



Association of autosomal dominant polycystic kidney disease with cardiovascular disease: a US-National Inpatient Perspective

Nassib Abou Heidar¹ · Omar Chehab^{2,3} · Rami Z. Morsi⁴ · Joseph Elias⁵ · Christopher El Mouhayyar⁶ · Amjad Kanj² · Mustafa Ajam² · Abdallah Haykal² · Mohit Pahuja² · Habib Dakik⁵ · Diane Levine² · Nashat Imran^{2,7} · Aiden Abidov^{2,8}

Received: 7 January 2022 / Accepted: 11 February 2022 / Published online: 25 February 2022
This is a U.S. government work and not under copyright protection in the U.S.; foreign copyright protection may apply 2022

Abstract

Purpose Data on the epidemiology of cardiovascular diseases (CVD) in patients with autosomal dominant polycystic kidney disease (ADPKD) are limited. In this study, we assess the prevalence of CVD in patients with ADPKD and evaluate associations between these two entities.

Methods Using the National Inpatient Sample database, we identified 71,531 hospitalizations among adults aged ≥ 18 years with ADPKD, from 2006 to 2014 and collected relevant clinical data.

Results The prevalence of CVD in the study population was 42.6%. The most common CVD were ischemic heart diseases (19.3%), arrhythmias (14.2%), and heart failure (13.1%). The prevalence of CVD increased with the severity of renal dysfunction (RD). We found an increase in hospitalizations of patients with ADPKD and CVD over the years ($p_{\text{trend}} < 0.01$), irrespective of the degree of RD. CVD was the greatest independent predictor of mortality in these patients (OR: 3.23; 95% CI 2.38–4.38 [$p < 0.001$]). In a propensity matched model of hospitalizations of patients with CKD with and without ADPKD, there was a significant increase in the prevalence of atrial fibrillation/flutter (AF), pulmonary hypertension (PHN), non-ischemic cardiomyopathy (NICM), and hemorrhagic stroke among patients with ADPKD when compared to patients with similar degree of RD without ADPKD.

Conclusions The prevalence of CVD is high among patients with ADPKD, and the most important risk factor associated with CVD is severity of RD. We found an increase in the trend of hospitalizations of patients with ADPKD associated with increased risk of AF, PHN, NICM, and hemorrhagic stroke. History of CVD is the strongest predictor of mortality among patients with ADPKD.

Keywords Autosomal dominant polycystic kidney disease · Cardiovascular disease · Mortality · Chronic kidney disease

A part of this study was presented at the American Heart Association Scientific Sessions on November 16, 2019.

Nassib Abou Heidar and Omar Chehab contributed equally to this study.

✉ Omar Chehab
omar.chehab@wayne.edu

¹ Division of Urology, Department of Surgery, American University of Beirut, Beirut, Lebanon

² Department of Medicine, Detroit Medical Center, Wayne State University, 3990 John R., Detroit, MI 48201, USA

³ Department of Medicine, Division of Cardiology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

⁴ Department of Neurology, University of Chicago, Chicago, IL, USA

Abbreviations

ADPKD Autosomal dominant polycystic kidney disease
CVD Cardiovascular disease
CKD Chronic kidney disease
NIS National Inpatient Sample

⁵ Cardiology Division, Department of Medicine, American University of Beirut, Beirut, Lebanon

⁶ Department of Medicine, St Elizabeth Medical Center, Boston, MA, USA

⁷ Nephrology Division, Department of Medicine, Detroit Medical Center, Wayne State University, Detroit, MI, USA

⁸ Department of Medicine, Cardiology Section, John D. Dingell VA Medical Center, Detroit, MI, USA

ESRD	End-stage renal disease
AF	Atrial fibrillation/flutter
PHN	Pulmonary hypertension
NICM	Non-ischemic cardiomyopathy
RD	Renal dysfunction

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a genetically inherited disorder leading to a myriad of renal and extrarenal manifestations. It is characterized by the progressive cystic dilation of renal tubules resulting in end-stage kidney disease due to fibrosis [1]. ADPKD is a disease of all races with a prevalence of 1:400 to 1:1000 and accounts for up to 5% of individuals who initiate dialysis in the United States every year [2, 3]. ADPKD is the fourth most common reason for initiation of dialysis worldwide [4]. It is caused by a variety of genetic mutations, such as polycystin 1 and polycystin 2, and, less commonly, glucosidase II alpha subunit and phosphomannomutase 2 [5]. People afflicted with this disease have a 1.6–3.2-fold higher mortality rate compared to the general population [6]. Moreover, with the advances in renal replacement therapies for patients with end-stage renal disease (ESRD), cardiovascular diseases have emerged as a major cause of morbidity and mortality in patients with ADPKD [7, 8]. A retrospective study of 426 patients with ADPKD by Hela et al. found that the most common cardiovascular manifestations reported were arrhythmias (25.9%), followed by peripheral vascular disorders (16.5%), and valvular heart disease (14.4%) [9]. Another study by Fick et al. found that out of 129 patients with ADPKD, 89% and 81% had cardiac hypertrophy and coronary artery disease on autopsy, respectively [10]. Moreover, the most common comorbidities recognized in ADPKD patients with CVD were hypertension (86.6%) and dyslipidemia (45.7%) [9]. The available studies on this subject are limited by their smaller sample size and, as such, prevalence of the various subtypes of CVD and their impact on patients with ADPKD remains elusive.

This study focuses on the epidemiology of different cardiovascular manifestations and identifies the clinical variables and outcomes associated with CVD in patients with ADPKD. The study also evaluates the impact of ADPKD on the prevalence of different CVD.

Methods

Data source

The National Inpatient Sample (NIS) database was created by the Agency of Healthcare Research and Quality (AHRQ) in the United States. It presents a sample of 20% of all inpatient discharges across different hospitals [11]. It provides the public with a broad set of data on individual hospitalizations. The database includes patient's age and gender, length of hospital stay, cost of hospitalization, mortality rates, comorbidities, in-hospital complications, in-hospital procedures and type of admission (emergency or elective). The data used in this study were from the years 2006 to 2014, inclusive. Recently, the AHRQ issued a change in the NIS design and how patient discharges are weighed to provide closer national estimates when performing trend analysis [11, 12]. To date, the new variable "Trend Weights" was developed for year 2012 and beyond. It is also well-adjusted for previous years. This method ensured the same level of patient analysis across all the years [11, 12].

Study population and variables

Patients with ADPKD were identified using the international classification of diseases, ninth revision, clinical modification (ICD-9-CM) of "753.13". Patients younger than 18 years of age, those with a history of autosomal recessive polycystic kidney disease (ICD-9-CM: 753.14) and those with missing outcomes, age, or gender, were excluded from the analysis. Demographics (i.e., age, gender, and race), along with comorbidities and procedures, were included in our analysis. Chronic comorbidities, such as hypertension, liver disease, and obesity, were obtained using the clinical classification of diseases (CCS) software. Patients with cardiovascular diseases were identified if they had at least one of the following diagnoses: ischemic heart disease, arrhythmias and conduction disorders, heart failure, cerebrovascular disease, vascular disorders, non-ischemic cardiomyopathy, valvular heart disease, pulmonary hypertension or endocarditis. Patients were then grouped as shown in Table 1 along with other details of the ICD-9-CM/CCS codes and Elixhauser comorbidity index that were used (eTable 1 and eTable 2). Renal function status was defined by identifying patients based on their chronic kidney disease (CKD) stage on discharge as previously done by other studies [13, 14]. Patients with normal kidney function were labeled as CKD 1 according to the staging classification of renal function in ADPKD patients [15, 16]. In this regard, patients diagnosed

Table 1 Baseline characteristics of ADPKD with and without cardiovascular disease

Variable	Outcome			
	Cardiovascular disease			
	N (% of Total)	No CVD N (% of Total)	CVD N (% of Total)	<i>p</i> value ^a
I. Total No. of observations (Weighted) (%)	71,531	41,170 (57.4)	30,361 (42.6)	
II. Demographic characteristic				
Age, mean (SD), years	55.9 ± 14.9	51.03 ± 13.92	61.9 ± 13.4	<0.001
18–39	9737 (13.6)	8324 (20.2)	1413 (4.7)	<0.001
40–59	33,673 (47.1)	22,029 (53.5)	11,644 (38.4)	
60–70	15,162 (21.2)	6809 (16.5)	8353 (27.5)	
> 70	12,960 (18.1)	4009 (9.7)	8951 (29.5)	
Male— No. (%)	35,675 (49.9)	18,308 (44.5)	17,367 (57.2)	<0.001
Female— No. (%)	35,856 (50.1)	22,862 (55.5)	12,994 (42.8)	
Race— No. (%)				
White	40,772 (64.6)	22,728 (63.1)	18,044 (66.6)	<0.001
Black	10,330 (16.4)	5652 (15.7)	4678 (17.3)	
Hispanic	7902 (12.5)	5186 (14.4)	2716 (10.0)	
Asian	1657 (2.6)	910 (2.5)	747 (2.8)	
III. CVD Risk Factors— o. (%)				
Alcohol abuse	1168 (1.6)	709 (1.7)	467 (1.5)	0.09
Smoking	14,798 (20.7)	7800 (18.9)	6998 (23.0)	<0.001
Obesity	6564 (9.2)	3847 (9.3)	2717 (8.9)	0.07
Hypertension	41,238 (57.7)	20,901 (50.8)	20,337 (67.0)	<0.001
Dyslipidemia	19,809 (27.7)	8921 (21.7)	10,888 (35.9)	<0.001
Diabetes	10,765 (15.0)	4771 (11.6)	5994 (19.7)	<0.001
IV. Comorbidities — No. (%)				
Anemia	31,868 (44.6)	17,419 (42.3)	14,449 (47.6)	<0.001
Chronic pulmonary disease	9610 (13.4)	3898 (9.5)	5712 (18.8)	<0.001
Coagulopathy	5491 (7.7)	2450 (6.0)	3041 (10.0)	<0.001
Hypothyroidism	6326 (8.8)	3147 (7.6)	3179 (10.5)	<0.001
Liver disease	2330 (3.3)	1204 (2.9)	1126 (3.7)	<0.001
Fluid and electrolyte disorders	24,599 (34.4)	13,595 (33.0)	11,004 (36.2)	<0.001
Weight loss	4356 (6.1)	1907 (4.6)	2449 (8.1)	<0.001
Lymphoma	392 (0.5)	177 (0.4)	215 (0.7)	<0.001
Metastatic cancer	684 (1)	352 (0.9)	332 (1.1)	<0.001
Solid tumor without metastasis	854 (1.2)	422 (1.0)	432 (1.4)	<0.001
Neurological disorders	4314 (6)	2039 (5.0)	2275 (7.5)	<0.001
Impaired renal function	51,794 (72.4)	26,950 (65.5)	24,844 (81.8)	<0.001
History of kidney transplant	6618 (9.3)	3800 (9.2)	2818 (9.3)	0.8
History of nephrectomy	7161 (10.0)	4605 (11.2)	2556 (8.4)	<0.001

Abbreviations: CVD Cardiovascular disease

^aChi-squared; *p* value < 0.05 is considered significant (CVD vs. No CVD)

* Impaired renal function was defined as patients who were diagnosed with any stage of CKD above 0 when discharged from the hospital

with renal insufficiency using ICD-9 CM codes in large national databases had a sensitivity, specificity, positive and negative predictive value—the extent to which a condition

in the administrative data is also present in the chart review data—of 81.9%, 98.6%, 71.2% and 99.2%, respectively [17].

Study endpoints

The primary endpoint was the prevalence of CVD in ADPKD patients. Secondary endpoints were variables (i.e., gender, renal function status, hypertension, etc.) and clinical outcomes (i.e., mortality and trends of hospitalization) associated with CVD and ADPKD based on renal function. Further endpoints include impact of CKD with ADPKD vs. CKD without ADPKD on CVD.

Statistical analysis

For our analysis, we adhered to the main practices proposed by Khara et al. on statistical and research methodologies using the NIS database [18]. Trend weights were used to estimate national hospitalizations. Stratification and clustering data was done to provide national estimates. For trend analysis, we reported hospitalizations and outcomes as absolute values for each calendar year and compared using one-way ANOVA. First, we looked at the baseline characteristics of ADPKD patients with CVD. Subsequently, we compared baseline demographics and comorbidities between groups using the Pearson χ^2 test for categorical variables and one-way linear regression for continuous variables. We reported categorical and continuous variables as percentages and mean \pm standard error (SE), respectively. We then performed multivariable logistic regression analysis to identify predictors that were associated with CVD after controlling for confounding factors such as age, gender and other comorbidities that are mentioned in the supplementary file. Furthermore, to assess CVD as a significant association with mortality, an analysis was done on ADPKD patients to identify variables associated with mortality and a second multivariable logistic regression was performed to determine the effect CVD on mortality. To prevent distortion of the data on predictive value of CVD on mortality in this population, patients with metastatic cancer were excluded from the analysis.

In addition, to determine the impact of ADPKD on the risk of CVD, we developed a propensity score-matching model to derive two matched groups for comparative outcome analysis, to account for potential confounding factors and to reduce the effect of selection bias. The model included all patients of CKD 3–5 (with and without ADPKD). For the propensity matching procedure, we used a multivariable logistic regression model with ADPKD as the outcome variable, and all co-morbidities listed in Tables 1 and 2 and patient-level NIS weights as covariates. We applied a one-to-one greedy matching protocol and a caliper width of 0.1 multiplied by the standard deviation of the logit of the propensity score to create a matched cohort that includes matched demographics, and comorbidities

Table 2 Adjusted ORs of predictors significantly associated* with CVD

Predictor	Adjusted OR ^a	95% CI (Adjusted)	<i>p</i> value
Age, every 5-year increase	1.28	1.26; 1.30	<0.001
Male	1.70	1.65; 1.76	<0.001
Smoking	1.25	1.13; 1.37	<0.001
Dyslipidemia	1.44	1.32; 1.57	<0.001
Hypertension	1.67	1.53; 1.81	<0.001
Diabetes	1.38	1.24; 1.54	<0.001
Coagulopathy	1.40	1.22; 1.62	<0.001
Chronic obstructive pulmonary disease	1.82	1.62; 2.04	<0.001
Neurological disorders	1.40	1.19; 1.46	<0.001
Renal function status			
CKD 1	Reference		
CKD 2	1.51	1.00; 2.30	0.05
CKD 3–4	1.86	1.62; 2.13	<0.001
CKD 5-ESRD	2.01	1.81; 2.23	<0.001

^aAdjusted for age, gender, race, smoking, dyslipidemia, hypertension, diabetes, anemia, chronic pulmonary disease, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, other neurological disorders, coagulopathy, neurological disorders, solid tumors without metastasis, and kidney status

[19, 20]. Patients with history of ischemic heart disease such as history of ischemic cardiomyopathy, myocardial infarction or history of coronary artery disease were also matched to avoid influence of ischemic heart disease on trends and outcomes.

Finally, trends of hospitalization rate of ADPKD patients with CVD were computed by fitting a Poisson regression model with a robust error variance to evaluate for changes in the number of outcomes (prevalence of CVD) per year stratified by renal function status (Chronic kidney disease (CKD) stage 1, CKD stage 2, CKD stages 3–4, CKD stage 5-ESRD) while inserting the year variable into the model assuming the association to be linear. All data extraction and analyses were performed using SPSS (Version 25.0 Armonk, NY). Two-sided *p* value <0.05 was used for statistical significance.

Ethics statement

The NIS is a public owned database and thus there was no need for IRB approval for this study.

Fig. 1 Prevalence of cardiovascular disease based on CKD Stages among patients with ADPKD

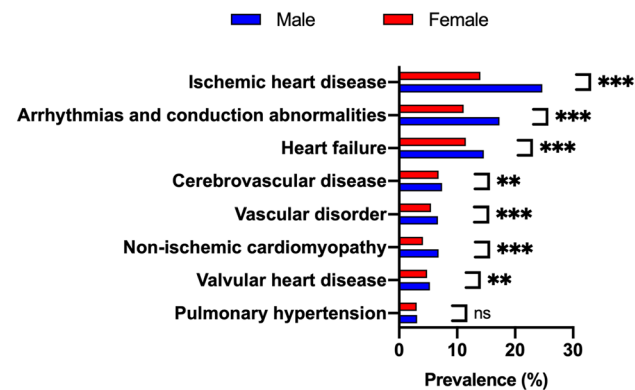
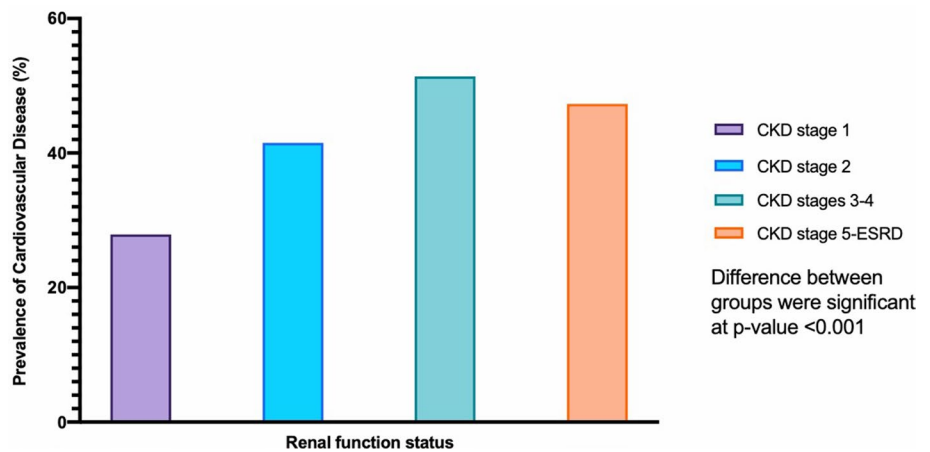


Fig. 2 Prevalence of cardiovascular manifestations in ADPKD patients stratified by gender

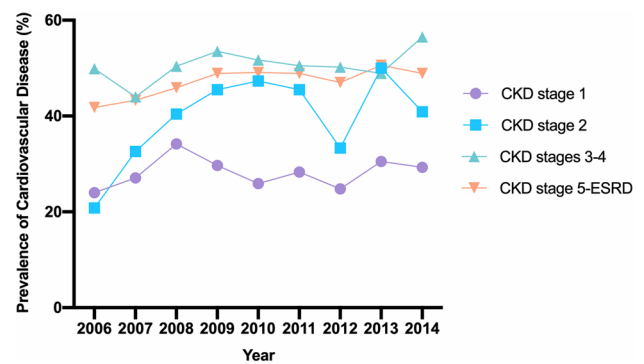


Fig. 3 Trend in hospitalization of patients with ADPKD and CVD based on CKD stages

Results

We identified a total of 71,531 hospitalizations with ADPKD in years 2006–2014 (Table 1). Demographic analysis revealed that 49.9% of hospitalized patients were males, 64.6% of white race and the mean age was 55.9 ± 14.9 years. Patients hospitalized with ADPKD had mostly CKD stage 5-ESRD (57.3%) followed by CKD stage 1 (27.9%), CKD stages 3–4 (13.9%), and CKD stage 2 (0.9%).

Cardiovascular disease

Among patients hospitalized for ADPKD, 42.6% had a diagnosis of CVD. Compared to ADPKD patients without CVD, those with CVD were more likely to be older (mean age: 61.9 vs. 51.0 years, $p < 0.001$), males (57.2% vs. 42.8%, $p < 0.0001$), and had a higher prevalence of CVD risk factors, such as smoking, hypertension, diabetes, and dyslipidemia ($p < 0.001$). Moreover, the prevalence of CVD increased with severity of renal dysfunction (Table 1, Fig. 1). Among hospitalized patients with ADPKD, the most

common CVD was ischemic heart disease (19.3%) followed by electrophysiological disorders (14.2%) and heart failure (13.1%). When stratified by gender, males with ADPKD had a significantly higher prevalence rate of ischemic heart disease, arrhythmias, heart failure, cerebrovascular disease, vascular disease, non-ischemic cardiomyopathy and valvular heart disease (Fig. 2). No significant difference in the prevalence of pulmonary hypertension was identified between males and females.

The rate of hospitalization of patients with ADPKD and CVD from 2006 to 2014 was higher in groups with worsening renal dysfunction and ESRD as compared to the group with normal renal function (81.8% vs. 65.5%, $p < 0.001$) (Table 1, Fig. 1). Moreover, there was an increase in the trend of hospitalizations of patients with ADPKD and CVD irrespective of degree of renal dysfunction across the years with a greater increase in those with CKD stage 2 (Fig. 3).

Predictors of cardiovascular disease in patients with ADPKD

Following multivariate logistic regression analysis, the main predictors of CVD were worsening renal function with CKD stage 5-ESRD (OR = 2.01, 95% CI [1.81–2.23]), CKD stages

Table 3 Adjusted ORs of predictors significantly associated* with mortality

Predictor	Adjusted OR ^a	95% CI (Adjusted)	<i>p</i> value
Age, every 5-year increase	1.23	1.17; 1.29	<0.001
Coagulopathy	1.81	1.29; 2.52	
Fluid and electrolyte disorders	2.02	1.57; 2.59	
Anemia	0.50	0.38; 0.65	
Dyslipidemia	0.34	0.24; 0.47	
Solid tumor without metastasis	2.69	1.45; 4.99	
Weight loss	2.37	1.71; 3.28	
Cardiovascular disease	3.23	2.38; 4.38	

^aAdjusted for: age, gender, diabetes, dyslipidemia, chronic pulmonary disease, coagulopathy, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, other neurological disorders, obesity, solid tumor without metastasis, weight loss, cardiovascular disease, and kidney status

3–4 (OR = 1.86, 95% CI [1.62–2.13]), chronic obstructive pulmonary disease (OR = 1.82, 95% CI [1.62–2.04]), male gender (OR = 1.70, 95% CI [1.65–1.76]), hypertension (OR = 1.67, 95% CI [1.53–1.81]), dyslipidemia (OR = 1.44, 95% CI [1.32–1.57]), and diabetes (OR = 1.38, 95% CI [1.24–1.54]) (Table 2).

Mortality

The overall mortality rate in our cohort of inpatients was 1.9% (eTable 3). Patients who died were more likely to be older (66.6 vs. 55.5, $p < 0.001$) and of female gender (53.0% vs. 47.0%, $p < 0.001$). Moreover, those who died had significantly higher rates of hypertension (64.2% vs. 57.5%, $p < 0.001$), coagulopathy (17.0% vs. 7.5%, $p < 0.001$), fluid

and electrolyte disorders (53.1% vs. 34.0%, $p < 0.001$), weight loss (18.9% vs. 5.8%, $p < 0.001$), malignancy (with [6.2% vs. 0.9%, $p < 0.001$] or without metastases [4.7% vs. 1.1%, $p < 0.001$]), impaired renal function (78.8% vs. 72.3%, $p < 0.001$) and history of prior CVD (77.8% vs. 41.7%, $p < 0.001$). After applying multivariable logistic regression, ADPKD patients with CVD (OR = 3.23, 95% CI [2.38–4.38]) had the highest risk of mortality irrespective of renal function, followed by patients with history of solid tumors without metastasis (OR = 2.69, 95% CI [1.45–4.99]) and weight loss (OR = 2.37, 95% CI [1.71–3.28]) (Table 3).

Table 4 Clinical outcomes of hospitalizations with and without ADPKD stratified by age after applying a 1:1 propensity match

	Age groups								
	18–39			40–64			≥ 65		
	CKD without ADPKD	CKD with ADPKD	OR (95%CI)	CKD without ADPKD	CKD with ADPKD	OR (95%CI)	CKD without ADPKD	CKD with ADPKD	OR (95%CI)
Acute myocardial infarction	3.2%	0.9%	0.27 (0.10–0.71)	5.0%	2.4%	0.46 (0.35–0.62)	5.1%	2.6%	0.49 (0.35–0.67)
Arrhythmias and conduction disorders	1.9%	6.3%	3.38 (1.83–6.26)	13.9%	12.4%	0.87 (0.75–1.02)	30.8%	34.4%	1.17 (1.04–1.33)
Atrial Fibrillation/Flutter	0.6%	3.6%	5.71 (2.13–15.30)	9.8%	8.5%	0.85 (0.71–1.02)	27.2%	28.0%	1.04 (0.92–1.18)
Non-ischemic cardiomyopathy	7%	7%	1.00 (0.65–1.53)	5.7%	7.2%	1.27 (1.03–1.58)	6.8%	7.1%	1.05 (0.84–1.32)
Pulmonary hypertension	1.3%	1.8%	1.39 (0.57–3.36)	2.5%	2.0%	0.81 (0.57–1.15)	3.2%	5.1%	1.62 (1.21–2.18)
Acute ischemic stroke	1.9%	1.6%	0.83 (0.36–1.91)	2.6%	1.4%	0.52 (0.35–0.77)	3.4%	2.9%	0.84 (0.60–1.17)
Acute hemorrhagic stroke	0%	0%	–	0.9%	2.0%	2.28 (1.43–3.65)	0.2%	1.5%	7.05 (2.76–18.04)

Propensity-matched analysis of in-hospital outcomes between patients with and without ADPKD

To assess the impact of ADPKD on the risk of CVD, a one-to-one propensity-matched cohort between ADPKD of CKD stages 3–5 ($n = 5844$) and those with CKD stages 3–5 but without ADPKD ($n = 5867$) was developed and stratified by age (eTable 4). A lower risk of acute myocardial infarction or acute ischemic stroke was observed in patients with CKD and ADPKD compared to patients with CKD without ADPKD across all age groups. However, higher risk of atrial fibrillation and atrial flutter was observed among ADPKD in the younger age group compared to those with CKD and without ADPKD (OR 5.71, 95% CI 2.13–15.30). Moreover, a higher risk of non-ischemic cardiomyopathy was observed in the ADPKD group across ages 40–64 (OR 1.27, 95% CI 1.03–1.58), as well as a higher risk of pulmonary hypertension in the patients of 65 years or older when compared to those without ADPKD (OR 1.62, 95% CI 1.21–2.18). Finally, there was a significant increase in risk hemorrhagic stroke in patients with ADPKD when compared to those without ADPKD (Table 4).

Discussion

Using the largest US national database, we report the CVD epidemiology in patients with ADPKD, predictors of in-hospital mortality, and impact of ADPKD on cardiovascular risk.

Smoking, hypertension, dyslipidemia, and diabetes appeared to be more common in ADPKD patients with CVD compared to those without CVD. These are well-known modifiable risk factors that could contribute to CVD in ADPKD patients as well as patients without ADPKD. Hypertension is present in more than two-thirds of ADPKD patients with CVD which is known to contribute to the decline in kidney function and independently add to the morbidity of valvular as well as aneurysmal disease [21].

In our study, CVD was the leading comorbidity among the patients hospitalized with ADPKD, with a prevalence of 42.6%, and the most common CV conditions in this population included ischemic heart disease, arrhythmias, and heart failure. Our results accord with previously published evidence showing that after the introduction of renal replacement therapy, cardiovascular complications have become the leading cause of morbidity and mortality in patients with ADPKD [6, 10, 22, 23].

Another important finding in our study is the incrementally increased risk of cardiovascular disease with severity

degree of renal dysfunction. Most importantly, CKD is the highest predictor of incidence of overall CVD. CKD is associated with substantial cardiovascular morbidity and mortality [24]. This is likely due the high concurrent prevalence of traditional cardiovascular risk, but also by the presence of CKD-specific non-traditional cardiovascular risk factors, such as vascular calcification, uremic toxins, uremic dyslipidemia as well as inflammation and oxidative stress [24, 25]. This constellation of traditional and non-traditional risk factors could elicit increased CVD in ADPKD patients. In addition, worsening renal function is associated with the activation of the renin–angiotensin–aldosterone system (RAAS) and hypertension [6]. With increase in renal volume—as part of the renal structural changes and cyst expansion in ADPKD, more renal ischemia ensues causing a chronic activation of the RAAS system [26–28]. This, in turn, leads to a cascade of events, causing increased systemic vascular resistance, sodium retention, renal fibrosis, and increased cyst growth, all ultimately leading to worsening renal disease, hypertension as well as cardiac remodeling [6, 27–30]. Chapman et al. confirmed activation of the RAAS in ADPKD after demonstrating that plasma renin activity and aldosterone concentrations were higher in patients with ADPKD than in patients with essential hypertension while correcting for all confounders [26].

Previous studies have also reported that patients with ADPKD are at higher risk of mortality after initiation of dialysis due to infection or cardiovascular disease [10, 31, 32]. Our study showed that CVD worsens risk of in-hospital mortality regardless of being on dialysis. In addition, we found that ADPKD to be associated with higher risk of atrial fibrillation and flutter among the younger age group compared to patients with CKD without ADPKD (OR 5.71, 95% CI 2.13–15.30). Several factors have been suggested to play a role in the development of arrhythmias in ADPKD including overactivation of the RAAS, autonomic function, idiopathic dilated cardiomyopathy as well as abnormal calcium handling conditions [33–35]. Polycystin-2 gene mutations have been associated with defects in calcium signaling, desensitization of calcium-contraction coupling in cardiomyocyte and abnormal changes in intracellular calcium levels [36]. Given this finding of higher risk of atrial fibrillation/flutter among young patients with ADPKD and higher risk of hemorrhagic stroke, the need in systemic anticoagulation in patients with ADPKD and CKD should be calculated differently compared to those with CKD not due to ADPKD, as their risk profile and bleeding risk is likely different. Other novel findings included higher risk of acute ischemic cardiovascular events in patients with CKD without ADPKD vs. higher risk of non-ischemic cardiomyopathy, pulmonary hypertension, and hemorrhagic stroke among patients with ADPKD. This could be explained by the fact that patients with secondary CKD due to comorbidities are different

compared to patients with a primary origin of CKD caused by ADPKD. It is likely linked to an association of these conditions with particular genes/gene clusters (such as diabetes, atherosclerosis, etc.) with different clinical presentations; thus, these two conditions should be differentiated, managed and stratified separately. Chickera et al., also observed lower rates of diabetes and albumin to creatinine ratio in CKD–ADPKD patients compared to CKD from other causes [37]. A proof to this concept is validated in Table 4 after there was a consistent increase in risk of hemorrhagic stroke in ADPKD compared to patients without ADPKD. This is likely linked to the genetic association of ADPKD and berry aneurysm [21].

Other interesting findings in our analysis were that patients diagnosed with dyslipidemia were at lower risk of mortality. One potential explanation to this finding is that patients diagnosed with dyslipidemia will likely be on statin-related therapy. In an attempt to study the effect of simvastatin on endothelial function in patients with ADPKD, Namli et al. found that in 16 patients after 1 month vs. 6 months of treatment with simvastatin, there was a progressive increase in endothelial-dependent dilation and a decrease in the inflammatory marker interleukin-6 (21.6 ± 21.7 pg/mL to 9.1 ± 3.5 pg/mL ($p = 0.002$)) [38]. Moreover, several studies supported the effects of statins in decreasing worsening progression of kidney function through decrease in the size of renal cysts and left ventricular mass index, and other structural modifications in ADPKD patients when started early [39–41]. Furthermore, in our study, it was found that patients diagnosed with anemia were associated with decreased risk of mortality. Importance of this finding is not clear. However, when present, same degree of anemia may play less clinical significance in ADPKD patients as compared to a general population with advanced CKD [15]. This mechanism was found to be likely secondary to an increase in release of erythropoietin from the renal cysts [15, 42]. However, a recent study by Ushio et al. found that in 115 patients with ADPKD, men and women with hemoglobin levels of less than 12 g/dl and 11 g/dl, respectively, were found to be associated with worsening renal progression [43].

Limitations

There are several limitations in this study that need to be acknowledged. The NIS is an administrative database that is de-identified and could, as a result, lead to possible coding errors, since validation of all individual ICD-9 codes would not be possible. Moreover, the NIS database does not provide specific mortality-related causes [44]. Another limitation is the lack of information on the outpatient course of disease and mortality, which would bias our sample to only inpatients. Also, the database does not indicate the

severity of ADPKD in terms of kidney cyst size and number, and presence or absence of proteinuria which could be an independent predictor of worsening CVD. It also does not provide objective measures, such as vital signs (e.g., blood pressure, temperature, heart rate, and respiratory rate), ejection fraction reports, cardiac catheterization results, laboratory data and specific creatinine/glomerular filtration rates. These limitations are offset by the use of the large sample size available which is the largest sample size, to date, of this population, and the lack of reporting bias that is found in most retrospective studies. Moreover, this study provides a clear overall prevalence of major cardiovascular manifestations across patients with ADPKD.

Conclusions

This study assessed the epidemiology of cardiovascular manifestations of patients with ADPKD. The prevalence of CVD is high among patients with ADPKD, and the most important risk factor predicting CVD in this population is severity of renal dysfunction. We found an increase in the trend of hospitalizations of patients with ADPKD and CVD in the recent years. CVD is the strongest independent predictor of mortality in patients with ADPKD irrespective of degree of renal dysfunction. When matched with patients with CKD and without ADPKD, those with ADPKD had higher risk of atrial fibrillation/flutter, non-ischemic cardiomyopathy, pulmonary hypertension and hemorrhagic stroke. This study highlights important epidemiological variables that can assist clinicians in understanding the clinical cardiovascular manifestations in ADPKD. Further prospective research is needed to address secondary prevention of CVD in the ADPKD population and genetic association of CVD and ADPKD.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10157-022-02200-5>.

Author contributions Study concept and design: all authors. Acquisition of data: OC, NAH. Analysis and interpretation of data: all authors. Drafting of the manuscript: all authors. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: OC, AK, RZM. Obtaining funding: none. Administrative, technical, or material support: RZM, OC. Supervision: NI, AA, HD. Other: none.

Funding This study has no external funding to disclose.

Availability of data and materials The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Competing interests Aiden Abidov MD, PhD—reports grant support: Astellas Pharma, NIH, GE Healthcare, Kiniksa, Boehringer Ingelheim. Other authors—none reported.

Ethics approval This study is a database study and is thus exempt from institutional review board approval.

Consent for publication All authors consent for publication of the manuscript.

Consent to participate Not applicable.

References

- Igarashi P, Somlo S. Polycystic kidney disease. *J Am Soc Nephrol*. 2007;18(5):1371–3.
- Torres VE, Harris PC. Autosomal dominant polycystic kidney disease: the last 3 years. *Kidney Int*. 2009;76(2):149–68.
- Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. *Lancet (London, England)*. 2007;369(9569):1287–301.
- Spithoven EM, Kramer A, Meijer E, Orskov B, Wanner C, Abad JM, et al. Renal replacement therapy for autosomal dominant polycystic kidney disease (ADPKD) in Europe: prevalence and survival—an analysis of data from the ERA-EDTA Registry. *Nephrol Dialysis Transp*. 2014;29(Suppl 4):iv15–25.
- Solazzo A, Testa F, Giovanella S, Busutti M, Furci L, Carrera P, et al. The prevalence of autosomal dominant polycystic kidney disease (ADPKD): a meta-analysis of European literature and prevalence evaluation in the Italian province of Modena suggest that ADPKD is a rare and underdiagnosed condition. *PLoS ONE*. 2018;13(1): e0190430.
- Ecder T, Schrier RW. Cardiovascular abnormalities in autosomal-dominant polycystic kidney disease. *Nat Rev Nephrol*. 2009;5(4):221–8.
- Reed-Gitomer B. Autosomal dominant polycystic kidney disease: cardiovascular complications. *Curr Hypertens Rev*. 2013;9(1):1.
- Cornec-Le Gall E, Alam A, Perrone RD. Autosomal dominant polycystic kidney disease. *Lancet (London, England)*. 2019;393(10174):919–35.
- Helal I, Reed B, Mettler P, Mc Fann K, Tkachenko O, Yan XD, et al. Prevalence of cardiovascular events in patients with autosomal dominant polycystic kidney disease. *Am J Nephrol*. 2012;36(4):362–70.
- Fick GM, Johnson AM, Hammond WS, Gabow PA. Causes of death in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 1995;5(12):2048–56.
- (HCUP) HCUP. Overview of the National (Nationwide) Inpatient Sample (NIS). Rockville, MD: Agency for Healthcare Research and Quality. <http://www.hcup-us.ahrq.gov/nisoverview>; Health-care Cost and Utilization Project (HCUP); 2019 [Available from: <http://www.hcup-us.ahrq.gov/nisoverview.jsp>].
- HCUP. Trend Weights for HCUP NIS Data May, 2015. Available from: <https://www.hcup-us.ahrq.gov/db/nation/nis/trendwghts.jsp>.
- Gupta T, Paul N, Kolte D, Harikrishnan P, Khera S, Aronow WS, et al. Association of chronic renal insufficiency with in-hospital outcomes after percutaneous coronary intervention. *J Am Heart Assoc*. 2015;4(6): e002069.
- Kumar G, Sakhuja A, Taneja A, Majumdar T, Patel J, Whittle J, et al. Pulmonary embolism in patients with CKD and ESRD. *Clin J Am Soc Nephrol*. 2012;7(10):1584–90.
- Chapman AB, Devuyst O, Eckardt KU, Gansevoort RT, Harris T, Horie S, et al. Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2015;88(1):17–27.
- Higashihara E, Horie S, Muto S, Mochizuki T, Nishio S, Nutahara K. Renal disease progression in autosomal dominant polycystic kidney disease. *Clin Exp Nephrol*. 2012;16(4):622–8.
- Quan H, Li B, Saunders LD, Parsons GA, Nilsson CI, Alibhai A, et al. Assessing validity of ICD-9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. *Health Serv Res*. 2008;43(4):1424–41.
- Khera R, Angraal S, Couch T, Welsh JW, Nallamothu BK, Girotra S, et al. Adherence to methodological standards in research using the National Inpatient sample. *JAMA*. 2017;318(20):2011–8.
- Haukoos JS, Lewis RJ. The propensity score. *JAMA*. 2015;314(15):1637–8.
- Dugoff EH, Schuler M, Stuart EA. Generalizing observational study results: applying propensity score methods to complex surveys. *Health Serv Res*. 2014;49(1):284–303.
- Harris PC, Torres VE. Polycystic kidney disease, autosomal dominant. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, et al., editors. *GeneReviews*(®). Seattle (WA): University of Washington, Seattle University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.; 1993
- Ecder T. Cardiovascular complications in autosomal dominant polycystic kidney disease. *Curr Hypertens Rev*. 2013;9(1):2–11.
- Graham JJ. Clinical practice. Autosomal dominant polycystic kidney disease. *New Eng J Med*. 2008;359(14):1477–85.
- Speer T, Schunk SJ, Fliser D. [Chronic kidney disease—a cardiovascular high-risk constellation]. *Der Internist*. 2019.
- Lai S, Mastroluca D, Martino S, Panebianco V, Vitarelli A, Capotosto L, et al. Early markers of cardiovascular risk in autosomal dominant polycystic kidney disease. *Kidney Blood Press Res*. 2017;42(6):1290–302.
- Chapman AB, Johnson A, Gabow PA, Schrier RW. The renin-angiotensin-aldosterone system and autosomal dominant polycystic kidney disease. *N Engl J Med*. 1990;323(16):1091–6.
- Gabow PA, Chapman AB, Johnson AM, Tangel DJ, Duley IT, Kaehny WD, et al. Renal structure and hypertension in autosomal dominant polycystic kidney disease. *Kidney Int*. 1990;38(6):1177–80.
- Graham PC, Lindop GB. The anatomy of the renin-secreting cell in adult polycystic kidney disease. *Kidney Int*. 1988;33(6):1084–90.
- Chapman AB, Johnson AM, Rainguet S, Hossack K, Gabow P, Schrier RW. Left ventricular hypertrophy in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 1997;8(8):1292–7.
- Gabow PA, Johnson AM, Kaehny WD, Kimberling WJ, Lezotte DC, Duley IT, et al. Factors affecting the progression of renal disease in autosomal-dominant polycystic kidney disease. *Kidney Int*. 1992;41(5):1311–9.
- Perrone RD, Ruthazer R, Terrin NC. Survival after end-stage renal disease in autosomal dominant polycystic kidney disease: contribution of extrarenal complications to mortality. *Am J Kidney Dis*. 2001;38(4):777–84.
- Shaw C, Simms RJ, Pitcher D, Sandford R. Epidemiology of patients in England and Wales with autosomal dominant polycystic kidney disease and end-stage renal failure. *Nephrol Dial Transp*. 2014;29(10):1910–8.
- Schrier RW. Renal volume, renin-angiotensin-aldosterone system, hypertension, and left ventricular hypertrophy in patients with

- autosomal dominant polycystic kidney disease. *J Am Soc Nephrol.* 2009;20(9):1888–93.
34. Martinez-Vea A, Valero FA, Bardaji A, Gutierrez C, Broch M, Garcia C, et al. Left ventricular hypertrophy in hypertensive patients with autosomal dominant polycystic kidney disease: influence of blood pressure and humoral and neurohormonal factors. *Am J Nephrol.* 2000;20(3):193–200.
 35. Paavola J, Schliffke S, Rossetti S, Kuo IY, Yuan S, Sun Z, et al. Polycystin-2 mutations lead to impaired calcium cycling in the heart and predispose to dilated cardiomyopathy. *J Mol Cell Cardiol.* 2013;58:199–208.
 36. Kuo IY, Kwaczala AT, Nguyen L, Russell KS, Campbell SG, Ehrlich BE. Decreased polycystin 2 expression alters calcium-contraction coupling and changes β -adrenergic signaling pathways. *Proc Natl Acad Sci USA.* 2014;111(46):16604–9.
 37. de Chickera S, Akbari A, Levin A, Tang M, Brown P, Djurdev O, et al. The risk of adverse events in patients with polycystic kidney disease with advanced chronic kidney disease. *Can J Kidney Health Dis.* 2018;5:2054358118774537.
 38. Namli S, Oflaz H, Turgut F, Alisir S, Tufan F, Ucar A, et al. Improvement of endothelial dysfunction with simvastatin in patients with autosomal dominant polycystic kidney disease. *Ren Fail.* 2007;29(1):55–9.
 39. Cadnapaphornchai MA, George DM, McFann K, Wang W, Gitomer B, Strain JD, et al. Effect of pravastatin on total kidney volume, left ventricular mass index, and microalbuminuria in pediatric autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol.* 2014;9(5):889–96.
 40. Zafar I, Tao Y, Falk S, McFann K, Schrier RW, Edelstein CL. Effect of statin and angiotensin-converting enzyme inhibition on structural and hemodynamic alterations in autosomal dominant polycystic kidney disease model. *Am J Physiol Renal Physiol.* 2007;293(3):F854–9.
 41. Gile RD, Cowley BD, Gattone VH, O'Donnell MP, Swan SK, Grantham JJ. Effect of lovastatin on the development of polycystic kidney disease in the Han:SPRD rat. *Am J Kidney Dis.* 1995;26(3):501–7.
 42. Abbott KC, Agodoa LY. Polycystic kidney disease in patients on the renal transplant waiting list: trends in hematocrit and survival. *BMC Nephrol.* 2002;3:7.
 43. Ushio Y, Kataoka H, Sato M, Manabe S, Watanabe S, Akihisa T, et al. Association between anemia and renal prognosis in autosomal dominant polycystic kidney disease: a retrospective study. *Clin Exp Nephrol.* 2020;24(6):500–8.
 44. Patel N, Kalra R, Doshi R, Arora H, Bajaj NS, Arora G, et al. Hospitalization rates, prevalence of cardiovascular manifestations, and outcomes associated with sarcoidosis in the United States. *J Am Heart Assoc.* 2018. <https://doi.org/10.1161/JAHA.117.007844>.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.