics, while means and SDs were used to represent continuous CCI scores and ED service utilization outcomes. All analyses were done using the SAS package 9.4 (Cary, NC). The alpha level was set at 0.05.

3.1.4 The Burden of ADPKD Among a Cohort of US Medicare Beneficiaries

The objective of this retrospective longitudinal analysis was to evaluate the all-cause and disease-related HCRU and cost outcomes among a cohort of US Medicare beneficiaries diagnosed with ADPKD using the 2011-2013 5% Medicare LDS. This analysis included Medicare beneficiaries with two or more diagnosis claims for ADPKD (ICD-9-CM: 753.13) with stratification by age (≤ 39, 40-64, ≥ 65 years old). All-cause and disease-specific HCRU outcomes included the following and were assessed for comparison between a 12-month pre-diagnosis and 12-month post-diagnosis period: outpatient (OP) visits, inpatient (IP) hospitalizations, ED visits, office visits (OV), LOS, and direct medical costs. Demographic and clinical characteristics included sex, age, CCI score, Charlson comorbidities, and related medical procedures. Frequencies (n) and percentages (%) were used to represent all binary/categorical demographic and clinical characteristics, while means and SDs were used to represent continuous CCI score, all-cause, and disease-related HCRU (IP, OP, OV, ED), all-cause and disease-related direct medical cost (United States Dollar $USD PPPY) outcomes. Comparisons were made using descriptive and inferential statistics, chi-square, and Student's t-tests. Analyses were done using the SAS package 9.3 (Cary, NC). The alpha level was set at 0.05.

3.1.5 The Burden of KTP Among a Cohort of US Medicare Beneficiaries with ADPKD

The objective of this retrospective longitudinal analysis was to assess the all-cause HCRU and direct medical and prescription drug costs among KTP recipients in a cohort of US Medicare beneficiaries with ADPKD using the 2011-2014 5% Medicare LDS. A beneficiary cohort of patients diagnosed with ADPKD (ICD-9-CM: 753.13) and/or PKD-U (ICD-9-CM: 753.12) and who received KTP (ICD-9-CM: 55.69, V42.0) was identified. Beneficiaries diagnosed with ARPKD (ICD-9-CM: 753.14) were excluded from the cohort for reasons previously discussed in other preliminary studies. Beneficiaries were indexed at the date of their first KTP, with outcomes observed during 12-month pre-KTP and 12-month post-KTP periods. Beneficiaries were stratified by age (<44, 45-54, 55-64, and >65 years old) to capture the variability in disease progression to ESRD and subsequent KTP. These age bands were narrower compared to the first preliminary 5% Medicare LDS sample (i.e., with age stratified by ≤39, 40-64, and ≥65 years old) to align with data distribution and account for heterogenous disease progression and subsequent KTP that is known to occur within the ADPKD population from ages 40-64 years old.

Baseline demographic and clinical characteristics included sex, race, US census region, CCI score, CCI group (i.e., the total number of Charlson comorbidities), Charlson comorbidities, and related medical procedures. Beneficiary characteristics were displayed for the total sample and by age groups with comparisons using descriptive and inferential statistics, chi-square, Cochran-Mantel-Haenszel, and Student's t-tests where appropriate. HCRU outcomes (OP, IP, ED, OV, and LOS) were assessed and compared between the 12-month pre-KTP and 12-month post-KTP period using a negative binomial regression model. Total direct medical costs ($USD PPPY) were assessed and compared between the

12-month pre-KTP and 12-month post-KTP periods using a generalized linear regression model with gamma distribution and log-link transformation. Frequencies (n) and percentages (%) were used to represent all binary/categorical demographic and clinical characteristics, with means and SDs used to represent continuous CCI score, HCRU, and direct medical cost outcomes. All analyses were done using the SAS package 9.4 (Cary, NC). The alpha level was set at 0.05.

3.1.6 Relative Risk and Crude Mortality among Cohorts of US Medicare Beneficiaries with ADPKD

The objective of this retrospective longitudinal analysis was to assess the crude mortality rate and risk difference among Medicare beneficiaries with ADPKD, ESRD, and having received RRT (dialysis or KTP) in the US using 2011-2014 5% Medicare LDS. Beneficiaries were identified for inclusion if they had a diagnosis of ADPKD (ICD-9-CM: 753.13) or PKD-U (ICD-9-CM: 753.12). Beneficiaries were also included if they had a comorbid diagnosis of ESRD (ICD-9-CM: 585.x) and either received dialysis (ICD-9-CM: V45.x) or KTP (ICD-9-CM: 55.69, V42.0) during the observation period. Beneficiaries diagnosed with ARPKD (ICD-9-CM: 753.14) were excluded from the dialysis and KTP cohorts for reasons previously discussed in other preliminary studies. Beneficiaries were indexed at the date of first ESRD diagnosis (i.e., dialysis cohort naïve to KTP) or date of first KTP diagnosis/procedure (i.e., KTP cohort) with observation during a 12-month pre-index period and 24-month post-index period.

Baseline demographic and clinical characteristics were assessed during the 12-month pre-index period and included sex, age, race/ethnicity, CCI score, CCI group, Charlson comorbidities, and related medical procedures. Beneficiary demographics and clinical characteristics were displayed per the dialysis and KTP cohort with comparison using chi-

square, Cochran-Mantel-Haenszel, and Student's t-tests where appropriate. Frequencies (n) and percentages (%) were used to represent all binary/categorical demographic and clinical characteristics. The total number of HCRU was assessed for OP, IP, ED, and OV among the dialysis and KTP cohorts in the 24-month post-index period. The total number of deaths and crude mortality rates with 95% confidence intervals (CIs) were also assessed among the dialysis and KTP cohorts in the 24-month post-index period. The risk difference was calculated by subtracting the crude mortality rate observed in the KTP cohort from the crude mortality rate observed in the dialysis cohort.

3.2 Inpatient Resource Use and Cost Outcomes Among Kidney Transplant Recipients with vs. without ADPKD

A key strategy for improving the quality of healthcare and containing costs is the reduction of hospital readmissions among patients living with ESRD in the US. Existing literature reports that HCRU and cost are higher among ESRD controls compared to those with ESRD due to ADPKD. Furthermore, there are better graft and patient survival rates following KTP surgery among ADPKD cases compared to CKD controls. In our preliminary research, we chose to focus on generating real-world data on HCRU and cost outcomes among the subset of ESRD patients with ADPKD and receiving KTP in the US leveraging the 5% Medicare LDS. We observed a significant increase in the cost of hospitalization following KTP among patients with ESRD due to ADPKD, but the analysis was not adjusted and did not compare to patients with ESRD due to other causes. This was the motivating factor to explore inpatient resource use and cost outcomes further among patients with vs. without ADPKD and receiving KTP surgery in the US, leveraging a database that is representative of all US payers. The aims of this dissertation were as follows:

1. At the encounter level, quantify and assess differences in the patient demographics, comorbidities, hospital characteristics, and inpatient resource use (i.e., LOS), and total patient cost at index hospitalization for KTP surgery among patients with vs. without ADPKD.
2. At the patient level, quantify and assess the differences in the 30-day all-cause readmission rates following index hospitalization for KTP surgery among patients with vs. without ADPKD. Also assess the association between ADPKD diagnosis and the 30-day all-cause readmission rate.
3. At the patient level, quantify and assess the differences in the inpatient resource use (i.e., LOS) and total patient cost of 30-dy all-cause readmissions among patients with vs. without ADPKD. Also assess the association between ADPKD diagnosis and LOS, as well as total patient cost, at 30-day all-cause readmissions.
4. At the patient level, quantify and assess the difference in the proportion of patients with death at 30-day all-cause readmissions among patients with vs. without ADPKD.

For the encounter-level analysis, we hypothesized that patients with ADPKD would be older, predominately male and White, with a lower comorbidity burden and better health status at index hospitalization for KTP surgery compared to patients without ADPKD. Given the comorbidity burden was anticipated to be lower among patients with ADPKD, the inpatient resource use (i.e., LOS) and total patient cost of index hospitalization for KTP surgery were also hypothesized to be lower among patients with ADPKD compared to those without ADPKD. For the patient-level analysis, we hypothesized that patients with ADPKD would have a lower rate of all-cause readmissions within 30 days of index

hospitalization for KTP surgery compared to patients without ADPKD and that there would be a decreased odds of readmission among those with ADPKD. We hypothesized the unadjusted median LOS and occurrence of death at 30-day all-cause readmissions would be lower among patients with ADPKD compared to those without ADPKD. Therefore, the unadjusted median total patient cost of 30-day all-cause readmissions was also hypothesized to be lower among patients with ADPKD compared to those without ADPKD. We hypothesized that there would be a negative association between ADPKD diagnosis and mean LOS, as well as median total patient cost, at 30-day all-cause readmissions.

3.2.1 Data Source

Surgical procedures are one of the largest expenditures in healthcare, projected to represent over 7% of the US gross domestic product (GDP) by 2025.(Alluri, Leland, & Heckmann, 2016) Institutions and surgeons are being held accountable for peri-operative complications, resource consumption, readmissions, and overall costs due to the shift towards bundled reimbursement with pay-for-performance models.(Alluri et al., 2016) Quality metrics, such as 30-day unplanned readmission rates, are used to track performance, and national clinical databases are increasingly leveraged to evaluate the expected risks and benefits of a given surgical procedure in cohorts of patients.(Alluri et al., 2016)

The Premier Healthcare Database (PHD) is a private, large, all-payer clinical database in the US.(Premier Applied Sciences, 2020) PHD includes data for over 244 million unique patients and over 127 million inpatient admissions since 2012, which represents nearly 25% of annual admissions occurring in the US.(Premier Applied Sciences, 2020) PHD is

a comprehensive electronic health records database consisting of patient demographics and disease states; admission and discharge diagnoses; information on billed services including costs, laboratory tests performed, diagnostic and therapeutic services; patient disposition and discharge health status.(Premier Applied Sciences, 2020) PHD enables hospital-level, service-level (i.e., encounter-level), and patient-level analyses across all US payers.(Premier Applied Sciences, 2020) PHD provides discharge-level weights for the generation of nationally representative estimates. Given the cohort inclusion and exclusion criteria, the patients included in this analysis were different from the source population. Therefore, weighted estimates were not prioritized for the analysis.

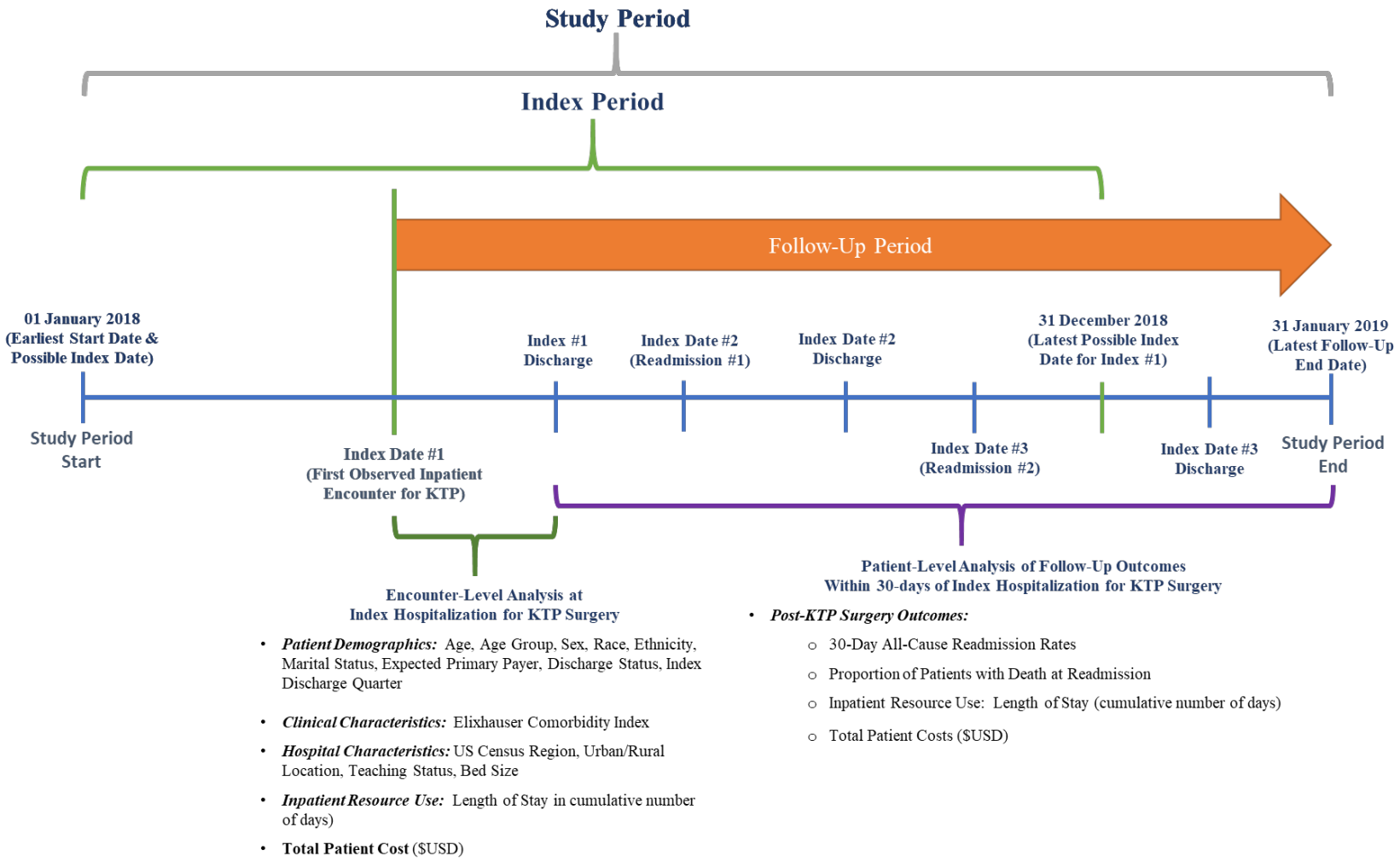
3.2.2 Study Design and Population

This study was a retrospective, longitudinal, case-cohort analysis of patients ≥18 years of age with an index hospitalization for KTP surgery (International Classification of Diseases, 10th Revision, Procedure Coding System [ICD-10-PCS] operating room procedure codes: 0TY00Z0, 0TY00Z1, 0TY00Z2, 0TY10Z0, 0TY10Z1, 0TY10Z2) as identified from 01 January 2018 and 31 December 2018 in the PHD (Figure 1 Study Scheme). Patients were then distinguished as cases if the presence of ADPKD and/or PKD-U (International Classification of Diseases, 10th revision, Clinical Modification [ICD-10-CM]: Q61.2, Q61.3) diagnoses were observed on the index hospitalization for KTP surgery. Hospitalizations were flagged as occurring among patients without ADPKD if no diagnosis of ADPKD or PKD-U was observed as ICD-10-CM diagnoses on the index hospitalization for KTP surgery. Index hospitalizations for KTP surgery were excluded if the presence of ARPKD (ICD-10-CM: Q61.1) diagnosis was observed on the encounter.

The likelihood of observing multiple KTP surgeries within 30 days apart is minimal in the context of organ donation and availability. It is possible a patient had KTP surgery in December 2017 and was readmitted for post-KTP complications in January 2018, but this patient would not have been included in the analysis given the required observation of KTP surgery as indexed from 01 January 2018 through 31 December 2018 in the PHD. Therefore, a clean period excluding patients with an index event in January 2018 was not necessary for the readmissions analysis.

The maximum follow-up observation for readmission outcomes (i.e., all-cause readmission rates, mortality, LOS, and total patient cost) was 30 days post-discharge for KTP surgery (i.e., index hospitalization). Therefore, the observation period was extended to 31 January 2019 for the subset of included patients with index discharge for KTP surgery in late December 2018 (e.g., 20 December 2018). It is common for patients with an index hospitalization in December 2018 to be excluded from readmissions analyses, given the lack of observation in the subsequent calendar year among cross-sectional databases. However, PHD enables patient-level analysis of readmission outcomes across data years leveraging the patient key (i.e., PAT_KEY) as the encounter-level identifier and the MEDREQ_KEY as the patient-level identifier. Therefore, patients with index discharge for KTP surgery between 01 December 2018 and 31 December 2018 were retained in the analysis.

Figure 1. Study Schematic



3.2.2.1 Definition of Index Hospitalization for KTP Surgery

The ICD-10-PCS is a catalog of procedural codes that is annually maintained by the Centers for Medicare and Medicaid Services (CMS) and is used by healthcare professionals for tracking services provided in hospital inpatient settings. Medical and surgical codes, having zero as the value of the first character, represent the vast majority of procedures reported in an inpatient setting. The second through seventh characters indicate the following: the general body system (e.g., urinary), root operation or specific objective of the procedure (e.g., transplant), specific body part on which the procedure was performed (e.g., kidney), the approach used to reach the procedure site (e.g., open), whether any device was used and remained at end of the procedure (e.g., synthetic substitute), and a qualifier that may have a specific meaning for a limited range of values (e.g., right or left). Patients were indexed at the first inpatient discharge for KTP surgery occurring between 01 January 2018 and 31 December 2018 in the PHD, which was defined as inpatient discharges having one or more of the following ICD-10-PCS operating room codes: transplantation of right kidney, allogeneic, open approach (0TY00Z0); transplantation of right kidney, syngeneic, open approach (0TY00Z1); transplantation of right kidney, zooplastic, open approach (0TY00Z2); transplantation of left kidney, allogeneic, open approach (0TY10Z0); transplantation of left kidney, syngeneic, open approach (0TY10Z1); transplantation of left kidney, zooplastic, open approach (0TY10Z2). Index hospitalizations for KTP surgery were allowed to be an "elective" admission type. This was due to the potential for observing patients with and without ADPKD and undergoing KTP surgery pre-emptively (i.e., CKD stage 4).

3.2.3 Statistical Analysis Plan

For this study, all data cleaning and management steps executed in the creation of analytic files, as well as statistical analyses, were conducted using the SAS® software, version 9.4 (SAS Institute Inc., Cary, NC, US). The alpha level was set at a priori 0.05 for all statistical testing conducted.

3.2.3.1 Aim #1: Compare Patient Demographics, Comorbidities, Hospital Characteristics, Inpatient Resource Use (LOS), and Total Patient Cost at Index Hospitalization for KTP Surgery

At the encounter level, all inpatient index hospitalizations for KTP surgery were quantified within a 365-day (12-month) timeframe (i.e., 01 January 2018 and 31 December 2018) and designated as occurring among patients with vs. without ADPKD. Patient demographics, comorbidities, hospital characteristics, inpatient resource use (i.e., LOS), and total patient cost were quantified for the total cohort at the first index hospitalization for KTP surgery using the following variables and were compared for patients with vs. without ADPKD:

- *Binary (n [%])*: sex (male, female), ethnicity (Hispanic, non-Hispanic), and Elixhauser comorbidities (see comorbidity category details in Section 3.2.3.1.1 below);
- *Nominal Categorical (n [%])*: race (white, black, other, unknown), expected primary payer (Medicare, Medicaid, private, self-pay, workers compensation, direct employer, other government payer, other), marital status (married, single, other, unknown/missing), US Census Region (northeast [NE], midwest [MW], south [S], west [W], unknown/missing), hospital location (urban, rural, unknown/missing), hospital teaching status (teaching, non-teaching, unknown/missing);

- *Ordinal Categorical (n [%]):* age group (18-24, 25-34, 35-44, 45-54, 55-64, 65-74, and ≥75 years) and hospital bed size (0-99, 100-199, 200-299, 300-399, 400-499, 500+, unknown/missing);
- *Count (median [interquartile range [IQR]]):* LOS (cumulative number of days);
- *Continuous (median [IQR]):* age (years) at admission, and total patient cost ($USD).

3.2.3.1.1 Elixhauser Comorbidity Index

It is important to understand the presence and severity of comorbid medical conditions that may influence not only the prognosis of patients with CKD, but also the treatment landscape and outcomes. Comorbidities are used to predict outcomes such as functional status, QoL, risk of HCRU, and mortality. The Elixhauser Comorbidity Index was developed as a measure of comorbidity to predict the risk of inpatient resource use (i.e., 30-day all-cause readmissions) and mortality leveraging secondary ICD-10-CM diagnosis codes present in administrative data sources in the US.(Elixhauser, Steiner, Harris, & Coffey, 1998) The Elixhauser Comorbidity Index groups ICD-10-CM diagnosis codes into 30 categories of medical conditions including the following and patients with one or more of these comorbid medical conditions are at increased risk of 30-day all-cause readmissions and mortality compared to patients without these comorbidities: congestive heart failure [CHF], cardiac arrhythmias, valvular disease [VD], pulmonary circulation disorders, peripheral vascular disorders, HTN-uncomplicated [HTN-U], HTN-complicated [HTN-C], paralysis, other neurological disorders, chronic pulmonary disease, diabetes-uncomplicated [DU], diabetes-complicated [DC], hypothyroidism, renal failure, liver disease, peptic ulcer disease, HIV/AIDS, lymphoma, metastatic cancer, solid tumor

without metastasis, rheumatoid arthritis [RA], obesity, weight loss [WL], fluid and electrolyte disorders, blood loss anemia, deficiency anemia, alcohol abuse [AA], drug abuse, psychoses, depression, and coagulopathy.(Elixhauser et al., 1998)

3.2.3.1.2 Descriptive Statistics

The chi-square test was conducted to compare the proportions of patients with vs. without ADPKD per the following binary and categorical (nominal or ordinal) variables: sex, race, ethnicity, marital status, US Census Region, age groups, expected primary payer, hospital bed size, hospital teaching status, and hospital location. The Fisher's exact test was conducted to compare the proportions of patients with vs. without ADPKD for any variable with observed/expected counts <20. The Wilcoxon Rank Sum test was conducted to compare the medians of patients with vs. without ADPKD for the count LOS variable, as well as the continuous age and total patient cost variables.

3.2.3.2 Aim #2: Quantify and Assess Differences in the Occurrence of 30-Day All-Cause Readmissions Following KTP Surgery Among Patients with vs. without ADPKD

Hospital readmission rates are often used for quality improvement and cost control.(Fischer et al., 2014) There is potential for hospitals to not receive any payer reimbursement or at least a reduction in payer reimbursement for an increasing number of avoidable readmissions.(Vest, Gamm, Oxford, Gonzalez, & Slawson, 2010) Specifically, the 30-day readmission rate is a quality metric that reflects differences in ambulatory care and/or coordination of care for all patients (and hospitals) included in this cohort. All inpatient readmission events within 30-days of the index hospitalization for KTP surgery were quantified for the total cohort and classified for comparison as all-cause readmissions occurring among patients with vs. without ADPKD. In conjunction with the

MEDREQ_KEY (i.e., patient-level identifier) and PAT_KEY (i.e., encounter-level identifier) variables, the discharge month (i.e., DISC_MON) and admission month (i.e., ADM_MON) variables were used to establish the patient-level temporal sequence of all hospitalizations observed within the study period (01 January 2018 and 31 January 2019). The difference in the total number of days was calculated between the discharge month at index hospitalization for KTP surgery and the admission month of any inpatient encounter observed within the study period. Only readmissions occurring within 30-days following discharge for KTP surgery were retained for the follow-up analysis. In calculation of the 30-day readmission rates (i.e., [numerator / denominator] * 100), the numerator was the total number of patients (with vs. without ADPKD) with at least one all-cause readmission event within 30 days of index hospitalization for KTP surgery and the denominator was the total number patients (with vs. without ADPKD) observed between 01 January 2018 and 31 January 2019.

3.2.3.2.1 Descriptive Statistics

The Chi-Square test was conducted to compare the 30-day all-cause readmission rates among patients with vs. without ADPKD.

3.2.3.2.2 Inferential Statistics

A logistic regression model was used to assess the adjusted odds of the occurrence of at least one all-cause readmission within 30-days of index discharge for KTP surgery among patients with vs. without ADPKD. Covariates used to adjust the regression model included age, sex, race, and Elixhauser comorbidities (i.e., CHF, VD, HTN-U, HTN-C, DC, RA, WL, and AA) identified as significantly different between patients with vs. without

ADPKD at index hospitalization for KTP surgery. The odds ratio (OR), 95% confidence interval (CI), and p-value were reported.

3.2.3.3 Aim #3: Quantify and Assess the Differences in the Inpatient Resource Use (LOS) and Total Patient Cost of 30-Day All-Cause Readmissions Following KTP Surgery Among Patients with vs. without ADPKD

The total patient cost associated with 30-day all-cause readmissions is the primary outcome interest as it relates to the economic burden to hospitals for potentially avoidable hospitalizations. Infinite continuous median (IQR) inpatient resource use (i.e., LOS) and total patient cost outcomes were quantified at all-cause readmissions occurring within 30-days of index discharge for KTP surgery and were compared among patients with vs. without ADPKD.

3.2.3.3.1 Descriptive Statistics

The Wilcoxon Rank Sum test was conducted to compare the medians for the count LOS variable, as well as the continuous total patient cost ($USD), of all-cause readmissions occurring within 30-days of index discharge for KTP surgery among patients with vs. without ADPKD.

3.2.3.3.2 Inferential Statistics

A generalized linear regression model with negative binomial distribution and log link transformation was conducted to assess the association between ADPKD diagnosis and the mean LOS at 30-day all-cause readmissions. Because of the influence of outliers observed in the mean total patient cost, a quantile regression model was conducted to assess the association between ADPKD diagnosis and median total patient cost of 30-day all-cause readmissions. Covariates used to adjust the generalized negative binomial and quantile regression models included age, sex, race, and Elixhauser comorbidities (i.e., CHF, VD,

HTN-U, HTN-C, DC, RA, WL, and AA) identified as significantly different between patients with vs. without ADPKD at index hospitalization for KTP surgery. The incident rate ratio (IRR), 95% CIs, and p-value were reported for the mean LOS outcome. The median incremental total patient cost, 95% CIs, and p-value were reported for the total patient cost outcome.

3.2.3.4 Aim #4: Quantify and Assess the Differences in the Occurrence of Mortality at 30-Day Readmissions Following KTP Surgery Among Patients with vs. without ADPKD

The total number and proportion (%) of patients with mortality at an all-cause readmission occurring within 30-days of index discharge for KTP surgery was quantified and compared for patients with vs. without ADPKD and having at least one 30-day readmission following index discharge for KTP surgery. Mortality at all-cause readmission was defined as any inpatient encounter with a discharge status of "expired." The cause of death could not be determined using available variables in the PHD.

3.2.3.4.1 Descriptive Statistics

The chi-square test was conducted to compare the proportion of patients with vs. without ADPKD with mortality at an all-cause readmission occurring within 30-days of index hospitalization discharge for KTP surgery. If the observed/expected counts of patients with vs. without ADPKD was <20, Fisher's exact test was conducted to compare the proportions instead of the chi-square test.

4 RESULTS

4.1 Characteristics of Hospitalized Children with ADPKD and Hypertension in the US

A sample of inpatient encounters among children diagnosed with ADPKD (N=301) was obtained from the 2012 HCUP NIS-KID database; 197 were non-hypertensive (65.4%), and 104 were hypertensive (34.6%) ($p < 0.0001$, Table 1). Among the overall cohort, a higher proportion of males were hypertensive (59.6% vs. 40.6%, $p = 0.0017$) and a higher proportion of females were non-hypertensive (59.4% vs. 40.4%, $p = 0.0017$) (Table 1). There was no significant difference observed in the mean (SD) age of children with vs. without HTN (Table 1). The majority of hypertensive and non-hypertensive children were Caucasian (55.8% and 57.4%, respectively), but there were no significant differences observed for this among children with vs. without HTN (Table 1). The majority of hypertensive and non-hypertensive children were hospitalized in the Southern region (32.7% and 29.9%, respectively) of the US, but no significant differences were observed for those with vs. without HTN (Table 1).

The majority of hypertensive and non-hypertensive children were hospitalized in central metropolitan areas of the US (30.8% and 26.9%, respectively), but no significant differences were observed between those with vs. without HTN (Table 1). The majority of hypertensive and non-hypertensive children had Commercial (51.9% and 45.7%, respectively) and Medicaid (30.8% and 35.5%, respectively) insurers as the expected primary payers on the hospital discharge, but there were no significant differences observed for those with vs. without HTN (Table 1). The mean (SD) CCI score was significantly higher among hypertensive than non-hypertensive children (3.15 [1.63] vs. 0.97 [1.51], $p = 0.0004$) (Table 1). A higher proportion of hypertensive children were observed to have

comorbid ESRD compared to non-hypertensive children (37.5% vs. 12.2%, $p < 0.0001$) (Table 1).

No significant differences were observed in the mean (SD) LOS and hospital charges for children with vs. without HTN (Table 2). The majority of hypertensive and non-hypertensive children were discharged home (83.7% and 95.4%, respectively), but there was no significant difference observed for those with vs. without HTN (Table 2). Mortality was assessed but was not reported (NR) due to low sample size ($n < 11$).

Table 1. 2012 NIS-KID: Demographic and Clinical Characteristics Among Children with ADPKD by HTN Status

	Hypertensive		Non-Hypertensive		*p* value
	N	%	N	%	
Sample Size	104	34.6%	197	65.4%	<0.0001*
Age, yrs.					
Mean (SD)	17.57	2.92	16.86	3.01	NS
Sex, n (%)					
Male	62	59.6%	80	40.6%	0.0017*
Female	42	40.4%	117	59.4%	
Race/Ethnicity, n (%)					
Caucasian	58	55.8%	113	57.4%	NS
African-American	21	20.2%	21	10.7%	
Hispanic	13	12.5%	35	17.8%	
Other	12	11.4%	28	14.2%	
US Census Region, n (%)					
Northeast	23	22.1%	42	21.3%	NS
Midwest	29	27.8%	45	22.8%	
South	34	32.7%	59	29.9%	
West	18	17.3%	51	25.9%	
Hospital Location, n (%)					
Central Metropolitan	32	30.8%	53	26.9%	NS
Fringe Metropolitan	18	17.3%	52	26.4%	
Medium Metropolitan	23	22.1%	38	19.3%	
Small Metropolitan	NR	NR	19	9.6%	
Micropolitan	NR	NR	29	14.7%	
Rural	13	12.5%	NR	NR	
Expected Primary Payer, n (%)					
Medicare	NR	NR	NR	NR	NS
Medicaid	32	30.8%	70	35.5%	
Commercial	54	51.9%	90	45.7%	
Self	NR	NR	16	8.1%	
Other	NR	NR	15	7.6%	
CCI Score					
Mean (SD) CCI Score	3.15	1.63	0.97	1.51	0.0004*
Median CCI Score	1.5		0.5		-
CCI Medical Diagnoses and Related Medical Procedures, n (%)**					
COPD	15	14.4%	16	8.1%	NS
ESRD	39	37.5%	24	12.2%	<0.0001*

Abbreviations: CCI – Charlson comorbidity index; NR – not reported due to sample size < 11; COPD – chronic obstructive pulmonary disease; NS – not significant; SD – standard deviation; yrs. – years; *$p < 0.05$

**The following CCI categories were NR due to sample size < 11 and were not significantly different for hypertensive vs. non-hypertensive children with ADPKD: myocardial infarction (MI), congestive heart failure (CHF), peripheral vascular disease (PVD), cerebrovascular disease, dementia, rheumatoid arthritis (RA), ulcerative disorder, mild liver disease (MLD), noncomplicated diabetes, complicated diabetes, paralysis/hemiplegia, non-metastatic cancer, moderate-to-severe liver disease, metastatic cancer, human immunodeficiency virus (HIV)/autoimmune deficiency syndrome (AIDS)

Table 2. 2012 NIS-KID: Inpatient Resource Use Outcomes Among Children with ADPKD by HTN Status

	Hypertensive		Non-Hypertensive		*p* value
	N	%	N	%	
Sample Size	104	34.6%	197	65.4%	<0.0001*
LOS					
Mean (SD)	5.1	6.08	4.33	4.63	0.2496
Median	3.25		3.5		-
Hospital Charges, $USD					
Mean (SD)	$51,372	$83,292	$43,882	$68,208	0.2670
Median	$22,045		$21,357		-
Discharge Location, n (%)**					
Home	87	83.7%	188	95.4%	NS

Abbreviations: LOS – length of stay; SD – standard deviation; USD – United States Dollars; NR – not reported due to sample size < 11; NS – not significant. **Significance:** *$p < 0.05$

**The following discharge location categories were NR due to sample size <11 and they were not significantly different for hypertensive vs. non-hypertensive children: short-term hospital, long-term care, home health care, other.

4.2 Characteristics of Hospitalized Children with ADPKD and Kidney-Related Complications in the US

A sample of inpatient encounters among children diagnosed with ADPKD (N=301) was obtained from the 2012 HCUP NIS-KID database; 175 did not have kidney-related complications (58.1%), and 126 did have kidney-related complications (41.9%) (p = 0.0047, Table 3). No significant differences were observed in mean (SD) age of children with vs. without kidney-related complications (16.9 [3.36] vs. 17.2 [2.72], respectively) (Table 3). No significant sex or racial differences were observed among children with vs. without kidney-related complications (Table 3). The majority of children with and without kidney-related complications were hospitalized in the Southern region (34.1% and 28.6%, respectively) of the US, but there were no significant differences observed among those with vs. without kidney-related complications (Table 3). Most of the children with and without kidney-related complications were hospitalized in hospitals located in central metropolitan (27.8% and 28.6%, respectively) areas of the US, but no significant differences were observed among those with vs. without kidney-related complications (Table 3).

The majority of children with and without kidney-related complications had Commercial (46.8% and 48.6%, respectively) and Medicaid (29.4% and 37.1%, respectively) as the expected primary payers on the hospital discharge, but there were no significant differences observed among those with vs. without kidney-related complications (Table 3). The mean (SD) CCI score was significantly higher among children with kidney-related complications than children without kidney-related complications (1.84 [1.7] vs. 0.69 [1.3], $p < 0.0001$) (Table 3). A significantly higher proportion of children with kidney-related complications

were observed to have comorbid ESRD compared to children without kidney-related complications (50.0% vs. 0.0%, $p < 0.0001$) (Table 3).

The mean (SD) LOS was significantly longer among children with kidney-related complications compared to children without kidney-related complications (5.54 [6.97] vs. 3.74 [3.29], $p = 0.0113$) (Table 4). The mean (SD) hospital charges were significantly higher among children with kidney-related complications compared to children without kidney-related complications ($66,362 [$97,671] vs. $31,871 [$45,034], $p = 0.0016$) (Table 4). No significant differences were observed in the proportion of children with vs. without kidney-related complications and discharged to home (90.5% vs. 92.0%, respectively) (Table 4). Mortality was assessed but was NR due to a low sample size (n < 11).

Table 3. 2012 NIS-KID: Demographic and Clinical Characteristics Among Children with ADPKD by Kidney-Related Complications Status

	Kidney-Related Complications		No Kidney-Related Complications		*p* value
	N	%	N	%	
Sample Size	126	41.9%	175	58.1%	0.0047*
Age, yrs.					
Mean (SD)	16.89	3.36	17.22	2.72	NS
Median	18		17.5		-
Sex, n (%)					
Male	54	42.9%	88	50.3%	NS
Female	72	57.1%	87	49.7%	
Race/Ethnicity, n (%)					
Caucasian	70	55.6%	101	57.7%	NS
African American	22	17.5%	20	11.4%	
Hispanic	22	17.5%	26	14.9%	
Other	12	9.5%	28	16.0%	
US Census Region, n (%)					
Northeast	28	22.2%	37	21.1%	NS
Midwest	31	24.6%	43	24.6%	
South	43	34.1%	50	28.6%	
West	24	19.0%	45	25.7%	
Hospital Location, n (%)					
Central Metropolitan	35	27.8%	50	28.6%	NS
Fringe Metropolitan	28	22.2%	42	24.0%	
Medium Metropolitan	26	20.6%	35	20.0%	
Small Metropolitan	NR	NR	23	13.1%	
Micropolitan	19	15.1%	19	10.9%	
Rural	13	10.3%	NR	NR	
Expected Primary Payer, n (%)					
Medicare	12	9.5%	NR	NR	NS
Medicaid	37	29.4%	65	37.1%	
Commercial	59	46.8%	85	48.6%	
Self	NR	NR	13	7.4%	
Other	NR	NR	11	6.3%	
CCI Score					
Mean (SD) CCI Score	1.84	1.7	0.69	1.33	<0.0001*
Median CCI Score	1.5		0		-
CCI Medical Diagnoses and Related Medical Procedures, n (%)**					
COPD	13	10.3%	18	10.3%	NS
Diabetes, non-complicated	11	8.7%	NR	NR	NS
ESRD	63	50.0%	0	0.0%	<0.0001*
Non-metastatic Cancer	NR	NR	17	9.7%	NS

Abbreviations: CCI – Charlson comorbidity index; NR – not reported due to sample size < 11; NS – not significant; SD – standard deviation; yrs. – years. **Significance:** *p<0.05

**The following CCI categories were NR due to sample size < 11 and were not significantly different for children with ADPKD and kidney-related complications vs. no kidney-related complications: MI, CHF, PVD, CVD, dementia, RA, ulcerative disorder, MLD, complicated diabetes, paralysis/hemiplegia, moderate-to-severe liver disease, metastatic cancer, HIV/AIDS

Table 4. 2012 NIS-KID: Inpatient Resource Use Outcomes Among Children with ADPKD by Kidney-Related Complications Status

	Kidney-Related Complications		No Kidney-Related Complications		*p* value
	N	%	N	%	
Sample Size	126	41.9%	175	58.1%	0.0047*
LOS					
Mean (SD)	5.54	6.97	3.74	3.29	0.0113*
Median	3.5		3		-
Hospital Charges, $USD					
Mean (SD)	$66,362	$97,671	$31,871	$45,033	0.0016*
Median	$27,836		$19,487		-
Discharge Location, n (%)					
Home	114	90.5%	161	92.0%	NS

Abbreviations: LOS – length of stay; NR – not reported due to sample size < 11; NS – not significant; SD – standard deviation; USD – United States Dollars. **Significance:** *$p < 0.05$

**The following discharge location categories were NR due to sample size <11 and they were not significantly different for children with ADPKD and kidney-related complications vs. no kidney-related complications: short-term hospital, long-term care, home health care, other

4.3 Emergency Department Use Among Patients Diagnosed with ADPKD in the US

A sample of ED encounters among patients diagnosed with ADPKD (N=8,871) was obtained from the 2010 HCUP NEDS database and then stratified by disposition from ED (hospitalized vs. discharged home). Inpatient hospitalization from the ED occurred more among older (57.86 vs. 42.85 years, $p < 0.0001$) female (51.34% vs. 48.66%, $p < 0.0001$) patients with ADPKD compared to those discharged to home. The top 10 principal diagnoses among hospitalized patients with ADPKD were observed as follows: PKD-U (n=4,296), ESRD (n=2,275), hypertensive CKD (n=1,857), hyperlipidemia (n=1,163), ADPKD (n=1,161), acute kidney failure (n=1,129), hypertensive kidney disease-unspecified (n=1065), post-surgical dialysis (n=1062), essential HTN-unspecified (n=970), and anemia of CKD (n=942) (Table 5).

The top 10 principal diagnoses among patients with ADPKD and discharged to home were as follows: PKD-U (n=3,163), essential HTN-unspecified (n=1,147), alcohol abuse-in remission (n=531), abdominal pain-unspecified (n=390), long-term use of other medications (n=360), ESRD (n=328), UTI (n=309), post-surgical dialysis (n=283), abdominal pain (n=277), and ADPKD (n=254) (Table 5). There were similar principal diagnoses among those hospitalized and discharged from the ED visits, including the following: PKD-U, ADPKD, ESRD, essential HTN-unspecified, and post-surgical dialysis (Table 5). The mean (SD) total hospital charges for ED services were found to be higher among discharged patients compared to those hospitalized ($4,663 [$5,969] vs. $1,704 [$1,317], $p < 0.0001$).

Table 5. 2010 NEDS: Top 10 Principal Diagnoses at ED Encounters Among Patients with ADPKD by Patient Disposition at Discharge

Hospitalized		Discharged Home	
Principal Diagnosis at ED Encounters	**Frequency**	**Principal Diagnosis at ED Encounters**	**Frequency**
PKD-U	4,296	PKD-U	3,163
ESRD	2,275	Essential HTN, Unspecified	1,147
Hypertensive CKD	1,857	Alcohol Abuse, In Remission	531
Hyperlipidemia	1,163	Abdominal Pain, Unspecified	390
ADPKD	1,161	Long-term Use of Other Medications	360
AKF	1,129	ESRD	328
Hypertensive Kidney Disease, Unspecified	1,065	UTI	309
Post-Surgical Dialysis	1,062	Post-Surgical Dialysis	283
Essential HTN, Unspecified	970	Abdominal Pain	277
Anemia in CKD	942	ADPKD	254

Abbreviations: ADPKD – autosomal dominant polycystic kidney disease; AKF – acute kidney failure; CKD – chronic kidney disease; ED – emergency department; ESRD – end-stage renal disease; HTN – hypertension; PKD-U – polycystic kidney disease, unspecified; UTI – urinary tract infections

4.4 The Burden of ADPKD Among a Cohort of US Medicare Beneficiaries

A sample of 1,850 beneficiaries diagnosed with ADPKD [males (52.3%), females (47.7%)] was obtained from the 2011-2013 5% Medicare LDS (Table 6). Age stratification revealed diagnosis of ADPKD is more prevalent with an increase in age (n=80 [≤39 years], n=671 [40-64 years], n=1099 [≥65 years]] (Table 6). A higher proportion of males compared to females were observed to have ADPKD (52.2% vs. 47.7%) (Table 6). In the total sample, hypertension (81.7%) was the most prevalent comorbid medical condition, and approximately 65% had three or more Charlson comorbidities (Table 6). ESRD occurred in 33.1% of the total sample, with a higher proportion of those aged 40-64 years old (56.6%) (Table 6). Mean (SD) CCI score trended upwards with an increase in age (3.25 [2.01] ≤39 years, 3.73 [2.76] 40-64 years, 4.06 [2.68] ≥65 years] indicating poorer health status with greater risk of mortality among older age groups (Table 6).

An increase in total all-cause HCRU was expected in insurance claims data following any ADPKD diagnostic claim. Among beneficiaries with ADPKD and aged ≤39 years old, there were significant mean differences observed between pre-and post-ADPKD diagnosis periods for all-cause OV (+2.42, $p \leq 0.05$) and disease-related OV (+0.24, $p \leq 0.05$) (Table 7). Among beneficiaries with ADPKD and aged 40-64 years old, significant mean differences were observed between pre-and post-ADPKD diagnosis periods for all-cause OP visits (+2.76, $p \leq 0.05$), OV (+2.54, $p \leq 0.05$), ED visits (+0.38, $p \leq 0.05$), IP hospitalizations (+0.72, $p \leq 0.05$) and LOS (+0.37, $p \leq 0.05$) (Table 7). Beneficiaries aged 40-64 years also experienced significant mean differences between pre-and post-ADPKD diagnosis periods for disease-related OP visits (+0.14, $p \leq 0.05$), OV (+0.19, $p \leq 0.05$), IP hospitalizations (+0.03, $p \leq 0.05$) and LOS (+0.18, $p \leq 0.05$) (Table 7). Among

beneficiaries with ADPKD and aged ≥65 years old, significant mean differences were observed between pre-and post-ADPKD diagnosis periods for all-cause OP visits (+0.66, $p \leq 0.05$), OV (-1.03, $p \leq 0.05$) and IP hospitalizations (+0.52, $p \leq 0.05$) (Table 7). Beneficiaries aged ≥65 years old also experienced significant mean differences between pre-and post-ADPKD diagnosis periods for disease-related OP visits (+0.09, $p \leq 0.05$) and OV (+0.12, $p \leq 0.05$) (Table 7).

An increase in total all-cause direct medical cost was also expected in insurance claims data following any ADPKD diagnostic claim. Among beneficiaries with ADPKD and aged ≤39 years old, there were significant mean differences observed between pre-and post-ADPKD diagnosis periods for all-cause ED visits (+$584, $p \leq 0.05$) and IP hospitalization (+$8,331, $p \leq 0.05$) costs (Table 8). Beneficiaries aged ≤39 years old also experienced a significant mean difference between pre-and post-ADPKD diagnosis periods for disease-related OV (+$29, $p \leq 0.05$) costs (Table 8). Among beneficiaries aged 40-64 years old, significant mean differences were observed between pre-and post-ADPKD diagnosis periods for all-cause OP visit (+$1,337, $p \leq 0.05$), OV (+$297, $p \leq 0.05$), ED visit (+$226, $p \leq 0.05$) and IP hospitalization (+$8,754, $p \leq 0.05$) costs (Table 8). Beneficiaries aged 40-64 years old also experienced significant mean differences between pre- and post-ADPKD diagnosis periods for disease-related OP visit (+$27, $p \leq 0.05$), OV (+$16, $p \leq 0.05$) and IP hospitalization (+$330, $p \leq 0.05$) costs (Table 8). Among beneficiaries aged ≥65 years old, significant mean differences were observed between pre-and post-ADPKD diagnosis periods for all-cause OP visits ($566, $p \leq 0.05$) and IP ($8,226, $p \leq 0.05$) costs (Table 8). Beneficiaries aged ≥65 years old also experienced significant mean differences

between pre-and post-ADPKD diagnosis periods for disease-related OP visits ($10, $p \leq 0.05$) and OV ($10, $p \leq 0.05$) costs (Table 8).

Table 6. 2011-2013 5% Medicare LDS: Demographic and Clinical Characteristics Among ADPKD Beneficiaries by Age Groups

	Total Sample (N=1850)	Age ≤ 39 yrs. (n=80)	Age 40-64 yrs. (n=671)	Age ≥ 65 yrs. (n=1099)
Sex, n (%)				
Male	967 (52.2%)	45 (56.3%)	334 (49.8%)	588 (53.5%)
Female	883 (47.7%)	35 (43.8%)	337 (50.2%)	511 (46.5%)
Age, yrs.				
Mean (SD)	-	31.51 (7.73)	54.20 (6.82)	74.67 (7.23)
CCI Score				
Mean (SD)	-	3.25 (2.01)	3.73 (2.76)	4.06 (2.68)
CCI Comorbidity Group, n (%)				
0	148 (8.0%)	7 (8.8%)	65 (9.7%)	76 (6.9%)
1-2	487 (26.3%)	25 (31.3%)	197 (29.4%)	265 (24.1%)
3-4	569 (30.8%)	28 (35.0%)	195 (29.1%)	346 (31.5%)
5+	646 (34.9%)	20 (25.0%)	214 (31.9%)	412 (37.5%)
CCI Medical Diagnoses and Related Medical Procedures, n (%)				
HTN	1511 (81.7%)	60 (75.0%)	538 (80.2%)	913 (83.1%)
Asthma	177 (9.6%)	9 (11.3%)	61 (9.1%)	107 (9.7%)
COPD	346 (18.7%)	17 (21.3%)	113 (16.8%)	216 (19.7%)
CKD	1364 (73.7%)	58 (72.5%)	492 (73.3%)	814 (74.1%)
ESRD	612 (33.1%)	42 (52.5%)	380 (56.6%)	190 (17.3%)
KTP	268 (14.5%)	16 (20.0%)	143 (21.3%)	109 (9.9%)
Diabetes	625 (33.8%)	18 (22.5%)	237 (35.3%)	370 (33.7%)
Stroke	378 (20.4%)	14 (17.5%)	116 (17.3%)	248 (22.6%)
Cancer	256 (13.8%)	10 (12.5%)	78 (11.6%)	168 (15.3%)

Abbreviations: CCI – Charlson comorbidity index; CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; ESRD – end-stage renal disease; HTN – hypertension; KTP – kidney transplant; SD – standard deviation; yrs. – years

Table 7. 2011-2013 5% Medicare LDS: All-Cause and Disease-Related Direct Medical HCRU Among ADPKD Beneficiaries by Age Groups

	Age ≤ 39 yrs. (n=80)			Age 40-64 yrs. (n=671)			Age ≥ 65 yrs. (n=1099)		
	Pre-Dx	Post-Dx	Mean Difference	Pre-Dx	Post-Dx	Mean Difference	Pre-Dx	Post-Dx	Mean Difference
All-Cause Direct Medical HCRU, Mean (SD)									
OP	10.59 (12.74)	13.09 (12.56)	2.5	9.75 (9.78)	12.51 (10.96)	2.76*	7.59 (8.6)	8.25 (9.29)	0.66*
OV	7.91 (7.82)	10.33 (9.01)	2.42*	10.29 (11.38)	12.83 (11.89)	2.54*	16.73 (14.96)	15.70 (14.24)	-1.03*
ED	3.46 (6.43)	4.23 (8.48)	0.77	0.85 (1.82)	1.23 (2.52)	0.38*	0.61 (1.19)	0.68 (1.79)	0.07
IP	1.40 (2.68)	1.99 (2.88)	0.59	0.63 (1.4)	1.35 (2.18)	0.72*	0.60 (1.27)	1.12 (1.64)	0.52*
LOS	0 (0)	0.43 (2.03)	0.43	0.08 (0.96)	0.45 (3.63)	0.37*	0.04 (0.74)	0.09 (1.18)	0.05
Disease-Related Direct Medical HCRU, Mean (SD)									
OP	0.31 (2.68)	0.33 (0.74)	0.02	0.14 (1.19)	0.28 (1.18)	0.14*	0.07 (0.36)	0.16 (0.16)	0.09*
OV	0.11 (0.45)	0.35 (0.7)	0.24*	0.18 (0.59)	0.37 (0.92)	0.19*	0.20 (1.17)	0.32 (0.79)	0.12*
ED	0 (0)	0.03 (0.16)	0.03	0.01 (0.04)	0.01 (0.11)	0	0.01 (0.03)	0.01 (0.03)	0
IP	0 (0)	0.05 (0.22)	0.05	0.01 (0.12)	0.04 (0.24)	0.03*	0.01 (0.06)	0.01 (0.09)	0
LOS	0 (0)	0.21 (1.01)	0.21	0.04 (0.48)	0.22 (1.81)	0.18*	0.02 (0.37)	0.04 (0.59)	0.02

Abbreviations: Dx – diagnosis; ED – emergency department visits; HCRU – healthcare resource utilization; IP – inpatient stays; LOS – length of stay; OP – outpatient visits; OV – office visits; SD – standard deviation; yrs. – years. **Significance:** *$p < 0.05$

Table 8. 2011-2013 5% Medicare LDS: All-Cause and Disease-Related Direct Medical Costs Among ADPKD Beneficiaries by Age Groups

	Aged ≤39 yrs. old (n=80)			Aged 40-54 yrs. old (n=671)			Aged ≥65 yrs. old (n=1,099)		
	Pre-Dx	**Post-Dx**	**Mean Difference**	**Pre-Dx**	**Post-Dx**	**Mean Difference**	**Pre-Dx**	**Post-Dx**	**Mean Difference**
All-Cause Direct Medical Costs, Mean (SD) $USD									
OP	$11,456 ($15,976)	$12,161 ($14,981)	+$706	$11,920 ($15,622)	$13,257 ($16,567)	+$1,337*	$5,017 ($10,369)	$5,584 ($10,903)	+$566*
OV	$1,026 ($22,524)	$1,068 ($1,262)	+$43	$1,414 ($3,040)	$1,710 ($2,757)	+$297*	$2,298 ($5,636)	$2,109 ($4,699)	-$189
ED	$1,208 ($2,510)	$1,793 ($3,456)	+$584*	$369 ($1,089)	$594 ($1,368)	+$226*	$292 ($737)	$325 ($724)	+$33
IP	$13,656 ($24,498)	$21,987 ($36,851)	+$8,331*	$8,781 ($31,094)	$17,535 ($31,198)	+$8,754*	$6,886 ($18,484)	$15,112 ($31,174)	+$8,226*
Disease-Related Direct Medical Costs, Mean (SD) $USD									
OP	$8 ($65)	$57 ($301)	+$49	$11 ($107)	$38 ($210)	+$27*	$8 ($64)	$18 ($82)	+$10*
OV	$8 ($30)	$37 ($102)	+$29*	$11 ($41)	$28 ($84)	+$16*	$16 ($88)	$26 ($74)	+$10*
ED	$0 ($0)	$13 ($94)	+$13	$0.60 ($16)	$3 ($47)	+$3	$0.21 ($7)	$0.53 ($18)	+$0.32
IP	$0 ($0)	$707 ($3,418)	+$707	$111 ($1,299)	$441 ($3,191)	+$330*	$64 ($1,172)	$89 ($1,210)	+$26

Abbreviations: Dx – diagnosis; ED – emergency department visits; IP – inpatient visits; OP – outpatient visits; OV – office visits; SD – standard deviation; USD – United States Dollars; yrs. – years. **Significance:** *$p < 0.05$

4.5 The Burden of KTP Among a Cohort of US Medicare Beneficiaries with ADPKD

A sample of 562 Medicare beneficiaries diagnosed with ADPKD and receiving KTP was obtained from the 2011-2014 5% Medicare LDS. KTP was more common among those aged ≥65 years old (n = 52 [≤44 years], n=126 [45-54 years], n=169 [55-64 years], n=214 [≥65 years]) and majority of KTP recipients were male (55.2% vs. 44.8%, respectively), but no significant sex differences were observed between age groups (Table 9). The majority of ADPKD beneficiaries were Caucasian (76.9%) or African American (14.1%) compared to Hispanic (3.2%) or Asian (1.3%) (Table 9). A higher proportion of ADPKD beneficiaries aged 55-64 years (78.7%) and ≥65 years (84.1%) were Caucasian, whereas a higher proportion of ADPKD beneficiaries aged ≤44 years and 45-54 years were African American (18.9% and 20.6%, respectively) or Hispanic (5.7% and 6.4%, respectively) (p = 0.0008; Table 9). A higher proportion of ADPKD beneficiaries aged 45-54 years and 55-64 years were Asian (2.4% and 1.8%, respectively) or Other (4.0% and 4.1%, respectively) (p = 0.0008; Table 9).

As expected, the majority of ADPKD beneficiaries lived in the Southern (37.0%) or Northeastern (22.2%) regions of the US, but there were no significant differences observed between age groups (Table 9). The mean (SD) CCI score increased with age (≤44 years: 2.13 [0.39], 45-54 years: 2.39 [0.66], 55-64 years: 2.59 [0.86], ≥65 years: 2.84 [1.50], p = 0.0016) indicating poorer health status and risk of mortality among the elderly with ADPKD and receiving KTP (Table 9). The majority of ADPKD beneficiaries had 1-2 (61.0%) or 3-4 (34.7%) Charlson comorbidities (Table 9). A higher proportion of ADPKD beneficiaries aged ≤44 years (88.7%) had 1-2 Charlson comorbidities compared to ADPKD beneficiaries aged 45-54 years (70.6%), 55-64 years (57.4%), and ≥65 years

(51.4%) old ($p < 0.0001$; Table 9). A higher proportion of ADPKD beneficiaries aged ≥65 years (40.2%) had 3-4 Charlson comorbidities compared to ADPKD beneficiaries aged ≤44 years (11.3%), 45-54 years (29.4%), and 55-64 years (39.1%) ($p < 0.0001$; Table 9). HTN was the most common Charlson comorbidity among 81.1% of the total sample, but no significant differences were observed between age groups (n=42 [≤44 years], n=105 [45-54 years], n=132 [55-64 years], n=177 [≥65 years], $p = 0.5974$) (Table 9). Significant differences were observed among ADPKD beneficiaries aged ≥65 years as evidenced by a greater presence of congestive heart failure (CHF) (n=34, $p = 0.0003$), peripheral vascular disease (PVD) (n=23, $p = 0.0089$), uncomplicated diabetes (n=59, $p = 0.0002$), non-metastatic cancer (n=18, $p = 0.0037$), and UTI (n=49, $p = 0.0186$) compared to younger age groups, thus, greater severity of illness before and on the date of KTP (Table 9).

The total direct medical HCRU (IP, OP, OV, ED) was approximately 18,106,420 visits for the pre-and post-KTP periods, collectively (Table 10). The mean difference in the total number of direct medical visits was highest among ADPKD beneficiaries aged ≥65 years (+1,637,788 visits) compared to ADPKD beneficiaries aged ≤44 years (+199,455 visits), 45-54 years (+469,221 visits), and 55-64 years (+441,028 visits) ($p < 0.0001$; Table 10). The mean difference in the number of OP visits between the pre-and post-KTP periods was highest among ADPKD beneficiaries aged 55-64 years (+12,624 visits) compared to ADPKD beneficiaries aged ≤44 years (-5,913 visits), 45-54 years (+10,917), and ≥65 years (-131 visits) ($p < 0.0001$; Table 10, Figure 1); ADPKD beneficiaries aged ≤44 years (-5,913 visits) had the greatest mean reduction in the number of OP visits following KTP (Table 10). The mean difference in the number of OV between the pre-and post-KTP periods was highest among ADPKD beneficiaries aged ≥65 years (+1,477,012 visits)

compared to ADPKD beneficiaries aged ≤44 years (-95,226 visits), 45-54 years (+425,962 visits), and 55-64 years (+364,538 visits) ($p < 0.0001$; Table 10); ADPKD beneficiaries aged ≤44 years (-95,226 visits) had the greatest mean reduction in the number of OV following KTP.

The mean difference in the number of ED visits between the pre-and post-KTP periods was highest among ADPKD beneficiaries aged ≥65 years (+80,198 visits) compared to ADPKD beneficiaries aged ≤44 years (+52,247 visits), 45-54 years (+21,531 visits), and 55-64 years (+38,009 visits) old ($p < 0.0001$; Table 10); no mean reductions were observed in the number of ED visits following KTP. The mean difference in the number of IP visits between the pre-and post-KTP periods was highest among ADPKD beneficiaries aged ≥65 years (+80,709 visits) compared to ADPKD beneficiaries aged ≤44 years (+57,895 visits), 45-54 years (+10,811 visits), and 55-64 years (+25,857 visits) ($p < 0.0001$; Table 10); no mean reductions were observed in the number of IP visits following KTP.

The mean difference in the total all-cause direct medical costs (IP, OP, OV, ED) was significantly lower among ADPKD beneficiaries aged ≥65 years (-$86,127) compared to ADPKD beneficiaries aged ≤44 years (+$636), 45-54 years (-$3,325), and 55-64 years (-$887) old ($p < 0.0001$; Table 11). ADPKD beneficiaries aged ≤44 years were the only age group to experience an increase in total all-cause direct medical costs following KTP (Table 11). The mean difference in the direct cost of OP visits was significantly higher among ADPKD beneficiaries aged ≥65 years (+$1,126,295) compared to ADPKD beneficiaries aged ≤44 years (+$21,291), 45-54 years (-$220,549), and 55-64 years (-$455,653) old ($p < 0.0001$; Table 11). ADPKD beneficiaries aged 55-64 years old had a greater reduction in direct cost of OP visits following KTP (Table 11).

The mean difference in the direct cost of OV was significantly lower among ADPKD beneficiaries aged 55-64 years (-$1,552,281) compared to ADPKD beneficiaries aged ≤44 years (+$114,922), 45-54 years (+$88,429), and ≥65 years (-$104,711) old ($p < 0.0001$; Table 11). ADPKD beneficiaries aged ≤44 years had a greater increase in the direct cost of OV following KTP (Table 11). The mean difference in the direct cost of ED visits was significantly higher among ADPKD beneficiaries aged ≤44 years (+$12,190,535) compared to ADPKD beneficiaries aged 45-54 years (+$104,761), 55-64 years (+$3,507,255), and ≥65 years (+$8,506,933) ($p < 0.0001$; Table 11); no mean reductions in direct cost of ED visits were observed for any age groups following KTP. The mean difference in the direct cost of IP visits was significantly higher among ADPKD beneficiaries aged ≤44 years (+$11,994,015) compared to ADPKD beneficiaries aged 45-54 years (+$552,805), 55-64 years (+$2,618,759), and ≥65 years (+$7,354,100) old ($p < 0.0001$; Table 11); no mean reductions in the direct cost of IP visits were observed for any age group following KTP.

Table 9. 2011-2014 5% Medicare LDS: Demographic and Clinical Characteristics Among ADPKD Beneficiaries by Age Groups

	Total (N=562)	≤44 yrs. (n=53)	45-54 yrs. (n=126)	55-64 yrs. (n=169)	≥65 yrs. (n=214)	*p* value
Sex, n (%)						
Male	310 (55.2%)	36 (67.9%)	64 (50.8%)	98 (58.0%)	112 (52.3%)	0.1272
Female	252 (44.8%)	17 (32.1%)	62 (49.2%)	71 (42.0%)	102 (47.7%)	
Race/Ethnicity, n (%)						
Caucasian	432 (76.9%)	38 (71.7%)	81 (64.3%)	133 (78.7%)	180 (84.1%)	0.0008*
African American	79 (14.1%)	10 (18.9%)	26 (20.6%)	19 (11.2%)	24 (11.2%)	
Hispanic	18 (3.2%)	3 (5.7%)	8 (6.4%)	4 (2.4%)	3 (1.4%)	
Asian	7 (1.3%)	0 (0%)	3 (2.4%)	3 (1.8%)	1 (0.5%)	
Other	18 (3.2%)	1 (1.9%)	5 (4.0%)	7 (4.1%)	5 (2.3%)	
US Census Region, n (%)						
Northeast	125 (22.2%)	15 (28.3%)	31 (24.6%)	33 (19.5%)	46 (21.5%)	0.5056
Midwest	118 (21.0%)	11 (20.8%)	21 (16.7%)	40 (23.7%)	46 (21.5%)	
South	208 (37.0%)	16 (30.2%)	43 (34.1%)	68 (40.2%)	81 (37.9%)	
West	51 (9.1%)	7 (13.2%)	14 (11.1%)	14 (8.3%)	16 (7.5%)	
CCI Score						
Mean (SD)	2.56 (1.07)	2.13 (0.39)	2.39 (0.66)	2.59 (1.86)	2.84 (1.50)	0.0016*
CCI Comorbidity Group, n (%)						
0	3 (0.5%)	0 (0%)	0 (0%)	1 (0.6%)	2 (0.9%)	<0.0001*
1-2	343 (61.0%)	47 (88.7%)	89 (70.6%)	97 (57.4%)	110 (51.4%)	
3-4	195 (34.7%)	6 (11.3%)	37 (29.4%)	66 (39.1%)	86 (40.2%)	
5-6	17 (3.0%)	0 (0%)	0 (0%)	5 (3.0%)	12 (5.6%)	
8+	4 (0.7%)	0 (0%)	0 (0%)	0 (0%)	4 (1.9%)	

Abbreviations: CCI – Charlson comorbidity index; SD – standard deviation; yrs. – years. **Significance:** *$p < 0.05$

Table 9. 2011-2014 5% Medicare LDS: Demographic and Clinical Characteristics Among ADPKD Beneficiaries by Age Groups (continued)

	Total (N=562)	≤44 yrs. (n=53)	45-54 yrs. (n=126)	55-64 yrs. (n=169)	≥65 yrs. (n=214)	*p* value
CCI Medical Diagnoses and Related Medical Procedures, n (%)						
HTN	456 (81.1%)	42 (79.3%)	105 (83.3%)	132 (78.1%)	177 (82.7%)	0.5974
MI	35 (6.2%)	0 (0%)	6 (4.7%)	10 (5.9%)	19 (8.9%)	0.0863
CHF	61 (10.9%)	2 (3.8%)	3 (2.4%)	22 (13%)	34 (15.9%)	0.0003*
PVD	37 (6.6%)	0 (0%)	5 (4.0%)	9 (5.3%)	23 (10.8%)	0.0089*
CVD	29 (5.2%)	0 (0%)	5 (4.0%)	7 (4.1%)	17 (7.9%)	0.072
Dementia	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)	0.6528
COPD	66 (11.7%)	3 (5.7%)	14 (11.1%)	18 (10.7%)	31 (14.5%)	0.2971
RA	4 (0.7%)	0 (0%)	0 (0%)	0 (0%)	4 (1.9%)	0.0877
Ulcerative Disorder	6 (1.1%)	4 (7.6%)	1 (0.8%)	3 (1.8%)	6 (2.8%)	
MLD	54 (9.6%)	3 (5.7%)	15 (11.9%)	15 (8.9%)	21 (9.8%)	0.6082
Moderate to Severe Liver Disease	3 (0.5%)	0 (0%)	0 (0%)	2 (1.2%)	1 (0.5%)	0.5084
Diabetes, non-Complicated	133 (23.7%)	1 (1.9%)	24 (19.1%)	49 (29.0%)	59 (27.6%)	0.0002*
Diabetes, Complicated	27 (4.8%)	1 (1.9%)	3 (2.4%)	11 (6.5%)	12 (5.6%)	0.2636
Paralysis, Hemiplegia	2 (0.4%)	0 (0%)	0 (0%)	1 (0.6%)	1 (0.5%)	0.8063
Non-Metastatic Cancer	33 (5.9%)	0 (0%)	1 (0.8%)	14 (8.3%)	18 (8.4%)	0.0037*
Metastatic Cancer	8 (1.4%)	0 (0%)	0 (0%)	2 (1.2%)	6 (2.8%)	0.1351
UTI	96 (17.1%)	4 (7.6%)	17 (13.5%)	26 (15.4%)	49 (22.9%)	0.0186*
Connective Tissue Disease	8 (1.4%)	1 (1.9%)	0 (0%)	1 (0.6%)	6 (2.8%)	0.1305
HIV / AIDS	1 (0.2%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)	0.3251
Kidney Stones	6 (1.1%)	0 (0%)	2 (1.6%)	1 (0.6%)	3 (1.4%)	0.6862

Abbreviations: AIDS – autoimmune deficiency syndrome; CCI – Charlson comorbidity index; COPD – chronic obstructive pulmonary disease; CHF – congestive heart failure; HIV – human immunodeficiency virus; HTN – hypertension; MI – myocardial infarction; MLD – mild liver disease; PVD – peripheral vascular disease; RA – rheumatoid arthritis. **Significance:** *$p < 0.05$

Table 10. 2011-2014 5% Medicare LDS: Pre- vs. Post-KTP Comparison of All-Cause Direct Medical HCRU Among ADPKD Beneficiaries by Age Groups

	Total Sample (N=562)	≤44 yrs. (n=53)	45-54 yrs. (n=126)	55-64 yrs. (n=169)	≥65 yrs. (n=214)	*p* value
		Mean Difference	Mean Difference	Mean Difference	Mean Difference	
All-Cause Direct Medical HCRU, Mean (SD)						
Total	18,106,420	+199,455	+469,221	+441,028	+1,637,788	<0.0001
OP	333,329	-5,913	+10,917	+12,624	-131	<0.0001
OV	16,152,286	+95,226	+425,962	+364,538	+1,477,012	<0.0001
ED	971,056	+52,247	+21,531	+38,009	+80,198	<0.0001
IP	649,749	+57,895	+10,811	+25,857	+80,709	<0.0001

Abbreviations: ED – emergency department visits; HCRU – healthcare resource utilization; IP – inpatient visits; KTP – kidney transplant; NN – native nephrectomy; OP – outpatient visits; OV – office visits; SD – standard deviation; yrs. – years. **Significance:** *$p < 0.05$

Table 11. 2011-2014 5% Medicare LDS: Pre- vs. Post-KTP Comparison of All-Cause Direct Medical Costs Among ADPKD Beneficiaries by Age Groups

	Total Sample (N=562)	≤44 yrs. (n=53)	45-54 yrs. (n=126)	55-64 yrs. (n=169)	≥65 yrs. (n=214)	p value
		Mean Difference	Mean Difference	Mean Difference	Mean Difference	
All-Cause Direct Medical Costs, Mean (SD) USD						
Total	$5,911 ($10,131)	$636	-$3,325	-$887	-$86,127	<0.0001
OP	$5,651,623	$21,291	-$220,549	-$455,653	$1,126,295	<0.0001
OV	$3,880,191	$114,922	$88,429	-$1,552,281	-$104,711	<0.0001
ED	$48,952,227	$12,190,535	$104,761	$3,507,255	$8,506,933	<0.0001
IP	$42,750,104	$11,994,015	$552,805	$2,618,759	$7,354,100	<0.0001

Abbreviations: ED – emergency department visits; IP – inpatient visits; KTP – kidney transplant; OP – outpatient visits; OV – office visits; SD – standard deviation; yrs. – years. **Significance:** *$p < 0.05$

4.6 Relative Risk and Crude Mortality among Cohorts of US Medicare Beneficiaries with ADPKD

A sample of 731 Medicare beneficiaries diagnosed with ADPKD, comorbid ESRD, and receiving RRT was obtained and then stratified by type of RRT (dialysis [n=401], KTP [n=330]) (Table 12). The majority of ADPKD beneficiaries in the dialysis and KTP cohorts were male (53.1% and 53.3%, respectively) compared to female (46.9% and 46.7%, respectively) (Table 12). A higher proportion of KTP beneficiaries were male compared to dialysis beneficiaries (53.5% vs. 53.1%; $p = 0.0034$) (Table 12). A higher proportion of dialysis beneficiaries were female compared to KTP beneficiaries (46.9% vs. 46.7%; $p = 0.0034$) (Table 12). ADPKD beneficiaries receiving KTP were older than those receiving dialysis (60.87 [11.22] vs. 58.36 [12.43]; $p < 0.0001$) (Table 12). No significant age group differences were observed among the dialysis vs. KTP beneficiaries (Table 12). A higher proportion of ADPKD beneficiaries receiving dialysis were African American (20.7% vs. 11.5%, respectively), Hispanic (4.5% vs. 3.3%, respectively), or Asian (2.5% vs. 1.2%, respectively) compared to those receiving KTP ($p = 0.0003$; Table 12). A higher proportion of ADPKD beneficiaries receiving KTP were Caucasian (77.9% vs. 68.3%, respectively), Other (3.9% vs. 2.7%, respectively), or had missing (2.1% vs. 1.3%, respectively) race/ethnicity ($p = 0.0003$; Table 12).

A higher proportion of ADPKD beneficiaries receiving dialysis lived in the Northeastern (22.7% vs. 20.0%, respectively), Midwestern (15.2% vs. 8.8%, respectively), Southern (43.4% vs. 40.0%, respectively), Western (10.5% vs. 8.8%, respectively) or had missing (8.2% vs. 7.6%, respectively) US Census Region ($p = 0.0202$; Table 12). The mean (SD) CCI score was higher among ADPKD beneficiaries receiving dialysis compared to those receiving KTP (3.34 [1.97] vs. 2.69 [1.31]; $p < 0.0001$) (Table 12). A higher proportion of

ADPKD beneficiaries receiving KTP had 0 (0.3% vs. 0.0%, respectively), 1-2 (62.1% vs. 47.1%, respectively), 3-4 (35.2% vs. 29.9%, respectively) Charlson comorbidities compared to those receiving dialysis ($p < 0.0001$; Table 12). A higher proportion of ADPKD beneficiaries receiving dialysis had 5+ (22.9% vs. 2.4%) Charlson comorbidities compared to those receiving KTP ($p < 0.0001$; Table 12). PVD (13.5% vs. 2.7%; $p = 0.014$), COPD (22.9% vs. 4.6%; $p = 0.0532$), RA (0.8% vs. 0.6%; $p < 0.0001$), peptic ulcer disease (2.2% vs. 1.5%; $p < 0.0001$), ischemic heart disease (29.4% vs. 8.8%; $p = 0.0006$) and arrhythmias (28.2% vs. 10.0%; $p = 0.0321$) were more common in ADPKD beneficiaries receiving dialysis compared to those receiving KTP (Table 12).

The total number of hospitalizations (523 vs. 310, respectively), ambulatory/ED visits (1,914 vs. 1,269, respectively), and OP visits (1,716 vs. 864, respectively) were higher among ADPKD beneficiaries receiving dialysis compared to those receiving KTP (Table 13). More deaths occurred among ADPKD beneficiaries receiving dialysis (n=49, 12.2%) compared to those receiving KTP (n=18, 5.5%) (Table 13). Crude mortality rate per patient year (PPY; 95% CI) was higher among ADPKD beneficiaries receiving dialysis (7.25% [6.17-8.52]) compared to those receiving KTP (4.14% [2.36-7.27]); a higher mortality risk difference (+3.11%) was observed for ADPKD beneficiaries receiving dialysis compared to those receiving KTP (Table 13).

Table 12. 2011-2014 5% Medicare LDS: Demographics and Clinical Characteristics Among ADPKD Beneficiaries by RRT Type

	Dialysis Cohort (n=401)	KTP Cohort (n=330)	*p* value
Sex, n (%)			
Male	213 (53.1%)	176 (53.3%)	0.0034*
Female	188 (46.9%)	154 (46.7%)	
Age (yrs.), n (%)			
Mean (SD)	58.36 (12.43)	60.87 (11.22)	<0.0001*
≤24-44 yrs.	41 (10.2%)	29 (8.8%)	0.0964
45-54 yrs.	88 (22.0%)	55 (16.7%)	
55-64 yrs.	116 (28.9%)	104 (31.5%)	
≥65 yrs.	156 (38.9%)	142 (43.0%)	
Race/Ethnicity, n (%)			
Caucasian	274 (68.3%)	257 (77.9%)	0.0003*
African American	83 (20.7%)	38 (11.5%)	
Hispanic	18 (4.5%)	11 (3.3%)	
Asian	10 (2.5%)	4 (1.2%)	
Other	11 (2.7%)	13 (3.9%)	
Missing	5 (1.3%)	7 (2.1%)	
US Census Region, n (%)			
Northeast	91 (22.7%)	66 (20.0%)	0.0202*
Midwest	61 (15.2%)	29 (8.8%)	
South	174 (43.4%)	132 (40.0%)	
West	42 (10.5%)	29 (8.8%)	
Missing	33 (8.2%)	25 (7.6%)	
CCI Score			
Mean (SD)	3.34 (1.97)	2.69 (1.31)	<0.0001*
CCI Comorbidity Group, n (%)			
0	0 (0%)	1 (0.3%)	<0.0001*
1-2	189 (47.1%)	205 (62.1%)	
3-4	120 (29.9%)	116 (35.2%)	
5+	92 (22.9%)	8 (2.4%)	

Abbreviations: CCI – Charlson comorbidity index; SD – standard deviation; yrs. – years.
Significance: *$p \leq 0.05$

Table 12. 2011-2014 5% Medicare LDS: Demographics and Clinical Characteristics Among ADPKD Beneficiaries by RRT Type (continued)

	Dialysis Cohort (n=401)	KTP Cohort (n=330)	*p* value
CCI Medical Diagnoses and Related Medical Procedures, n (%)			
MI	19 (4.7%)	3 (0.9%)	0.8166
CHF	104 (25.9%)	22 (6.7%)	0.1003
PVD	54 (13.5%)	9 (2.7%)	0.014*
CVD	25 (6.2%)	9 (2.7%)	0.376
Hemiplegia or paraplegia	7 (1.8%)	2 (0.6%)	0.6804
Dementia	12 (3.0%)	1 (0.3%)	0.1989
COPD	92 (22.9%)	15 (4.6%)	0.0532*
RA	3 (0.8%)	2 (0.6%)	<0.0001*
Peptic ulcer disease	9 (2.2%)	5 (1.5%)	<0.0001*
Diabetes without chronic complications	85 (21.2%)	73 (22.1%)	0.7796
Diabetes with chronic complications	39 (9.7%)	11 (3.3%)	0.1498
Any malignancy, including leukemia and lymphoma	38 (9.5%)	24 (7.3%)	0.1215
Metastatic solid tumor	9 (2.2%)	3 (0.9%)	0.364
MLD	89 (22.2%)	44 (13.3%)	0.0894
Moderate or severe liver disease	40 (10.0%)	19 (5.8%)	0.2089
HIV / AIDS	0 (0%)	0 (0%)	N/A
Stroke / transient ischemic attack	13 (3.2%)	6 (1.8%)	0.8448
Ischemic heart disease (IHD)	118 (29.4%)	29 (8.8%)	0.0006*
Hip fracture	7 (1.8%)	2 (0.6%)	0.364
Syncope	7 (1.8%)	4 (1.2%)	0.8166
Arrhythmias	113 (28.2%)	33 (10.0%)	0.0321*
HTN	342 (85.3%)	261 (79.1%)	0.0882
Osteoarthritis	38 (9.5%)	20 (6.1%)	0.9896
Depressive symptoms	45 (11.2%)	15 (4.6%)	0.4071
Others	27 (6.7%)	50 (15.2%)	0.1396

Abbreviations: AIDS – autoimmune deficiency syndrome; CCI – Charlson comorbidity index; COPD – chronic obstructive pulmonary disease; CHF – congestive heart failure; HIV – human immunodeficiency virus; HTN – hypertension; IHD – ischemic heart disease; MI – myocardial infarction; MLD – mild liver disease; N/A – not applicable; PVD – peripheral vascular disease; RA – rheumatoid arthritis. **Significance:** $*p \leq 0.05$

Table 13. 2011-2014 5% Medicare LDS: Direct Medical HCRU and Crude Mortality Among ADPKD Beneficiaries by RRT Type

	Dialysis Cohort (n=401)	KTP Cohort (n=330)	Mean / % Difference
Post-Period HCRU, Mean (SD)			
IP	523	310	213
Ambulatory and ED Visits	1,914	1,269	645
OP Visits	1,716	864	852
Post-Period Mortality			
Total Deaths, n (%)	49 (12.2%)	18 (5.5%)	31
Crude Mortality Rate PPY, % (95% CI)	7.25% (6.17-8.52)	4.14% (2.36-7.27)	+3.11%
Abbreviations: CI – confidence interval; ED – emergency department visits; HCRU – health care resource utilizations; IP – inpatient visits; OP – outpatient visits; PPY – per patient year			

4.7 Inpatient Resource Use and Cost Outcomes Among Kidney Transplant Recipients with vs. without ADPKD

4.7.1 Aim #1: Patient Demographics, Comorbidities, Hospital Characteristics, Inpatient Resource Use (LOS), and Total Patient Cost at Index Hospitalization for KTP Surgery

A total sample of 3,512 patients receiving KTP was obtained and stratified as ADPKD (n=285) and non-ADPKD (n=3,227) for comparison of patient demographics, comorbidities, hospital characteristics, inpatient resource use (i.e., LOS), and total patient cost at index hospitalization for KTP surgery. The proportion of patients with index discharge for KTP surgery was slightly higher in Q2 (27%) and Q4 (27%) compared to Q1 (21%) and Q3 (26%) of the 2018 PHD (Table 14). The median (IQR) age for the total cohort receiving KTP was approximately 55 (43-63) years old, and the majority of patients were 55-64 (30%) and 45-54 years old (22%) (Table 14). Approximately 61% of the total cohort were male, with the majority of patients being White (52%) and non-Hispanic (54%) (Table 14). Half of the patients in the cohort were married, and the majority of patients were discharged home (77%) or home under home health (HHO) (20%) (Table 14). Medicare and managed care organizations were the primary expected payers for the index discharge for KTP surgery (67% and 17%, respectively) (Table 14).

It was expected that renal failure (100%) was the most common Elixhauser comorbidity among patients with and without ADPKD and receiving KTP in this cohort (Table 15). Complicated HTN (89%), fluid and electrolyte disorders (54%), and complicated diabetes (42%) were also common among the total cohort (Table 15). Approximately 48% of index hospitalizations for KTP surgery occurred in the Southern US region (Table 16). The majority of index discharges for KTP surgery occurred among teaching hospitals (79%) with a bed size of 500+ (77%) and were located in urban areas (92%) (Table 16). The

median (IQR) LOS and total patient cost of index hospitalization for KTP surgery among the total cohort was approximately 5 (4-7) days and $112,000 ($75,000 - $137,000), respectively (Table 17).

No significant difference was observed in the median (IQR) age of patients with vs. without ADPKD at index hospitalization for KTP surgery (56 [47-62] vs. 55 [43-63] years; p = 0.1658) (Table 14). However, a higher proportion of patients with ADPKD were aged 55-64 and 45-54 years old compared to patients without ADPKD (35% vs. 29% and 28% vs. 21%, respectively; $p < 0.0001$) (Table 14; Figure 2). A higher proportion of patients with ADPKD were female compared to those without ADPKD (46% vs. 38%, respectively; p = 0.0050) (Table 14; Figure 3). A higher proportion of patients with ADPKD were White (71% vs. 51%, respectively), while a higher proportion of patients without ADPKD were of Other or Black race (24 vs. 18% and 23% vs. 11%, respectively) ($p < 0.0001$) (Table 14; Figure 4). A higher proportion of patients with ADPKD had primary managed care and private insurance coverage (24% vs. 17% and 12% vs. 7%, respectively) while a higher proportion of patients without ADPKD had primary Medicare and Medicaid coverage (67% vs. 57% and 5% vs. 3%, respectively) (p = 0.0030) (Table 14; Figure 5).

Patients without ADPKD were found to have a greater comorbidity presence with a higher proportion of patients without ADPKD having CHF (11% vs. 7%; p = 0.0498), VD (5% vs. 3%; p = 0.0452), HTN-C (90% vs. 78%; $p < 0.0001$), DC (45% vs. 9%; $p < 0.0001$), RA (7% vs. 1%; $p < 0.0001$), WL (4% vs. 1%; p = 0.0427), and AA (2% vs. 0%; p = 0.0315) compared to those with ADPKD (Table 15; Figure 6). However, a higher proportion of patients with ADPKD were identified to have HTN-U compared to those without ADPKD (17% vs. 7%, respectively; $p < 0.0001$) (Table 15; Figure 6). A higher

proportion of patients with ADPKD had index discharges for KTP surgery at hospitals in rural locations compared to those without ADPKD (5% vs. 3%, respectively; $p = 0.0157$) (Table 16). The unadjusted median (IQR) LOS (4 [4-6] vs. 5 [4-7] days, respectively; $p = 0.0006$) and total patient cost ($103,000 [$72,000-$128,000] vs. $113,000 [$75,000-$139,000], respectively; $p = 0.0010$) at index hospitalization for KTP surgery were significantly lower among patients with ADPKD compared to those without ADPKD (Table 17).

Table 14. 2018 PHD: Demographics Among Patients with vs. without ADPKD at Index Discharge for KTP Surgery

Data Element	Estimates			
	Total Sample (N=3,512)	ADPKD (n=285)	Non-ADPKD (n=3,227)	p value
Age at Admission, yrs.				
Median (IQR)	55 (43 - 63)	56 (47 - 62)	55 (43 - 63)	0.1658
Age Groups (yrs.), n (%)				
18-24	78 (2.22%)	1 (0.35%)	77 (2.39%)	<0.0001*
25-34	333 (9.48%)	12 (4.21%)	321 (9.95%)	
35-44	564 (16.06%)	39 (13.68%)	525 (16.27%)	
45-54	765 (21.78%)	81 (28.42%)	684 (21.20%)	
55-64	1,037 (29.53%)	99 (34.74%)	938 (29.07%)	
65-74	670 (19.08%)	52 (18.25%)	618 (19.15%)	
≥75	65 (1.85%)	1 (0.35%)	64 (1.98%)	
Sex, n (%)				
Male	2,158 (61.45%)	153 (53.68%)	2,005 (62.13%)	0.0050*
Female	1,354 (38.55%)	132 (46.32%)	1,222 (37.87%)	
Race, n (%)				
White	1,837 (52.31%)	202 (70.88%)	1,635 (50.67%)	<0.0001*
Black	757 (21.55%)	30 (10.53%)	727 (22.53%)	
Other	818 (23.29%)	50 (17.54%)	768 (23.80%)	
Unknown	100 (2.85%)	3 (1.05%)	97 (3.01%)	
Ethnicity, n (%)				
Hispanic	667 (18.99%)	42 (14.74%)	625 (19.37%)	0.1557
Non-Hispanic	1,899 (54.07%)	164 (57.54%)	1,735 (53.77%)	
Unknown	946 (26.94%)	79 (27.72%)	867 (26.87%)	

Abbreviations: ADPKD-autosomal dominant polycystic kidney disease, IQR-interquartile range, KTP-kidney transplantation, PHD-Premier Healthcare Database, yrs.-years.

Significance: $p \leq 0.05$*; ***Chi-Square test*** was conducted to compare the proportions of patients for binary and categorical variables (age groups, sex, race). ***Fisher's Exact test*** was conducted to compare the proportions of patients for all binary and categorical variables (age groups, sex, race) having sample size <20. ***Wilcoxon Rank Sum test*** was conducted to compare the median for continuous age variable.

Table 14. 2018 PHD: Demographics Among Patients with vs. without ADPKD at Index Discharge for KTP Surgery (continued)

Data Element	Estimates			
	Total Sample (N=3,512)	ADPKD (n=285)	Non-ADPKD (n=3,227)	p value
Marital Status, n(%)				
Married	1,759 (50.09%)	158 (55.44%)	1,601 (49.61%)	0.2161
Single	1,396 (39.75%)	100 (35.09%)	1,296 (40.16%)	
Other	333 (9.48%)	24 (8.42%)	309 (9.58%)	
Missing	24 (0.68%)	3 (1.05%)	21 (0.65%)	
2018 Index Discharge Quarter, n(%)				
Q1 (January - March)	745 (21.21%)	65 (22.81%)	680 (21.07%)	0.1279
Q2 (April - June)	933 (26.57%)	80 (28.07%)	853 (26.43%)	
Q3 (July - September)	904 (25.74%)	73 (25.61%)	831 (25.75%)	
Q4 (October - December)	930 (26.49%)	67 (23.51%)	863 (26.74%)	
Discharge Status, n(%)				
Home	2,686 (76.48%)	238 (83.51%)	2,448 (75.86%)	0.3012
Home Under Home Health (HHO)	690 (19.65%)	44 (15.44%)	646 (20.02%)	
Short-Term General Hospital	1 (0.03%)	0 (0.00%)	1 (0.03%)	
Skilled Nursing Facility	43 (1.22%)	2 (0.70%)	41 (1.27%)	
Transfer to Hospice Home	1 (0.03%)	0 (0.00%)	1 (0.03%)	
Transfer to Other Rehab Facility	57 (1.62%)	1 (0.35%)	56 (1.74%)	
Transfer to Long-Term Care Hospital	7 (0.20%)	0 (0.00%)	7 (0.22%)	
Other	4 (0.12%)	0 (0.00%)	4 (0.12%)	
Expired (i.e., Death)	23 (0.65%)	0 (0.00%)	23 (0.71%)	

Abbreviations: ADPKD-autosomal dominant polycystic kidney disease, HHO-home health organization, KTP-kidney transplantation, PHD-Premier Healthcare Database, Q-quarter.

Significance: $p \leq 0.05$*; ***Chi-Square test*** was conducted to compare the proportions of patients for binary and categorical variables (discharge quarter, and discharge status). ***Fisher's Exact test*** was conducted to compare the proportions of patients for all categorical variables (marital status, index discharge quarter, and discharge status) having sample size <20.

Table 14. 2018 PHD: Demographics Among Patients with vs. without ADPKD at Index Discharge for KTP Surgery (continued)

Data Element	Estimates			
	Total Sample (N=3,512)	ADPKD (n=285)	Non-ADPKD (n=3,227)	p value
Expected Primary Payer, n (%)				
Medicare	2,335 (66.49%)	162 (56.84%)	2,173 (67.34%)	0.0030*
Medicaid	172 (4.90%)	8 (2.80%)	164 (5.08%)	
Managed Care	608 (17.31%)	68 (23.86%)	540 (16.73%)	
Private Insurance	260 (7.40%)	34 (11.93%)	226 (7.00%)	
Self-Pay	22 (0.63%)	3 (1.05%)	19 (0.59%)	
Workers Compensation	5 (0.14%)	0 (0.00%)	5 (0.15%)	
Direct Employer	13 (0.37%)	2 (0.70%)	11 (0.34%)	
Other Government Payer	68 (1.94%)	8 (2.81%)	60 (1.86%)	
Other	29 (0.83%)	0 (0.00%)	29 (0.90%)	

Abbreviations: ADPKD-autosomal dominant polycystic kidney disease, KTP-kidney transplantation, PHD-Premier Healthcare Database.

Significance: $p \leq 0.05$*; ***Chi-Square test*** was conducted to compare the proportions of patients for categorical variables (expected primary payer). ***Fisher's Exact test*** was conducted to compare the proportions of patients for categorical variables (expected primary payer) having sample size <20.

Figure 2. 2018 PHD: Proportion of Patients with vs. without ADPKD and Receiving KTP by Age Group

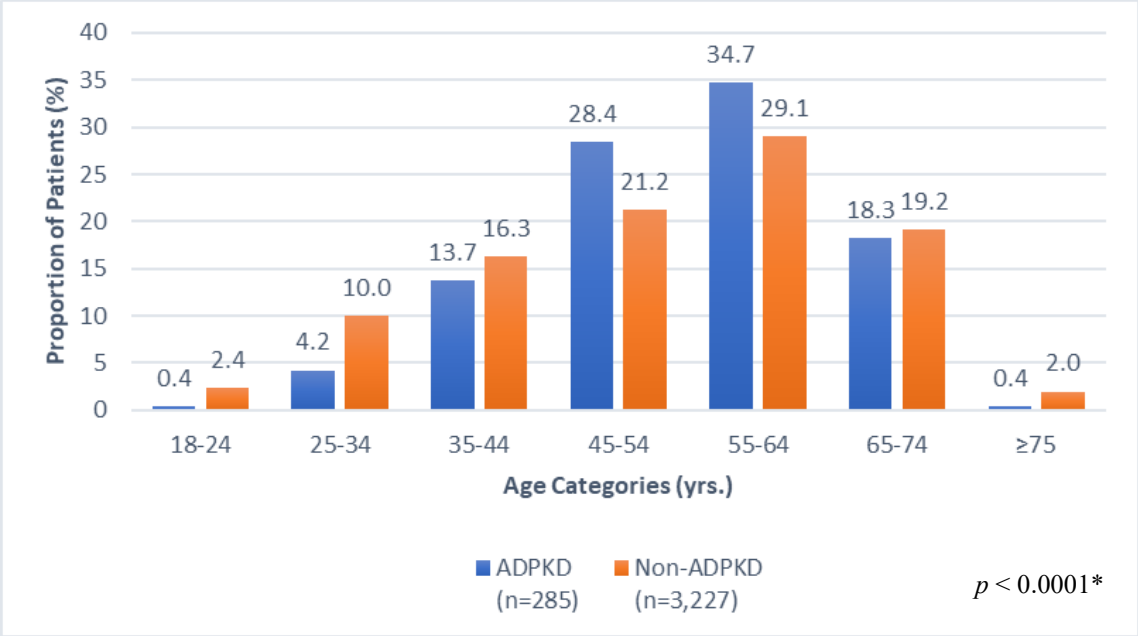


Figure 3. 2018 PHD: Proportion of Patients with vs. without ADPKD and Receiving KTP by Sex

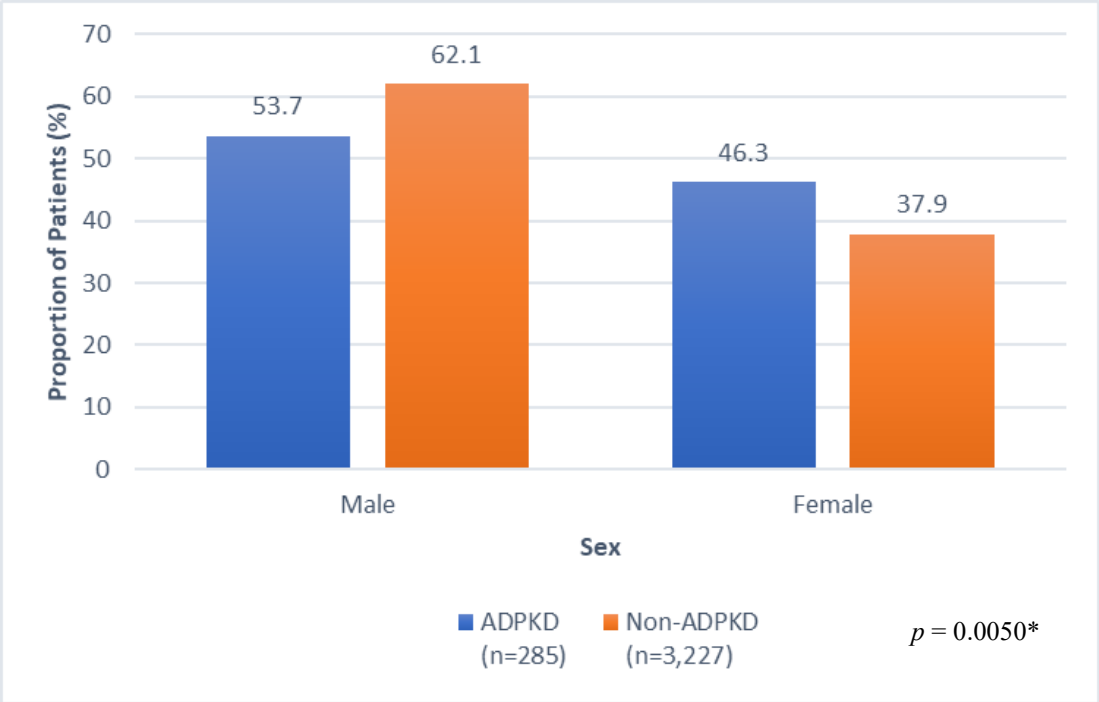


Figure 4. 2018 PHD: Proportion of Patients with vs. without ADPKD and Receiving KTP by Race

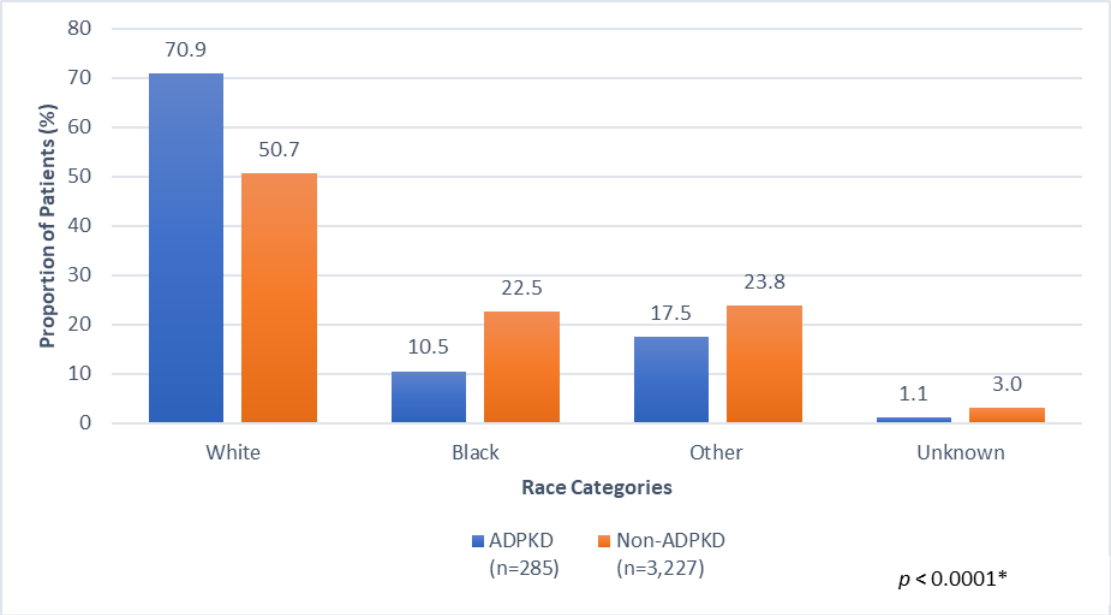


Figure 5. 2018 PHD: Expected Primary Payer at Index Hospitalization for KTP Surgery Among Patients with vs. without ADPKD

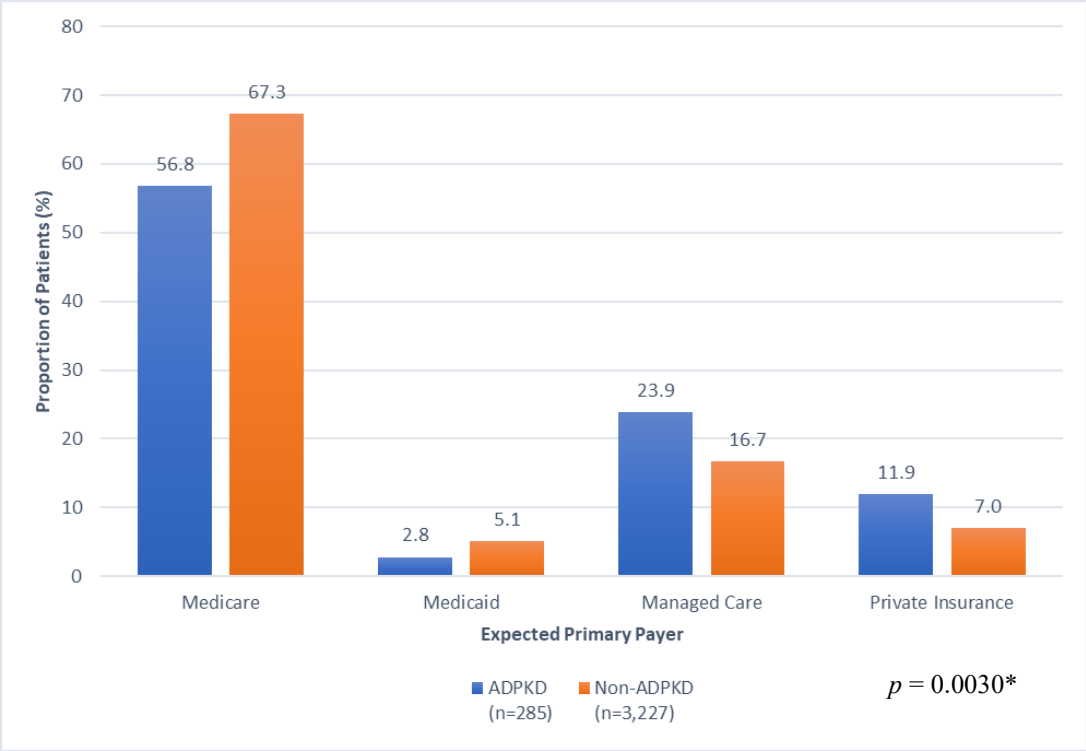


Table 15. 2018 PHD: Comorbidities Among Patients with vs. without ADPKD at Index Discharge for KTP Surgery

Data Element	Estimates			
	Total Sample (N=3,512)	ADPKD (n=285)	Non-ADPKD (n=3,227)	p value
Elixhauser Comorbidity Index, n (%)				
Congestive Heart Failure (CHF)	366 (10.42%)	20 (7.02%)	346 (10.72%)	0.0498*
Cardiac Arrhythmia	504 (14.35%)	38 (13.33%)	466 (14.44%)	0.6093
Valvular Disease (VD)	175 (4.98%)	7 (2.46%)	168 (5.21%)	0.0452*
Pulmonary Circulation Disorders	135 (3.84%)	6 (2.11%)	129 (4.00%)	0.1454
Peripheral Vascular Disorders	225 (6.41%)	12 (4.21%)	213 (6.60%)	0.1295
Hypertension, Uncomplicated (HTN-U)	283 (8.06%)	48 (16.84%)	235 (7.28%)	<0.0001*
Hypertension, Complicated (HTN-C)	3,117 (88.75%)	222 (77.89%)	2,895 (89.71%)	<0.0001*
Paralysis	6 (0.17%)	1 (0.35%)	5 (0.15%)	0.3984
Other Neurological Disorders	126 (3.59%)	9 (3.16%)	117 (3.63%)	0.8676
Chronic Pulmonary Disease	272 (7.74%)	27 (9.47%)	245 (7.59%)	0.2547
Diabetes, Uncomplicated	40 (1.14%)	2 (0.70%)	38 (1.18%)	0.7683
Diabetes, Complicated (DC)	1,484 (42.26%)	26 (9.12%)	1,458 (45.18%)	<0.0001*
Hypothyroidism	414 (11.79%)	35 (12.28%)	379 (11.74%)	0.7879
Renal Failure	3,509 (99.91%)	285 (100.00%)	3,224 (99.91%)	0.6066
Liver Disease	213 (6.06%)	11 (3.86%)	202 (6.26%)	0.1195
Peptic Ulcer Disease (excluding bleeding)	12 (0.34%)	0 (0.00%)	12 (0.37%)	0.6155

Abbreviations: ADPKD-autosomal dominant polycystic kidney disease, CHF-congestive heart failure, DC-complicated diabetes, HTN-C-complicated hypertension, HTN-U-uncomplicated hypertension, VD-valvular disease.

Significance: $p \leq 0.05$*; ***Chi-Square test*** was conducted to compare the proportions of patients for all binary comorbidity variables. ***Fisher's Exact test*** was conducted to compare the proportions of patients for all binary comorbidity variables having sample size <20.

Table 15. 2018 PHD: Comorbidities Among Patients with vs. without ADPKD at Index Discharge for KTP Surgery (continued)

Data Element	Estimates			
	Total Sample (N=3,512)	**ADPKD (n=285)**	**Non-ADPKD (n=3,227)**	**p value**
Elixhauser Comorbidity Index, n (%)				
Human Immunodeficiency Virus / Autoimmune Deficiency Syndrome (HIV/AIDS)	23 (0.65%)	0 (0.00%)	23 (0.71%)	0.2525
Lymphoma	7 (0.20%)	0 (0.00%)	7 (0.22%)	1.0000
Metastatic Cancer	2 (0.06%)	0 (0.00%)	2 (0.06%)	1.0000
Solid Tumor without Metastasis	25 (0.71%)	1 (0.35%)	24 (0.74%)	0.7170
Rheumatoid Arthritis (RA)	231 (6.58%)	3 (1.05%)	228 (7.07%)	<0.0001*
Obesity	609 (17.34%)	51 (17.89%)	558 (17.29%)	0.7966
Weight Loss (WL)	122 (3.47%)	4 (1.40%)	118 (3.66%)	0.0427*
Fluid and Electrolyte Disorders	1,880 (53.53%)	146 (51.23%)	1,734 (53.73%)	0.4162
Blood Loss Anemia	28 (0.80%)	1 (0.35%)	27 (0.84%)	0.7234
Deficiency Anemia	65 (1.85%)	6 (2.11%)	59 (1.83%)	0.6484
Alcohol Abuse (AA)	50 (1.42%)	0 (0.00%)	50 (1.55%)	0.0315*
Drug Abuse	49 (1.40%)	2 (0.70%)	47 (1.46%)	0.4302
Psychoses	9 (0.26%)	0 (0.00%)	9 (0.28%)	1.0000
Depression	280 (7.97%)	17 (5.96%)	263 (8.15%)	0.2106
Coagulopathy	486 (13.84%)	41 (14.39%)	445 (13.79%)	0.7800

Abbreviations: AA-alcohol abuse, ADPKD-autosomal dominant polycystic kidney disease, AIDS-autoimmune deficiency syndrome; HIV-human immunodeficiency virus; RA-rheumatoid arthritis, WL-weight loss.

Significance: $p \leq 0.05$*; ***Chi-Square test*** was conducted to compare the proportions of patients for all binary comorbidity category variables. ***Fisher's Exact test*** was conducted to compare the proportions of patients for all binary comorbidity variables having sample size <20.

Figure 6. 2018 PHD: Comorbidities Among Patients with vs. without ADPKD at Index Discharge for KTP Surgery

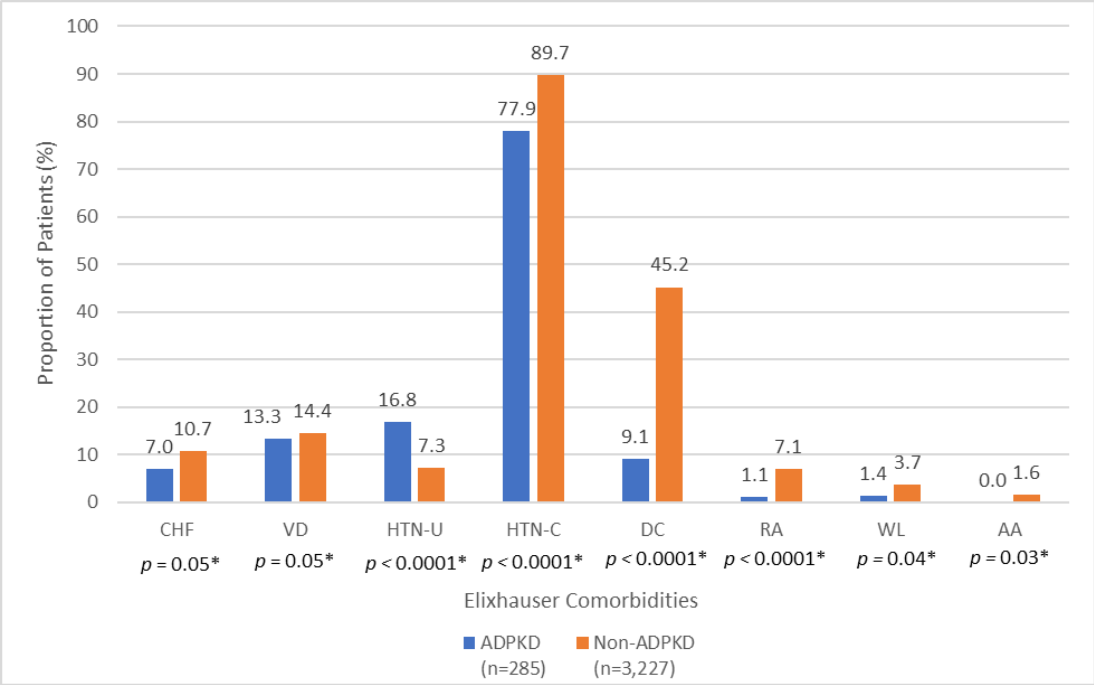


Table 16. 2018 PHD: Hospital Characteristics Among Patients with vs. without ADPKD and Receiving KTP Surgery

Data Element	Estimates			
	Total Sample (N=3,512)	ADPKD (n=285)	Non-ADPKD (n=3,227)	p value
US Census Region, n (%)				
Northeast	782 (22.27%)	66 (23.16%)	716 (22.19%)	0.1525
Midwest	442 (12.59%)	43 (15.09%)	399 (12.36%)	
South	1,689 (48.09%)	138 (48.42%)	1,551 (48.06%)	
West	429 (12.22%)	32 (11.23%)	397 (12.30%)	
Unknown/Missing	170 (4.84%)	6 (2.11%)	164 (5.08%)	
Hospital Bed Size, n (%)				
0-99	0 (0.00%)	0 (0.00%)	0 (0.00%)	0.2588
100-199	1 (0.03%)	0 (0.00%)	1 (0.03%)	
200-299	0 (0.00%)	0 (0.00%)	0 (0.00%)	
300-399	504 (14.35%)	41 (14.39%)	463 (14.35%)	
400-499	119 (3.39%)	11 (3.86%)	108 (3.35%)	
500+	2,718 (77.39%)	227 (79.65%)	2,491 (77.19%)	
Unknown/Missing	170 (4.84%)	6 (2.11%)	164 (5.08%)	
Hospital Teaching Status, n (%)				
Non-Teaching	553 (15.75%)	50 (17.54%)	503 (15.59%)	0.0651
Teaching	2,789 (79.41%)	229 (80.35%)	2,560 (79.33%)	
Unknown/Missing	170 (4.84%)	6 (2.11%)	164 (5.08%)	
Hospital Urban / Rural Location, n (%)				
Urban	3,244 (92.37%)	266 (93.33%)	2,978 (92.28%)	0.0157*
Rural	98 (2.79%)	13 (4.56%)	85 (2.63%)	
Unknown/Missing	170 (4.84%)	6 (2.11%)	164 (5.08%)	

Abbreviations: ADPKD-autosomal dominant polycystic kidney disease (ADPKD), KTP-kidney transplantation, PHD-Premier Healthcare Database, US-United States.

Significance: $p \leq 0.05$*; ***Chi-Square test*** was conducted to compare the proportions of patients for all binary and categorical variables (US Census Region, hospital bed size, hospital teaching status, hospital urban/rural location). ***Fisher's Exact test*** was conducted to compare the proportions of patients for all binary and categorical variables having sample size <20.

Table 17. 2018 PHD: Inpatient Resource Use (LOS) and Total Patient Cost Among Patients with vs. without ADPKD at Index Discharge for KTP Surgery

Data Element	Estimates			
	Total Sample (N=3,512)	**ADPKD (n=285)**	**Non-ADPKD (n=3,227)**	**p value**
Length of Stay (LOS), cumulative number of days				
Median (IQR)	5 (4 - 7)	4 (4-6)	5 (4-7)	0.0006*
Total Costs, $USD				
Median (IQR)	$112,123.83 ($74,865.34 - $137,314.36)	$102,940.74 ($72,312.10 - $127,647.76)	$112,940.57 ($75,308.88 - $138,577.07)	0.0010*

Abbreviations: ADPKD-autosomal dominant polycystic kidney disease, IQR-interquartile range, KTP-kidney transplantation, LOS-length of stay, PHD-Premier Healthcare Database, USD-United States dollars.

Significance: $p \leq 0.05$*; ***Wilcoxon Rank Sum tests*** were conducted to compare the medians for continuous variables (LOS and total costs).

4.7.2 Aim #2: 30-Day All-Cause Readmission Rates

A total of 1,582 patients (45.05%) of the total cohort were observed to have at least one all-cause readmission within 30 days of index discharge for KTP surgery (Table 18). A significantly lower proportion of patients with ADPKD (n=112) were observed to have at least one all-cause readmission within 30-days of index discharge for KTP surgery compared to those without ADPKD (n=1,470) (39.30% vs. 45.55%, respectively; p = 0.0419; Table 18). With multivariable adjustment for factors associated with the probability of ADPKD diagnosis (i.e., age, sex, race, comorbidities), there was an observed 0.01% lower odds of at least one all cause readmission within 30-days of index discharge for KTP surgery, but it was not significant (OR: 0.99, 95% CI: 0.76 to 1.28, p = 0.9272) (Table 20). Therefore, we failed to reject the null hypothesis and determined there was no association between ADPKD diagnosis and the odds of at least one all-cause readmission within 30-days of index discharge for KTP surgery.

Table 18. 2018-2019: 30-Day All-Cause Readmission Rates Following KTP Surgery Among Patients with vs. without ADPKD

Outcome	Total Sample (N=3,512)	ADPKD (n=285)	Non-ADPKD (n=3,227)	p value
All-Cause Readmissions Rates within 30-Days of Index Discharge for KTP Surgery**				
Patients Readmitted within 30-Days	1,582	112	1,470	0.0419*
Rate	45.05%	39.30%	45.55%	

Abbreviations: ADPKD-autosomal dominant polycystic kidney disease, KTP-kidney transplantation.

Significance: $p \leq 0.05$*; ***Chi-Square test*** was conducted to compare the proportion of patients with vs. without ADPKD having at least one 30-day all-cause readmission.

****30-Day All-Cause Readmission Rates:*** Numerator = total number of patients with at least one all-cause readmission event within 30 days; Denominator = total number of patients observed between 01 January 2018 and 31 January 2019.

4.7.3 Aims #3 and #4: Inpatient Resource Use (LOS), Total Patient Cost, and Mortality at 30-Day All-Cause Readmissions

Inpatient resource use (i.e., LOS), total patient cost, and mortality at 30-day all-cause readmissions was assessed among the 1,582 total patients (112 with ADPKD and 1,407 without ADPKD) with at least one all-cause readmission within 30-days of index discharge for KTP surgery. The unadjusted median (IQR) LOS at 30-day all-cause readmissions for the total cohort was approximately 5 (7) and 3 (2-6) days, respectively (Table 19). There was no significant difference in the unadjusted median (IQR) LOS (3 [2-5] vs. 3 [2-6] days, respectively; p = 0.4421) of 30-day all-cause readmissions among patients with ADPKD compared to those without ADPKD (Table 19). With the multivariable adjustment for factors associated with the probability of ADPKD diagnosis (i.e., age, sex, race, comorbidities), there was an observed 15% lower odds of a longer mean LOS per the incidence rate ratio (IRR) at 30-day all-cause readmissions, but it was not significant (IRR: 0.85, 95% CI: 0.72 to 1.01, $p = 0.0687$) (Table 20). Therefore, we failed to reject the null hypothesis and determined there was no association between ADPKD diagnosis and the odds of a longer mean LOS at 30-day all-cause readmissions.

The unadjusted median (IQR) total patient cost at 30-day all-cause readmissions for the total cohort was approximately $8,550 ($4,806 - $16,670) (Table 19). There was no significant difference in the unadjusted median (IQR) total patient cost ($8,575 [$4,904-$14,744] vs. $8,550 [$4,774-$16,940], respectively; $p = 0.5364$) of 30-day all-cause readmissions among patients with ADPKD compared to those without ADPKD (Table 19). With multivariable adjustment for factors associated with the probability of ADPKD diagnosis (i.e., age, sex, race, comorbidities), a higher incremental median total patient cost was observed at 30-day all-cause readmissions, but it was not significant ($1,252; 95% CI:

-$1,057 to $3,088; p≥ 0.05) (Table 20). Therefore, we failed to reject the null hypothesis and determined there was no association between ADPKD diagnosis and a higher median total patient cost at 30-day all-cause readmissions. A total of 9 patients (0.57%) in the cohort died at an all-cause readmission within 30 days of index discharge for KTP surgery (Table 19). There was no significant difference in the unadjusted proportion of patients with vs. without ADPKD and experiencing death at 30-day all-cause readmissions (0.89% vs. 0.54%, p = 0.4845; Table 19). Thus, multivariable regression was not conducted for mortality at 30-day all-cause readmissions.

Table 19. 2018-2019 PHD: Inpatient Resource Use (LOS), Total Patient Cost, and Mortality at 30-Day All-Cause Readmissions Following KTP Surgery Among Readmitted Patients with vs. without ADPKD

Outcome	Total Sample (N=1,582)	ADPKD (n=112)	Non-ADPKD (n=1,470)	p value
LOS for 30-Day All-Cause Readmissions, cumulative number of days				
Median (IQR)	3 (2 - 6)	3 (2 - 5)	3 (2 - 6)	0.4421
Total Cost of 30-Day All-Cause Readmissions, $USD				
Median (IQR)	$8,550.19 ($4,805.57 - $16,670.40)	$8,574.55 ($4,904.18 - $14,743.81)	$8,550.19 ($4,773.64 - $16,939.48)	0.5364
Mortality at 30-Day All-Cause Readmission, n (%)				
All-Cause Mortality	9 (0.57%)	1 (0.89%)	8 (0.54%)	0.4845

Abbreviations: ADPKD-autosomal dominant polycystic kidney disease, IQR-interquartile range, KTP-kidney transplantation, LOS-length of stay, USD-United States Dollars.

Significance: $p \leq 0.05$*; ***Wilcoxon Rank Sum tests*** were conducted to compare the medians for continuous variables (LOS and total costs). ***Fisher's Exact test*** was conducted to compare the proportion of patients with vs. without ADPKD having mortality at 30-day all-cause readmissions.

Table 20. 2018-2019 PHD: Adjusted 30-Day All-Cause Readmission Outcomes Following KTP Surgery Among Patients with vs. without ADPKD*

Dependent Variable	Estimate	95% Confidence Intervals		*p* value
30-Day All-Cause Readmission Outcomes				
At least One 30-Day All-Cause Readmission	0.99	0.76	1.28	0.9272
Incidence Rate Ratio (IRR) for Mean LOS	0.85	0.72	1.01	0.0687
Median Incremental Total Patient Cost	$1,251.93	-$1,056.84	$3,087.90	≥0.05

*Adjustment for age, gender, race, congestive heart failure (CHF), valvular disease (VD), uncomplicated hypertension (HTN-U), complicated hypertension (HTN-C), complicated diabetes (DC), rheumatoid arthritis (RA), weight loss (WL), and alcohol abuse (AA).

Significance: $p \leq 0.05$*; ***Logistic Regression*** was conducted for the binary variable of at least one 30-day all-cause readmission. ***Generalized Linear (Negative Binomial with log link) Regression*** was conducted for the mean LOS at 30-day all-cause readmissions. ***Quantile Regression Model*** was conducted for the median total patient cost of 30-day all-cause readmissions.

5 DISCUSSION

5.1 Preliminary Research

Preliminary research using cross-sectional data (i.e., NIS-KID) demonstrated high inpatient burden among patients diagnosed with ADPKD and advanced stages of CKD. An initial analysis was conducted to explore inpatient outcomes among children with ADPKD and stratified by status of HTN (i.e., evidence of HTN or lack thereof). Hypertensive children with ADPKD were found to experience significantly poorer health status, as evidenced by a higher mean CCI score (3.15 vs. 0.97, $p = 0.0004$; Table 1) and greater presence of ESRD (37.5% vs. 12.2%, $p < 0.0001$; Table 1) compared to non-hypertensive children with ADPKD. Thus, HTN was confirmed as an indicator of rapid progression, given the mean age of patients included in the NIS-KID cohort was approximately 17 years old and the significantly greater presence of ESRD among hypertensive children with ADPKD compared to those without HTN. However, ESRD was observed among non-hypertensive children with ADPKD, which indicates other manifestations drive the progression of ADPKD to ESRD.

Inpatient resource use (i.e., LOS) and hospital charges were higher but not significantly different for hypertensive children with ADPKD vs. non-hypertensive children with ADPKD (Table 2), which indicates there were other reasons these children with ADPKD were admitted for inpatient care, such as kidney-related complications. When the NIS-KID cohort of children with ADPKD was stratified by status of kidney-related complications (i.e., evidence of kidney-related complications or lack thereof), children with kidney-related complications were found to experience significantly poorer health status (mean CCI score of 1.84 vs. 0.69, $p < 0.0001$; Table 3) and greater presence of ESRD

(50% vs. 0%, $p < 0.0001$; Table 3) compared to children without kidney-related complications. Children with kidney-related complications were found to experience significantly longer LOS (approximately six vs. four days, $p = 0.113$; Table 4) and higher hospital charges (approximately $66,000 vs. $32,000, $p = 0.0016$; Table 4) compared to children without kidney-related complications. Thus, kidney-related complications among children with ADPKD were confirmed as an indicator of ADPKD progression to ESRD and the reason for greater inpatient resource use burden to the US healthcare system. These NIS-KID analyses contribute to the existing literature by providing real-world estimates of inpatient resource use and evidence of rapid progression of ADPKD to ESRD among children with HTN and kidney-related complications in the US.

Using the NEDS database, an analysis was conducted to expand beyond children and distinguish characteristics of all individuals with ADPKD seeking care at EDs and either discharged home vs. hospitalized in the US. Individuals with ADPKD and discharged to home appeared to primarily seek care in the ED for symptom management, such as PKD-U, ADPKD, HTN, abdominal pain, long-term exposure to medication, UTI, ESRD, and post-surgical dialysis (Table 5). A higher number of ED visits resulted in hospitalization due to PKD-U, ESRD, ADPKD, AKF, and post-surgical dialysis (Table 5). There were ED visits due to HTN, hyperlipidemia, and anemia in CKD that also resulted in hospitalization (Table 5). It may be inferred that the severity of the kidney-related complication or comorbidity influenced the inpatient admission vs. discharge home from ED outcome. The frequency of ED visits observed for symptom management among patients living with ADPKD indicates the presence of unmet needs in terms of access to and use of routine outpatient clinical care (i.e., primary and specialist settings) in the US.

It is possible that the ED visits resulting in hospitalization due to AKF and post-surgical dialysis were complications following KTP, but the data elements and cross-sectional nature of the NEDS did not permit temporal assessments of HCRU outside of the ED visits included in the analysis.

Preliminary research using longitudinal data (i.e., 5% Medicare LDS) demonstrated significant all-cause direct medical HCRU and costs among Medicare beneficiaries diagnosed with ADPKD, comorbid ESRD, and receiving RRT (i.e., dialysis and/or KTP) in the US. An initial cohort analysis was conducted to understand the burden of illness associated with an ADPKD diagnosis by age category. Medicare beneficiaries aged ≤39 years old were only observed to have a significant mean increase in the number of all-cause and disease-related OV following ADPKD diagnosis (Table 7), but there were significant mean increases in all-cause cost of ED visits and IP admissions, as well as disease-related cost of OV, following ADPKD diagnosis (Table 8). Approximately 53% of beneficiaries ≤39 years old were rapid progressors with comorbid ESRD, given they were identified in the database as having continuous medical enrollment for Medicare Parts A and B coverage before the age of 65 years old (Table 6). These rapid progressors were likely the drivers of the significant mean increases in all-cause and disease-related HCRU and cost following ADPKD diagnosis in this age group (Tables 7 and 8). Medicare beneficiaries aged 40-64 years old were found to experience significantly higher all-cause and disease-related direct medical HCRU (i.e., IP, LOS, OP, OV, ED) and costs following ADPKD diagnosis (Tables 7 and 8). This was expected given the majority of patients with ADPKD develop ESRD by the fourth to seventh decades of life and require RRT to extend their life. A higher proportion of Medicare beneficiaries aged 40-64 years old had ESRD (57%) at the time of

their ADPKD diagnosis compared to other age groups, which is likely the driver of their significant mean increases in HCRU and cost following ADPKD diagnosis in this age group (Table 6). This is evidence that Medicare assumes responsibility for the significant economic burden occurring among those diagnosed with ADPKD, aged 40-64 years old, and having comorbid ESRD in the US.

A subsequent cohort analysis was conducted to understand the burden of illness associated with KTP by age category among Medicare beneficiaries with ADPKD. Overall, significant variations in all-cause direct medical HCRU and costs were observed among patients with ADPKD following KTP in the US. Significant economic burdens due to the total mean increases in all-cause direct medical resource use (IP, OP, OV, ED) post-KTP were observed among Medicare beneficiaries in all age groups (Tables 10 and 11). The only observed post-KTP reduction in HCRU was for OP visits among beneficiaries aged ≤44 and ≥65 years old (-5,913 vs. -131, $p < 0.0001$; Table 10). These mean reductions in OP visits were likely due to ADPKD beneficiaries no longer requiring routine dialysis and nephrologist follow-up visits for dialysis management.

Medicare beneficiaries aged ≥65 years old had significantly higher mean increases in OV, ED, and IP admissions post-KTP compared to those in other age groups ($p < 0.0001$; Table 10). This was likely due to a greater presence of age- and gender-related comorbidities (e.g., CHF, PVD, non-metastatic cancer, UTI) that prompt Medicare beneficiaries with ADPKD and aged ≥65 years old to seek care post-KTP (Table 9). However, there were mean increases in OV, ED, and IP admissions for younger Medicare beneficiaries (i.e., aged ≤44, 45-54, and 55-64 years old) who tend to be healthier in terms of comorbidity presence (Table 10). This is an indicator that there may be complications due to the native

polycystic kidneys or related to the transplanted graft that prompt Medicare beneficiaries to seek care post-KTP regardless of age.

Significant differences were observed in the total all-cause direct medical costs across age groups post-KTP; it decreased among those aged 45-54, 55-64, and ≥65 (-$86,127), 45-54 ($-3,325), and 55-64 (-$887) years old, but increased among those aged ≤44 years old (+$636, $p < 0.0001$; Table 11). The observed decreases in total all-cause direct medical costs across older age groups likely occurred due to the decreased reliance on dialysis post-KTP. Medicare beneficiaries aged ≥65 years old had a significantly higher mean cost of OP visits ($1,126,295) compared to other age groups post-KTP ($p < 0.0001$; Table 11). However, Medicare beneficiaries aged ≤44 years old had significantly higher mean cost of OV ($114,922), ED visits ($12,190,535), and IP admissions ($11,994,015) compared to other age groups post-KTP ($p < 0.0001$; Table 11).

Immunosuppression exposure is meant to reduce the likelihood and rate of graft rejection and failure among patients post-KTP, and it was assumed equal regardless of age among Medicare beneficiaries included in this analysis. However, there is still a risk of acute kidney injury, graft rejection, and/or failure post-KTP among patients living with and without ADPKD. Furthermore, other kidney-related complications may occur in the native polycystic kidneys, such as cyst ruptures, hematuria, kidney stones, and/or infection. Medicare beneficiaries ≤44 years old and included in this cohort, may have been rapid ADPKD progressors with a risk of native polycystic kidney-related complications and a need for NN post-KTP. Either of these scenarios would be reasons patients with ADPKD would seek care (i.e., OV, ED, and/or IP) post-KTP. The observed mean increase in total IP admissions and cost among Medicare beneficiaries, regardless of age, post-KTP (Tables

10 and 11) inspired further exploration into the rate of 30-day all-cause readmissions among patients living with ADPKD and receiving KTP in the US.

A final preliminary analysis was conducted to generate real-world estimates of the risk difference in mortality among Medicare beneficiaries with ADPKD and receiving dialysis vs. KTP in the US. Medicare beneficiaries with ADPKD and receiving dialysis were observed to have poorer health status compared to those receiving KTP, as evidenced by a higher mean CCI score and multi-morbidity (i.e., presence of 5+ Charlson comorbidities), specifically a greater presence of cardiovascular, pulmonary, rheumatologic, and gastrointestinal diseases (Table 12). As expected, Medicare beneficiaries with ADPKD and receiving dialysis were observed to have a greater crude mortality rate compared to those receiving KTP (7.25% vs. 4.14%; Table 13). Medicare beneficiaries with ADPKD and receiving dialysis also consumed more healthcare resources (IP, ambulatory/ED visits, OP visits) compared to those who had a KTP (Table 13). These observations support existing literature indicating that KTP is the first-line treatment for patients with ADPKD and ESRD in the US. Even though KTP is provided at a cost to payers, the economic burden they accrue due to dialysis is greater than that resulting from the KTP process. However, KTP does not completely address all of the challenges patients living with ADPKD experience.

5.2 Inpatient Resource Use and Cost Outcomes Among Kidney Transplant Recipients with vs. without ADPKD

5.2.1 Patient Profile, Inpatient Resource Use (LOS), and Total Patient Cost at Index Hospitalization for KTP Surgery

The profile of patients with and without ADPKD was characterized by leveraging patient demographics, Elixhauser comorbidities, hospital characteristics, inpatient resource use

(i.e., LOS), and total patient cost outcomes for unadjusted comparison at index hospitalization for KTP surgery. The PHD was beneficial in providing enough sample size for analysis of patients with a rare disease like ADPKD (n=285), but the larger sample of patients without ADPKD (n=3,227) may have influenced statistically significant differences in favor of those without ADPKD for the demographics, comorbidities, hospital characteristics, LOS, and total patient cost outcomes at index hospitalization for KTP surgery. Furthermore, the significant differences observed between patients with vs. without ADPKD at index hospitalization for KTP surgery may not be of clinical significance.

No significant difference was observed in the median (IQR) age of patients with vs. without ADPKD at index hospitalization for KTP surgery (56 [47-62] vs. 55 [43-63] years; p = 0.1658; Table 14). Therefore, we failed to reject the null hypothesis. This finding contradicts prior literature reporting patients with ADPKD and receiving their first KTP tend to be older compared to non-diabetic controls.(Bhutani et al., 2021; Goncalves et al., 2009; Johnston et al., 2009; Tsai et al., 2022) Furthermore, a higher proportion of patients with ADPKD were aged 55-64 (35% vs. 29%) and 45-54 (28% vs. 21%) years old at index hospitalization for KTP surgery compared to patients without ADPKD ($p < 0.0001$; Table 14 and Figure 2), which aligns with literature reporting the average age of patients with ADPKD diagnosed with ESRD and requiring RRT is approximately 40-70 years old.(Spithoven et al., 2014) Approximately 61% of the total cohort were male, and there was a significantly higher proportion of male patients without ADPKD compared to those with ADPKD (62% vs. 54%, $p = 0.0050$; Table 14 and Figure 3). The null hypothesis was rejected and our alternate hypothesis that patients without ADPKD would be

predominately male at index hospitalization for KTP surgery was confirmed even though there were more male patients without ADPKD included in the cohort. However, there was a significantly higher proportion of female patients with ADPKD compared to those without ADPKD (46% vs. 38%, $p = 0.0050$; Table 14 and Figure 3) at index hospitalization for KTP surgery. This may be an indicator of improved access to KTP among females with ADPKD compared to those without ADPKD in this study.

A significantly higher proportion of patients with ADPKD were White compared to those without ADPKD (71% vs. 51%, $p < 0.0001$; Table 14 and Figure 4) at index hospitalization for KTP surgery. Thus, the null hypothesis was rejected and our alternate hypothesis that the majority of patients with ADPKD would be White race at index hospitalization for KTP surgery was confirmed. Interestingly, a significantly larger proportion of patients without ADPKD were of a racial minority, Other (24% vs. 18%) or Black (23% vs. 11%) race, compared to those with ADPKD at index hospitalization for KTP surgery ($p < 0.0001$; Table 14 and Figure 4). This may be an indicator of racial disparities in access to KTP, given the observed lower sample size among racial minorities with ADPKD compared to those without ADPKD in this study. Existing literature reports the negative impact that racial disparities have on the health outcomes of patients with ADPKD; Black and Hispanic patients with ADPKD reach ESRD earlier in life but receive KTP less often than White patients with ADPKD.(Harrison et al., 2023; McGill et al., 2022) While this analysis may support existing literature on racial disparities among patients with ADPKD and receiving RRT in the US, it is also possible more patients without ADPKD and of racial minority were diagnosed with ESRD due to other causes, such as diabetes. Therefore, the larger sample size of patients without ADPKD and of racial minorities likely influenced the

significant difference observed for race at index hospitalization for KTP surgery in this analysis.

A significantly higher proportion of patients without ADPKD had Medicare (67% vs. 57%) and Medicaid (5% vs. 3%) as the expected primary payer at index hospitalization for KTP surgery, while a higher proportion of patients with ADPKD had managed care (24% vs. 17%) or private insurance (12% vs. 7%) (p = 0.0030; Table 14 and Figure 5). This was expected given patients with ADPKD tend to be healthier and are likely to continue working with other insurance benefits despite their ESRD diagnosis and Medicare eligibility. The greater presence of Medicare and Medicaid coverage among KTP patients without ADPKD and managed care and commercial coverage among KTP patients with ADPKD observed in this study is similar to that reported by Saha et al. (2022) in a cohort of ESRD patients with vs. without ADPKD and receiving inpatient dialysis services in the US.

Given existing literature indicates patients with ADPKD are more likely to undergo KTP within the first year of initiating dialysis, it is also possible a higher proportion of patients with ADPKD received KTP surgery during the Medicare coordination of benefits period, thus their managed care and private insurance were the expected primary payers at index hospitalization for KTP surgery. After a patient enrolls in Medicare within 12 months of receiving their ESRD diagnosis, Medicare imposes a 3-month waiting period before coverage begins and a 30-month coordination of benefits period for those who currently have employer-based union group or other commercial health insurance coverage.(Centers for Medicare and Medicaid Services, 2017) Therefore, Medicare defaults to secondary payers during the 30-month coordination of benefits period, and other insurers (i.e., managed care

and commercial) are expected to cover the majority of the cost of index hospitalization for KTP surgery.(Centers for Medicare and Medicaid Services, 2017)

The null hypothesis was rejected and our alternate hypothesis that patients with ADPKD would have a lower comorbidity presence and better health status at index hospitalization for KTP surgery was confirmed. A significantly higher proportion of patients without ADPKD were observed to have CHF, VD, HTN-C, DC, RA, WL, and AA compared to those with ADPKD at index hospitalization for KTP surgery ($p \leq 0.05$; Table 15 and Figure 6). Patients without ADPKD were observed to have a greater presence of end-organ damage due to more CHF, VD, HTN-C, and DC diagnoses observed compared to those with ADPKD at index hospitalization for KTP surgery. However, a higher proportion of patients with ADPKD were observed to have HTN-U without end-organ damage compared to those without ADPKD at index discharge for KTP surgery (17% vs. 7%, $p < 0.0001$; Table 15). Existing literature reports that HTN is the most common manifestation of ADPKD and a predictor of progression to ESRD.(A. B. Chapman, 2008) Therefore, our observation of a greater presence of HTN-U among patients with ADPKD and receiving KTP surgery aligns with existing literature. Elixhauser comorbidity index enables us to identify the presence or diagnosis of comorbid medical conditions using ICD-10-CM diagnosis codes, but it does not permit analysis and adjustment for the severity of comorbidities.

The null hypothesis was rejected and our alternate hypothesis that the median (IQR) LOS and total patient cost at hospitalization for KTP surgery would be lower for patients with ADPKD was confirmed. Patients without ADPKD had a significantly lower unadjusted median (IQR) LOS (4 [4-6] vs. 5 [4-7] cumulative days, $p = 0.0006$) compared to those

without ADPKD at index hospitalization for KTP surgery (Table 17). As a result, patients with ADPKD also had significantly lower unadjusted median (IQR) total patient cost ($102,941 [$72,312-$127,648] vs. $112,941 [$75,309-$138,577], $p = 0.0010$) at index hospitalization for KTP surgery compared to those without ADPKD (Table 17). This study is the first to generate an estimate of the median (IQR) LOS and total patient cost at index hospitalization for KTP surgery among patients with vs. without ADPKD in the US. Findings reveal that patients with ADPKD consume fewer inpatient resources and impose less cost to payers at index hospitalization for KTP surgery compared to those without ADPKD in the US. The reduced comorbidity burden with end-organ damage observed among patients with ADPKD likely resulted in shorter post-surgical observation for complications and, thus, the lower economic burden to payers at index hospitalization for KTP surgery.

Saha et al. (2022) conducted a cross-sectional analysis of patients hospitalized for ESRD on dialysis with and without ADPKD in the 2013-2018 NRD. The median (IQR) ($10,395 [$5,703-$18,055] vs. $8,918 [$5,626-$14,928], $p < 0.0001$) total patient cost of index hospitalizations was significantly higher among ESRD patients with ADPKD than those without ADPKD.(Saha et al., 2022) The median total patient cost of index hospitalizations among ESRD patients with and without ADPKD in the 2013-2018 NRD was an estimate of the economic burden to hospitals among a prevalent dialysis population. The estimates of the median (IQR) total patient cost at index hospitalization for KTP surgery are much higher in this study compared to the estimates provided by Saha et al. (2022) for patients with vs. without ADPKD at index hospitalizations for dialysis-related services. When the KTP surgery becomes the primary exposure of interest, the median total cost of the index

hospitalization is nearly ten-fold higher because of the type of surgical or peri- and post-operative resources utilized in the KTP process compared to the inpatient services required to manage patients receiving dialysis in the US (i.e., $102,941 [$72,312-$127,648] for KTP patients with ADPKD in this study vs. $10,395 [$5,703-$18,055] for ESRD patients with ADPKD in the NRD study). (Saha et al., 2022) Furthermore, the median (IQR) total patient cost at index hospitalization for KTP surgery was significantly lower for patients with ADPKD in this study, whereas the median total patient cost at index hospitalization for dialysis-related services was significantly higher among patients with ADPKD in the NRD study.(Saha et al., 2022)

In 2020, the average cost of KTP was approximately $442,500 in the US, and charges for the surgery were reported to account for the largest portion (34% or $150,450) of the total cost of KTP that year.(Wang & Hart, 2021) When using the Consumer Price Index (CPI) Inflation calculator to adjust the estimated total cost of KTP surgery from 2020 to 2018, the average total cost of KTP was approximately $425,169. The average cost of KTP surgery in 2018 was approximately $144,558 when applying the 34% as reported in 2020. This study provides more reliable median (IQR) estimates of total patient cost at index hospitalization for KTP surgery than the mean (SD) because of the impact of outliers on the mean. As expected, the median total patient cost at index hospitalization for KTP surgery in this study was lower than the estimated mean total cost of KTP as reported by Wang et al. (2021) and adjusted to 2018 using the CPI. It is possible that patients included in this study experienced prior hospitalizations and outpatient visits for procedures necessary in preparation for the KTP surgery that weren't considered in this analysis.

5.2.2 30-Day All-Cause Readmission Outcomes

It is critical to explore the rate of 30-day all-cause readmissions following KTP, given the burden that is imposed on hospitals in terms of their quality rating and accountability for the cost of 30-day all-cause readmissions regardless of the cause. This study was the first to utilize a hospital discharge database to generate patient-level 30-day all-cause readmission rates, inpatient resource use (i.e., LOS), and total patient cost at 30-day all-cause readmissions following KTP surgery among patients with vs. without ADPKD in the US. Patients with ADPKD were found to have a significantly lower unadjusted 30-day all-cause readmission rate following KTP surgery compared to those without ADPKD (39.30% vs. 45.55%, $p = 0.0419$; Table 18). Therefore, the null hypothesis was rejected and our alternate hypothesis was confirmed. However, after adjustment for factors associated with the probability of having ADPKD, there was no association between the odds of at least one 30-day all-cause readmission and ADPKD diagnosis (OR: 0.99, 95% CI: 0.76 to 1.28, p = 0.9272) (Table 20).

Saha et al. (2022) reported ESRD patients with ADPKD and receiving dialysis had a lower 30-day unplanned, all-cause readmission rate (18.8% vs. 23.8%, $p < 0.0001$) and odds (OR: 0.79, 95% CI: 0.72 to 0.87, $p < 0.0001$) of 30-days all-cause readmission compared to those without ADPKD in the 2013-2018 NRD. The 30-day all-cause readmission rates and odd ratio were higher among KTP patients with and without ADPKD in this study compared to those estimated by Saha et al. (2022) for ESRD patients with ADPKD and receiving dialysis in the NRD. The lower estimates provided in the NRD analysis are likely due to differences in the inclusion criteria for the cohort (i.e., dialysis vs. KTP patients) and in the definition of the 30-day readmission rates (i.e., both planned and unplanned vs.

unplanned only). Saha et al. (2022) restricted the readmissions analysis to only unplanned (i.e., non-elective) readmissions and excluded planned (i.e., elective) readmissions from the analysis. In this analysis, we retained all elective and non-elective readmissions occurring within 30 days of index discharge for KTP surgery because hospital-based quality metrics and associated payment mechanisms are not dependent on the planned vs, unplanned designation of the readmission. Furthermore, KTP surgery is an elective and planned procedure. Thus, the 30-day all-cause readmission rates and OR aligns with Saha et al. (2022), but were higher in this study compared to the NRD study. In addition, the 30-day all-cause readmission rates observed in this study are likely an underestimation of the true 30-day all-cause readmission rates for KTP patients with and without ADPKD included in this study. A key limitation of the PHD is the inability to track readmissions outside of the institution or network from which the index hospitalization for KTP surgery occurred due to the patient being given multiple medical record identifiers (i.e., MEDREQ).

There was no significant difference in the unadjusted median LOS at 30-day all-cause readmissions among patients with ADPKD compared to those without ADPKD in this study. Therefore, we failed to reject the null hypothesis. Saha et al. (2022) reported the mean total cost of 30-day unplanned, all-cause readmissions among ESRD patients receiving dialysis in the NRD was significantly lower for those with ADPKD compared to those without ADPKD ($16,455 vs. $17,391, $p < 0.0001$).(Saha et al., 2022) This study generated median (IQR) estimates of the total patient cost at 30-day all-cause readmissions, which is a more reliable estimate for comparison given the mean significant difference reported by Saha et al. (2022) was subject to the impact of outliers. The median total

patient cost of 30-day all-cause readmissions in this study was slightly higher for KTP patients with ADPKD ($8,575 vs. $8,550, p = 0.5364), but there was no significant difference compared to those without ADPKD (Table 19). Therefore, we failed to reject the null hypothesis in this study. Once the influence of patient outliers (i.e., those with extremely lower or higher costs) is removed, the economic burden imposed on hospitals for 30-day all-cause readmissions occurring among KTP patients with vs. without ADPKD is no different. As a result, our findings of no significant difference in the unadjusted median (IQR) total patient cost at 30-day all-cause readmissions contradicts the significant higher mean findings reported for ESRD patients with vs. without ADPKD and receiving dialysis ($17,391 vs. $16,455; $p < 0.0001$).(Saha et al., 2022) With adjustment for factors associated with the probability of ADPKD diagnosis, no associations were observed between ADPKD diagnosis and a longer mean LOS (IRR: 0.85; 95% CI: 0.72 to 1.01; p = 0.0687) or higher incremental median total patient cost ($1,251; 95% CI: -$1,057 to $3,088; $p \geq 0.05$) at 30-day all-cause readmissions in this study (Table 20). Therefore, we failed to reject the null hypotheses in the multivariable regression analyses. This indicates the diagnosis of a rare genetic disease such as ADPKD has no bearing on the inpatient resource use and economic burden to hospitals financially responsible for 30-day all-cause readmissions in the US.

5.2.3 Limitations of the PHD Analysis

There are limitations and assumptions regarding the study design, data source, and the analytic methods applied in conducting this study that should be considered when interpreting the outcomes.

5.2.3.1 Limitations of Study Design and Data Source

The PHD is a compilation of annual data files containing inpatient records for patients discharged from US hospitals in a calendar year. The PHD has patient-level identifier (MEDREQ_KEY) and encounter-level identifier (PAT_KEY) variables that enable year-long tracking of patients discharged for KTP surgery at the end of 2018 and readmitted in the subsequent year of 2019. In addition, there were discharge month (DISC_MON) and admission month (ADM_MON) variables that enabled us to determine the temporal sequence between inpatient encounters for patients included in the cohort. However, the readmissions identified in this study may have been biased lower since we were only able to observe those patients who were readmitted to the same hospital or system with the same medical record number (i.e., MEDREQ_KEY). Patients who were readmitted to a hospital outside of the original network would have been given a different medical record number relative to that of their index hospitalization for KTP surgery and their readmissions data would not have been observed.

Furthermore, there are some inherent limitations to all observational studies conducted with retrospective hospital discharge data, including variable definitions based on the presence of codes on the hospital discharge abstract (i.e., medical and pharmacy encounters). The presence of a code does not guarantee that the patient had the diagnosis or underwent the procedure and the results may not be generalizable to the source population from which the sample was derived. Additionally, missing data (i.e., demographics, comorbidities, or hospital characteristics) may have impacted the interpretation of the study results.

5.2.3.1.1 Selection Bias

The use of retrospective hospital discharge data is a form of selection bias that is inherent when using these types of data to identify, characterize, and analyze the outcomes of patients living with or without ADPKD and receiving KTP in the US. ICD-10-PCS procedure and ICD-10-CM diagnosis code lists were developed using clinical coding references from prior ADPKD and ESRD literature. Although the PHD is constructed from a wide geographic distribution and inpatients included in the PHD are similar to the general US population, results and conclusions drawn from this analysis are limited to the sample of inpatients with and without ADPKD and receiving KTP surgery in the PHD. Selection bias poses a threat to the external validity of the study results, which may not be representative of the source population or the general US population. Missing data due to input errors is a common issue when leveraging retrospective cross-sectional data sources, and there were patient demographics and hospital characteristics with missing values in the PHD analysis. Therefore, our study findings may be biased if data were not missing at random, but quality control checks were completed to confirm data missing at random; no imputation methods were implemented in this study.

5.2.3.1.2 Misclassification of Disease or Exposure

There was the potential for misclassification of disease (i.e., ADPKD) and other comorbid medical conditions captured in the Elixhauser Comorbidity Index, given diagnosis was only determined using observed ICD-10-CM codes on the inpatient discharge abstract. To minimize the misclassification of disease bias, patients included in this cohort were required to have ICD-10-CM diagnosis codes for ADPKD and/or PKD-U at multiple encounters, including the index discharge for KTP surgery and subsequent readmissions.

There was also potential for misclassification of exposure (i.e., KTP) given the KTP surgery was only determined as occurring with observation of ICD-10-PCS operating room procedure codes on the index inpatient discharge abstract. The index discharge for KTP surgery among patients with and without ADPKD was identified as the first discharge with observation of the respective operating room procedure codes in the 2018 calendar year. The temporal sequence between the index discharge for KTP surgery and readmissions was determined with the calculation of the time between the discharge month of the index discharge for KTP surgery and the admission month of the subsequent readmission.

5.2.3.2 Limitations of Statistical Analyses

5.2.3.2.1 Descriptive Statistics

Bivariate analyses were conducted to test for significant differences in the demographics, comorbidities, and hospital characteristics among patients with vs. without ADPKD at index hospitalization for KTP surgery. It was also used to test for significant differences in the unadjusted 30-day all-cause readmission rates, inpatient resource use (i.e., LOS), total patient cost, and mortality outcomes. These analyses did not equate to causation and did not indicate which or if any characteristics were responsible for influencing readmission outcomes (i.e., 30-day readmission rates, LOS, total patient cost, mortality) following KTP surgery. Confounding is inherent in bivariate testing, for which other factors mask an actual association or falsely demonstrate an apparent association between patient demographics, comorbidities, hospital characteristics, and outcomes when no real association between them exists.

The chi-square and Fisher's exact tests were used to assess significant differences in the proportion of patients with vs. without ADPKD per the binary and nominal/ordinal

categorical demographics, comorbidities, and hospital characteristics at index hospitalization for KTP surgery, as well as the 30-day all-cause readmission rates and mortality at readmission outcomes. The chi-square test is sensitive to sample size, and relationships may appear to be significant when they are not because a very large sample was used (i.e., 3,227 KTP patients without ADPKD vs. 285 KTP patients with ADPKD).(Hayes, 2024; Kim, 2017) The Fisher's exact test was used when any binary and nominal/ordinal categorical variable had a cell with a sample size of < 20; it is more accurate than the chi-square test when the total sample size is lower.(Kim, 2017)

The Student's t-test was considered to assess significant differences in the continuous mean age, LOS, and total patient cost for patients with vs. without ADPKD at index hospitalization for KTP surgery and at 30-day all-cause readmissions. Violations in the random sampling, normality, and homogeneity of variance assumptions of the Student's t-test would have likely led to inaccurate results for the mean age, LOS, and total patient cost variables; outliers may disproportionately impact the results, particularly among the ADPKD group with smaller sample size.(360 Studies, 2023; Bobbitt, 2021) Therefore, this study generated median (IQR) estimates instead of mean (SD) estimates. The Wilcoxon Signed-Rank Sum test can reduce the impact of outliers on results. Thus, it was used to assess significant differences in the median age, LOS, and total patient cost at index hospitalization for KTP surgery and at 30-day all-cause readmissions.

5.2.3.2.2 Inferential Statistics

Logistic regression was used to assess the association between ADPKD diagnosis and the odds of at least one all-cause readmission within 30 days on index discharge for KTP surgery. Logistic regression is limited by its assumption of linearity to the log odds

between the independent variables (i.e., ADPKD event) and dependent variables (i.e., at least one 30-day all-cause readmission).(Ranganathan, Pramesh, & Aggarwal, 2017) Logistic regression also requires little to no multicollinearity between independent variables included in the model.(Ranganathan et al., 2017) The inclusion of too many independent variables may also dilute true associations with large standard errors and wide confidence intervals that are likely imprecise.(Ranganathan et al., 2017) Therefore, the ADPKD event was the primary independent variable, and covariates (age, sex, race, CHF, VD, HTN-C, HTN-U, RA, WL, and AA) were limited to only those that were significantly different (i.e., $p \leq 0.05$) between patients with vs. without ADPKD at index hospitalization for KTP surgery.

The generalized linear model (GLM) is limited due to its sensitivity to outliers with extremely low or high estimates for the mean LOS.(Singh, 2024) A generalized linear model with negative binomial distribution and log link transformation was used to assess the association between ADPKD diagnosis and mean (SD) LOS at 30-day all-cause readmissions. Negative binomial regression allowed us to account for overdispersion in the data while estimating the effect that the independent variables have on the count (i.e., the cumulative number of days for LOS) outcome.(Psychological Scales, 2024) The GLM is also limited due to its sensitivity to outliers with extremely low or high estimates for the mean total patient cost.(Singh, 2024) To eliminate the impact of outliers in the GLM, a quantile regression model was used to assess significant differences in quantiles (i.e., median) of the total patient cost between patients with vs. without ADPKD at 30-day all-cause readmissions. The quantile regression is more robust when homoscedasticity, or the

assumed homogeneity of variance between patients with vs. without ADPKD, is violated in GLM of the mean total patient cost at 30-day all-cause readmissions.(Waldmann, 2018)

5.2.4 Conclusions

Patients with ADPKD and receiving KTP impose less inpatient resources and cost burden on hospitals at index hospitalization for KTP surgery compared to those without ADPKD. Nearly half of patients included in this cohort experienced a 30-day all-cause readmission following KTP surgery, thus, there is a need for improvement in the quality of KTP care delivered across hospitals in the US. There was no association found between ADPKD diagnosis and the odds of at least one 30-day all-cause readmission. Furthermore, no association was found between ADPKD diagnosis and the burden imposed on hospitals (i.e., mean LOS and median total patient cost) at 30-day all-cause readmissions. Lower comorbidity burden at index hospitalization for KTP surgery among patients with ADPKD likely impacted the readmission results. Ultimately, the economic burden to hospitals financially responsible for 30-day all-cause readmissions was determined equivalent for KTP patients with and without ADPKD in this study.

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