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Original Investigation

Kidney Versus Combined Kidney and Liver Transplantation in Young People With Autosomal Recessive Polycystic Kidney Disease: Data From the European Society for Pediatric Nephrology/European Renal Association–European Dialysis and Transplant (ESPN/ERA-EDTA) Registry

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Background: The choice for either kidney or combined liver-kidney transplantation in young people with kidney failure and liver fibrosis due to autosomal recessive polycystic kidney disease (ARPKD) can be challenging. We aimed to analyze the characteristics and outcomes of transplantation type in these children, adolescents, and young adults.

Study Design: Cohort study.

Setting & Participants: We derived data for children, adolescents, and young adults with ARPKD with either kidney or combined liver-kidney transplants for 1995 to 2012 from the ESPN/ERA-EDTA Registry, a European pediatric renal registry collecting data from 36 European countries.

Factor: Liver transplantation.

Outcomes & Measurements: Transplantation and patient survival.

Results: 202 patients with ARPKD aged 19 years or younger underwent transplantation after a median of 0.4 (IQR, 0.0-1.4) years on dialysis therapy at a median age of 9.0 (IQR, 4.1-13.7) years. 32 (15.8%) underwent combined liver-kidney transplantation, 163 (80.7%) underwent kidney transplantation, and 7 (3.5%) were excluded because transplantation type was unknown. Age- and sex-adjusted 5-year patient survival posttransplantation was 95.5% (95% CI, 92.4%-98.8%) overall: 97.4% (95% CI, 94.9%-100.0%) for patients with kidney transplantation in contrast to 87.0% (95% CI, 75.8%-99.8%) with combined liver-kidney transplantation. The age- and sex-adjusted risk for death after combined liver-kidney transplantation was 6.7-fold (95% CI, 1.8- to 25.4-fold) greater than after kidney transplantation ($P = 0.005$). Five-year death-censored kidney transplant survival following combined liver-kidney and kidney transplantation was similar (92.1% vs 85.9%; $P = 0.4$).

Limitations: No data for liver disease of kidney therapy recipients.

Conclusions: Combined liver-kidney transplantation in ARPKD is associated with increased mortality compared to kidney transplantation in our large observational study and was not associated with improved 5-year kidney transplant survival. Long-term follow-up of both kidney and liver involvement are needed to better delineate the optimal transplantation strategy.

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Autosomal recessive polycystic kidney disease (ARPKD; OMIM [Online Mendelian Inheritance of Man] 263200) appears in 1:20,000 live births; it is the most common cystic kidney disease in childhood.[1,2] It is associated with mutations in one gene, polycystic kidney and hepatic disease 1 (*PKHD1*), on chromosome 6p12.[3] Although the clinical phenotype of ARPKD is highly heterogeneous, it is a significant cause of kidney- and liver-related morbidity and mortality in children.[4] Death occurs in 25% to 30% of affected neonates, and of the surviving patients, nearly 50% progress to end-stage renal disease (ESRD) within the first decade of life. Only a few patients are diagnosed in adulthood, with kidney function ranging from normal to that of ESRD.[4,5] Apart from kidney disease, biliary dysgenesis with intrahepatic bile duct dilatations (Caroli disease) and ultimately hepatic fibrosis due to a developmental defect in remodeling of the fetal ductal plate always occurs to a certain extent in ARPKD.[4,6] The hepatic complications, such as cholangitis, portal hypertension with hypersplenism, and variceal bleeding, may be life-threatening and ultimately warrant liver transplantation.[4,6]

Because kidney and liver disease progress at a different rate in ARPKD and the progression of especially liver involvement is often unpredictable,[7,8] decision making for the most favorable transplantation strategy, either isolated kidney transplantation or combined liver-kidney transplantation, for individual patients with ESRD can be challenging. Recently, it has been suggested that combined liver-kidney transplantation be the first treatment option in selected patients with ARPKD with ESRD.[6,9,10] Combined liver-kidney transplantation instead of kidney transplantation in these patients could be preferable for 2 reasons. First, 64% to 80% of the mortality occurring in patients with ARPKD following kidney transplantation is attributed to cholangitis or sepsis related to liver disease.[11,12] Second, combined liver-kidney transplantation from the same donor might improve long-term outcome as a result of the immunoprotective role provided by the liver for the kidney transplant.[13-16] Telega et al[6] suggested an empirically based paradigm for the management of patients with ARPKD with kidney and liver complications. However, to date, there are no data that support their proposed algorithm for either kidney or combined liver-kidney transplantation and there is a lack of a validated and predictive risk model for this unique ARPKD population. The aim of the current work was to analyze the results of transplantation type, combined liver-kidney transplantation versus kidney transplantation, on kidney transplant outcomes and patient survival in children, adolescents, and young adults with ARPKD with ESRD using data extracted from the European Society for Pediatric Nephrology/European Renal Association−European Dialysis and Transplant Association (ESPN/ERA-EDTA) Registry.

METHODS

Patient Characteristics and Study Design

The ESPN/ERA-EDTA Registry collects data for all European pediatric patients initiating renal replacement therapy (RRT) on an annual basis. Due to the nature of the Registry, only patients with kidney or combined liver-kidney transplantation were included and there were no patients with isolated liver transplantation. Within the framework of the ESPN/ERA-EDTA Registry, information was available for 202 patients aged 19 years or younger with ARPKD who received a transplant and were in Austria, Belarus, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Greece, Hungary, Iceland, Italy, Montenegro, The Netherlands, Norway, Poland, Romania, Russia, Serbia, Slovakia, Spain, Sweden, Switzerland, or the United Kingdom. Data collected from these countries had to include the following minimum information to be accepted by the Registry: date of birth, sex, initial RRT modality (hemodialysis, peritoneal dialysis, or preemptive transplantation), changes in RRT modality during follow-up, underlying kidney disease, mortality, and causes of death.[17] No ethics committee approval or informed consent was required because the Registry is based on retrospective and anonymized patient data collection. Patients with ARPKD were identified using the ERA-EDTA Registry primary renal disease coding system.[18]

Because liver data are not collected by the ESPN/ERA-EDTA Registry, a questionnaire regarding patients who underwent combined liver-kidney transplantation was administered in order to evaluate the phenotype of their liver disease, which may affect the choice of combined liver-kidney transplantation strategy. The clinician who is the national registry representative and responsible for the data collection in each country was asked to fill in the questionnaire or forward the questionnaire to a colleague treating the respective patient. We collected data for pretransplantation liver involvement, including laboratory results for calculation of the PELD (Pediatric End-Stage Liver Disease) and MELD (Model for End-Stage Liver Disease) scores, liver complications (number of episodes and management of cholangitis, portal hypertension, and cholestasis), and the main reason for the choice of a combined liver-kidney transplantation strategy instead of kidney transplantation.

PELD/MELD scores are predictors of survival on a waiting list for liver transplantation and are used to prioritize patients for transplantation. The United Network for Organ Sharing (UNOS) uses the PELD score for patients younger than 12 years and MELD score for those older than 12 years. However, Eurotransplant uses

the MELD score independent of age,[19,20] and it should also be noted that currently, both Eurotransplant and UNOS provide exceptions for the pediatric population and for patients with ARPKD.

Statistical Analysis

Data were presented as median and interquartile range (IQR) for continuous variables and percentage for categorical variables. Differences in patient characteristics between groups were examined using χ^2 tests for categorical and Kruskal-Wallis tests for continuous parameters. Unadjusted 5-year patient survival is calculated using the Kaplan-Meier method. Survival curves for unadjusted 5-year transplant survival of the first transplant were calculated taking the competing event death into account by using cumulative-incidence competing-risk analysis.[21,22] Five-year adjusted patient and transplant survival probabilities were calculated using the Cox regression model and adjusted for fixed values of age at transplantation (9.1 years) and sex (49.7% female). We compared kidney transplant and patient survival since transplantation of patients with ARPKD receiving kidney and combined liver-kidney transplants. Patients were followed up from the time of transplantation (time = 0) onward.

Survival was compared using hazard ratios (HRs) and 95% confidence intervals (CIs) derived from Cox proportional hazards regression, adjusted for the confounding factors of age at transplantation and sex. Analyses were performed using SAS, version 9.3, computer software (SAS Institute Inc). $P < 0.05$ was considered statistically significant.

RESULTS

Population Characteristics

Of 13,007 Registry patients who have initiated RRT since 1995, a total of 202 patients with ARPKD aged 19 years or younger who received a transplant were identified. The first transplantation was combined liver-kidney in 32 (15.8%) patients and kidney in 163 (80.7%). Seven (3.5%) patients were excluded from further analyses because type of transplantation was not reported. Half (n = 97) of the 195 patients with known type of transplantation were female (Table 1) and 39% were younger than 5 years when they initiated RRT. Two peaks were observed in age at RRT initiation, one in infancy and another around puberty (Fig S1, available as online supplementary material).

The first RRT modality was peritoneal dialysis in 69 (35.4%), hemodialysis in 54 (27.7%), and preemptive transplantation in 71 (36.4%) patients (Table 1). There were 216 transplantations performed in 195 patients. First transplantations were performed at a median age of 9.0 (IQR, 4.1-13.7) years after a median period of 0.4 (IQR, 0.0-1.4) years on dialysis therapy. Median age at transplantation was 5.6 (IQR, 1.7-13.9) years in combined liver-kidney transplantation and 9.5 (IQR, 1.6-17.8) years in kidney transplantation ($P = 0.03$). Nineteen patients underwent 2 transplantations (2 of whom underwent an initial combined liver-kidney transplantation) and one patient underwent 3 transplantations. All retransplantations were kidney transplantation.

Patient Survival Posttransplantation

After a median of 4.1 (IQR, 1.7-6.7) years posttransplantation, 12 patients had died (3 after transplant loss in the kidney transplantation group) at a median age of 5.9 (IQR, 3.1-15.3) years. Seven had undergone kidney transplantation and 5 had undergone combined liver-kidney transplantation. Causes of death were cardiovascular disease (2 kidney transplantation and 2 combined liver-kidney transplantation; 33%), infection (2 kidney transplantation, 1 combined liver-kidney transplantation; 25%), malignancy (2 kidney transplantation; 17%), and other/unknown (1 kidney transplantation, 2 combined liver-kidney transplantation; 25%). Infection as cause of death was found in 1 combined liver-kidney transplantation (septicemia) and 2 kidney transplantation (1 viral pulmonary infection and 1 peritonitis) patients. Of the 4 patients who died within 1 month after transplantation, 3 had received combined liver-kidney transplants. Age at transplantation was not associated with patient survival posttransplantation.

Overall age- and sex-adjusted 5-year patient survival posttransplantation was 95.5% (95% CI, 92.4%-98.8%), whereas this was 97.4% (95% CI, 94.9%-100.0%) for patients with kidney transplantation

Table 1. Characteristics of Patients With ARPKD Who Underwent Either Kidney Transplantation Alone or Combined Liver-Kidney Transplantation

	Overall (N = 195)	Kidney Tx (n = 163)	Combined Tx (n = 32)
Female sex	97 (49.7)	81 (49.7)	16 (50)
Age at RRT initiation, y	7.9 [2.4-13.3]	8.7 [0.0-17.6]	5.0 [0.0-13.7]
Time to Tx, y	0.4 [0.0-1.4]	0.5 [0.0-3.3]	0.2 [0.0-4.7]
Age at Tx, y	9.0 [4.1-13.8]	9.5 [1.6-17.8]	5.6 [1.7-13.9]
Initial RRT modality			
Hemodialysis	54 (27.7)	44 (27.0)	10 (31)
Peritoneal dialysis	69 (35.4)	61 (37.4)	8 (25)
Preemptive Tx	71 (36.4)	57 (35.0)	14 (44)

Note: Values for categorical variables are given as count (percentage); values for continuous variables, as median [5th percentile-95th percentile].

Abbreviations: ARPKD, autosomal recessive polycystic kidney disease; RRT, renal replacement therapy; Tx, transplantation.

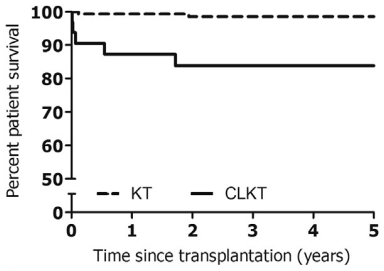
in contrast to 87.0% (95% CI, 75.8%-99.8%) for those undergoing combined liver-kidney transplantation. Unadjusted 5-year patient survival is shown in Fig 1. The age- and sex-adjusted risk for death after combined liver-kidney transplantation was 6.7-fold (95% CI, 1.8- to 25.4-fold) higher than after kidney transplantation ($P = 0.005$). Of the patients who died, the median time between transplantation and death was 1.0 (IQR, 0.1-3.8) year in kidney transplantation and 0.1 (IQR, 0.0-0.5) year in combined liver-kidney transplantation. Age- and sex-adjusted 6-month patient survival following transplantation was 98.1% for kidney transplantation and 92.5% for combined liver-kidney transplantation.

Transplantation Outcomes

Age- and sex-adjusted 5-year kidney transplant survival in first transplant recipients (with patient death as a competing event) was 86.6% (95% CI, 81.1%-92.5%). Age at transplantation did not affect the prognosis after transplantation. There was no significant difference in age- and sex-adjusted 5-year death-censored kidney transplant survival between patients with ARPKD with combined liver-kidney transplantation compared with kidney transplantation: 92.1% (95% CI, 81.7%-100.0%) and 85.9% (95% CI, 79.8%-92.4%), respectively ($P = 0.4$; Fig 2). Death-censored age- and sex-adjusted transplant failure risk was similar in both groups (adjusted HR for combined liver-kidney transplantation vs kidney transplantation, 0.5; 95% CI, 0.1-2.6).

Liver Involvement Prior to Transplantation in Patients With Combined Liver-Kidney Transplantation

Data for liver disease at the time of combined liver-kidney transplantation were available for 23 of the 32 patients (72%; Table 2). Nineteen (83%) patients had a least 1 symptom of liver disease. Although portal hypertension and esophageal varices were documented in the majority of cases, only 2 (9%) patients had intractable pruritus; 3 (13%), recurrent cholangitis; and



Number of patients at risk						
KT	163	137	119	101	84	68
CLKT	32	27	21	18	16	11

Figure 1. Kaplan Meier plot shows unadjusted patient survival after first transplantation for kidney alone (KT) versus combined liver-kidney transplantation (CLKT).

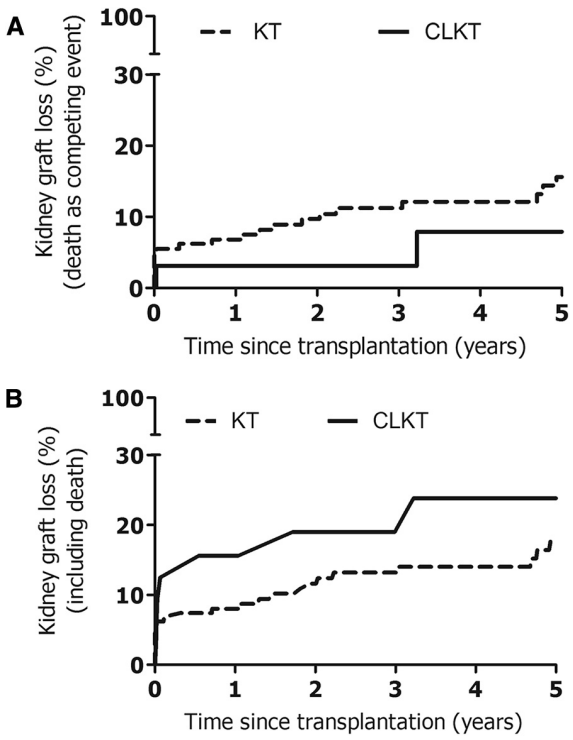


Figure 2. Cumulative-incidence competing-risk analysis shows (A) unadjusted kidney transplant survival excluding death and (B) kidney transplant survival including death. Kidney transplant survival was not significantly different between patients with autosomal recessive polycystic kidney disease with kidney-alone (KT) and combined liver-kidney transplantation (CLKT). This was true both when including and excluding death.

4 a history of variceal bleeding (17%). Only a single patient had undergone transjugular intrahepatic portosystemic stent shunt placement; no surgical portosystemic shunt placements had been performed. All patients had normal synthetic liver function with normal serum albumin, bilirubin, and international normalized ratio for prothrombin time values (Table 2). Consequently, median PELD/MELD score at the time of combined liver-kidney transplantation was −1 (IQR, −6 to 15).

DISCUSSION

In this study, to our knowledge, we describe the largest observational cohort of children, adolescents, and young adults with ARPKD who underwent transplantation ever reported.[23-26] We observed an overall 5-year survival rate for patients with ARPKD of 95.5% posttransplantation (97.4% after kidney transplantation compared to 87.0% after combined liver-kidney transplantation). Consequently, type of transplantation appeared to be an important determinant of mortality in our cohort and patients undergoing combined liver-kidney transplantation had a 6.7-fold increased risk for death compared with those receiving a kidney transplant. Notably, the majority of

Table 2. Laboratory and Clinical Features of Liver Disease in 23 ARPKD Patients Undergoing Combined Liver-Kidney Transplantation

Feature	Value
Bilirubin, mg/dL	0.58 [0.41 to 0.95]
INR	1.19 [1.03 to 1.23]
Albumin, g/dL	4.01 [3.60 to 4.50]
Serum creatinine, mg/dL	4.07 [2.50 to 5.57]
PELD/MELD score	−1 [−6 to 15]
Portal hypertension	16 (70)
Esophageal varices	15 (65)
Variceal bleeding	4 (17)
Transjugular portosystemic shunt	1 (4)
Intractable pruritus	2 (9)
Ascites	4 (17)
Recurrent cholangitis	3 (13)
≥1 above-mentioned symptom	19 (83)

Note: Values for categorical variables are given as count (percentage); values for continuous variables, as median [interquartile range]. Conversion factors for units: bilirubin in mg/dL to μmol/L, ×17.1; creatinine in mg/dL to μmol/L, ×88.4.

Abbreviations: ARPKD, autosomal recessive polycystic kidney disease; INR, international normalized ratio for prothrombin time; MELD, Model for End-Stage Liver Disease; PELD, Pediatric End-Stage Liver Disease.

patients with combined liver-kidney transplantation had no history of life-threatening liver involvement, highlighting the lack of defined selection criteria for the choice of transplantation type.

The most striking finding in our study was the relatively high mortality in patients with combined liver-kidney transplants who had undergone transplantation despite the absence of severe and recurrent cholangitis, intractable pruritis, or severe variceal bleeding in the majority of cases. Although a randomized prospective study controlling for degree of portal hypertension and cholangitis would be required to confirm the adverse mortality outcomes in combined liver-kidney transplantation, the rarity of ARPKD hampers the conduct of a sufficiently powered study. Furthermore, combined liver-kidney transplantation has been suggested for select patients with ARPKD with ESRD even if they may not meet the criteria qualifying for liver transplantation in isolated liver disease.[6,27] It is known that nearly all patients with ARPKD have preserved synthetic liver function and may require adapted criteria for liver transplantation.[28-30] The PELD/MELD scoring system does not adequately reflect the relevant clinical consequences in the ARPKD population. Some have therefore suggested that a more adjusted score for liver transplantation indication be used instead of MELD or PELD, based on the presence of liver symptoms such as therapy-resistant portal hypertension, recurrent and therapy-resistant ascending cholangitis, or unbearable pruritus with severe cholestasis and indication for portosystemic shunt.[6] However, even following this paradigm, only a subgroup of patients with ARPKD would be eligible for liver transplantation.[6] Unexpectedly, we did not find advanced liver disease to an extent that would have encouraged immediate liver transplantation in the ARPKD combined liver-kidney transplantation group of our cohort. As expected, none of the patients with combined liver-kidney transplantation had signs of relevant synthetic dysfunction. So even using the adjusted paradigm as suggested,[6] only 26% met criteria for combined liver-kidney transplantation, 1 patient had transjugular intrahepatic portosystemic stent shunting, 2 had intractable pruritis, and 3 had recurrent cholangitis. Our data therefore did not demonstrate a causal association between the liver condition before transplantation and the relatively high mortality in this group.

Because combined liver-kidney transplantation is a rare surgical intervention in children, with no more than 10 to 30 operations performed annually worldwide,[1] the pediatric experience regarding optimal pre-, peri-, and postoperative management is still limited.[31] In our cohort, the combined liver-kidney transplantation patients usually underwent transplantation at a younger age than those who only underwent kidney transplantation. Furthermore, most deaths in combined liver-kidney transplant recipients occurred in the very early posttransplantation period, whereas mortality in deceased donor kidney transplant recipients peaked around 1 year following transplantation. We can speculate that this early mortality in combined liver-kidney transplant recipients in our cohort might be related to the high technical challenge in young patients, which is also reported in the UNOS report among patients younger than 18 years old revealing that 20.1% of 111 cases of pediatric combined liver-kidney transplantation for a variety of underlying causes lost their kidney transplant within the first 6 posttransplantation months compared with 5.9% of patients with isolated kidney transplantation.[32] However, it is very difficult to draw firm conclusions with our observational study in a small number of patients and no adequate control groups. Furthermore, the combined liver-kidney transplantations in our cohort were performed in 7 different countries. Unfortunately, because of the small numbers, we were unable to demonstrate a possible center effect; nonetheless, this cannot be ruled out.

A major argument commonly raised in favor of combined over sequential kidney transplantation and liver transplantation is that simultaneous combined liver-kidney transplants from the same donor may provide better long-term kidney function and allow less intense immunosuppressive protocols.[1,13,14] The death-censored 5-year kidney transplant survival (>6 months) of the UNOS database was better in

combined liver-kidney transplantation compared with isolated kidney transplantation (88% vs 72%), suggesting a long-term protective effect of combined transplantation attributed to the immunomodulatory or tolerogenic properties of the liver.[15,32] However, this was not confirmed by our study.

A further rationale for performing combined liver-kidney transplantation in ARPKD has been the potential higher risk for liver disease−associated infections after kidney transplantation. Infection is a well-known and important cause of morbidity and mortality in patients with ARPKD. In the North American Pediatric Renal Transplantation Cooperative Study (NAPRTCS), sepsis was the cause of death in 64% of patients with ARPKD undergoing kidney transplantation compared to 32% in kidney transplant recipients with other primary kidney diseases. The authors speculated that the difference was attributable to hepatobiliary disease/cholangitis in those with ARPKD.[11] Nevertheless, although ours was a small study, infection as a cause for mortality after transplantation was not the major cause in our cohort. Notably, deaths from infection were similarly frequent after kidney transplantation and combined liver-kidney transplantation.

This study has some limitations. First, because the ESPN/ERA-EDTA Registry is focused on kidney disease outcomes, liver data for patients with ARPKD are missing. We succeeded in collecting the pretransplantation liver information for the combined liver-kidney transplantation patients; nonetheless, it was not possible to obtain this for the large number of patients with kidney transplantation. Although we cannot rule out the existence of selection bias in offering combined liver-kidney transplantation to sicker patients, it would be plausible to assume that kidney transplantation patients have a milder hepatic phenotype than those who were selected for combined liver-kidney transplantation, which was the reason for choosing the kidney transplantation strategy. Second, we do not have information for whether patients had an isolated liver transplantation as a first transplantation strategy. The recently established comprehensive international ARPKD registry will help in understanding the complete phenotype of patients with ARPKD.[33]

The increased mortality risk that we found for combined liver-kidney transplantation in patients with ARPKD and the absence of clinical benefits of the combined approach over kidney transplantation supply arguments to select only patients with ARPKD with symptomatic liver involvement, such as therapy-resistant portal hypertension, recurrent and therapy-resistant ascending cholangitis, or unbearable pruritus with severe cholestasis, for combined liver-kidney transplantation. An individualized approach and multidisciplinary discussion should be considered.

In conclusion, in this large observational study of transplantation outcomes in young patients with ARPKD, we found combined liver-kidney transplantation to be a significant risk factor for early mortality and not associated with improved 5-year kidney transplant survival. Systematic long-term monitoring of the natural history of both kidney disease and hepatic outcomes, as well as the success rates with different transplantation strategies, will be required to better delineate the optimal management in this complex patient population and establish an evidence base for individualized treatment decisions in patients with this rare disorder. The development and validation of an adapted assessment score is needed in this unique population.

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Contributions: Research idea and study design: DM, FS, JWG; data analysis/interpretation: DM, MB, KJJ, FS, JWG; statistical analysis: KJvS, MB, KJJ; supervision or mentorship: FS, JWG; data acquisition: all authors. All authors contributed important intellectual content during manuscript drafting or revision and accept accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. DM, FS, JWG take responsibility that this study has been reported honestly,

accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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SUPPLEMENTARY MATERIAL

Figure S1: Age at RRT initiation in ARPKD patients.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2016.06.019) is available at www.ajkd.org

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