Risk Factors for Early Dialysis Dependency in Autosomal Recessive Polycystic Kidney Disease

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Objective To identify prenatal, perinatal, and postnatal risk factors for dialysis within the first year of life in children with autosomal recessive polycystic kidney disease (ARPKD) as a basis for parental counseling after prenatal and perinatal diagnosis.

Study design A dataset comprising 385 patients from the ARegPKD international registry study was analyzed for potential risk markers for dialysis during the first year of life.

Results Thirty-six out of 385 children (9.4%) commenced dialysis in the first year of life. According to multivariable Cox regression analysis, the presence of oligohydramnios or anhydramnios, prenatal kidney enlargement, a low Apgar score, and the need for postnatal breathing support were independently associated with an increased hazard ratio for requiring dialysis within the first year of life. The increased risk associated with Apgar score and perinatal assisted breathing was time-dependent and vanished after 5 and 8 months of life, respectively. The predicted probabilities for early dialysis varied from 1.5% (95% CI, 0.5%-4.1%) for patients with ARPKD with no prenatal sonographic abnormalities to 32.3% (95% CI, 22.2%-44.5%) in cases of documented oligohydramnios or anhydramnios, renal cysts, and enlarged kidneys.

Conclusions This study, which identified risk factors associated with onset of dialysis in ARPKD in the first year of life, may be helpful in prenatal parental counseling in cases of suspected ARPKD. *(J Pediatr 2018;199:22-8).*

Autosomal recessive polycystic kidney disease (ARPKD) is a rare but severe early-onset ciliopathy mainly caused by mutations in the *PKHD1* gene.[1-3] Mutations in *DZIPL1* also have been described in 4 unrelated families.[4] The disease results in loss of renal function in ~50% of patients within the first 2 decades of life.[5] Despite the low incidence (1:20 000 live births), ARPKD is a major cause of end-stage renal disease necessitating renal replacement therapy in early childhood.

ARPKD has a broad phenotypic spectrum, both across and within affected families. Whereas some patients show a minimal kidney phenotype but pronounced hepatic pathology, others have intrauterine oligohydramnios, subsequent pulmonary hypoplasia, and early renal failure.[6] Both prenatal parental counseling and immediate postnatal decision making are challenged by the scarcity of reported

AIC	Akaike information criterion
ARPKD	Autosomal recessive polycystic kidney disease
AUC	Area under the curve
CVVH	Continuous venovenous hemofiltration
PD	Peritoneal dialysis

Detailed affiliations available at www.jpeds.com (**Appendix 1**).

*Lists of additional members of the ESCAPE Study Group and GPN Study Group for the ARegPKD consortium are available at www.jpeds.com (**Appendix 2**).

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natural history information, including a lack of appropriately powered risk assessments regarding early postnatal end-stage renal disease and patient survival.

The predictive value of prenatal ultrasound findings appears to be limited. Although renal enlargement and oligohydramnios are generally considered risk factors for neonatal renal failure and respiratory insufficiency, preserved kidney function is not uncommon, even in children with massive prenatal sonographic pathology. Prenatal genetic diagnostics is of limited predictive usefulness in ARPKD, because genotype–phenotype correlations in *PKHD1* disease are rather loose. The prevailing concept of biallelic truncating mutations associated with perinatal or neonatal mortality[5,7] has recently been challenged by case reports of patients surviving the neonatal period with both homozygous[8] and compound heterozygous truncating *PKHD1* mutations.[9] Furthermore, prenatal genetic diagnostics requires invasive sample collection, which carries a significant risk of complications.[10] Molecular analysis of *PKHD1* is time-consuming and complex, which may delay parental counseling.

To address the need for natural history data in ARPKD, we established the longitudinal ARegPKD registry study, which is currently following >400 patients.[11,12] Here we use the comprehensive prenatal, perinatal, and postnatal information captured in ARegPKD to identify risk factors associated with the need for renal replacement therapy in the first year of life in children with ARPKD.

Methods

Children and adults with a clinical diagnosis of ARPKD were enrolled in the international ARegPKD registry study according to clinical diagnostic criteria for ARPKD described previously.[11-13] Exclusion criteria encompass genetic, histological, or clinical proof of other cystic kidney disorders. The study protocol was approved by the Ethics Committee of the Faculty of Medicine of Cologne University and the Institutional Review Boards of the participating sites. Subject pseudonymization is performed at the local center after written informed consent. Pseudonymized data are entered into a password-restricted, web-based database (www.aregpkd.org) by authorized medical personnel.

Both prospective and, as available, retrospective data are collected. Although visits are scheduled to be entered annually, documentation at flexible time intervals is possible. Basic data encompass age and clinical symptoms at primary manifestation as well as the perinatal period, genetic testing and family history. Prenatal and perinatal data capture includes fetal ultrasound findings ("oligohydramnios or anhydramnios", "increased renal echogenicity", enlarged kidneys indicated as "renal hyperplasia" [without quantification], "renal cysts", "other renal abnormalities", "hepatic abnormalities", "other prenatal abnormalities"), prenatal interventions (eg amnioinfusions), gestational age at birth, birth weight and length, Apgar scores, mode of delivery, admission to neonatal intensive care unit, induction of lung maturation, poor postnatal adaptation, ventilation or assisted breathing, pulmonary hypertension, Potter facies, and other abnormalities or clinical problems. All reported *PKHD1* variants were classified with regards to pathogenicity according to the revised criteria of the American College of Medical Genetics[14] and were further categorized by their putative impact on protein translation (missense vs truncating). The documentation of clinical visits encompasses a set of clinical, imaging and laboratory variables, as described previously.[11,12]

Automated checks for coherence, plausibility, and validity of the submitted information are performed according to a detailed data validation plan. Erroneous entries are recognized by application of predefined plausibility ranges for measurements, laboratory values, and medication doses. Queries are sent at regular intervals to local investigators to complete data records and solve plausibility problems or discrepancies.

Statistical Analyses

Analyses were conducted using R version 3.4.1. Percentiles and standard deviation scores of birth weight and birth height were calculated by reference to a healthy neonatal population.[15] Due to the partially retrospective data collection, data completeness varied by item. The total numbers of informative cases by item are shown in **Table I**. Data analysis was performed on the dataset available in May 2017.

Association with early onset of dialysis (within the first 12 months of life) were assessed using the χ^2 test for nominal and the Mann-Whitney *U* test for continuous variables. No formal adjustment for multiplicity was applied due to the exploratory nature of the analysis and no imputation was performed. A P value <.05 was considered significant in distinguishing between the groups.

To identify independent risk factors for dialysis during the first year of life, a multivariate Cox model was fitted. Missing values were handled via multiple imputation using chained equations (MICE algorithm).[16] In total, 20.6% of all values were imputed (see the number of informative cases in **Table I**). Partial mean matching[17] was used for continuous variables, and logistic regression modeling was used for binary outcomes. Statistical quantities (estimates, standard errors, P values) of the models were obtained from the imputed data set by aggregation via Rubin's rule.[18]

Many of the variables considered as potential risk factors are strongly correlated. To resolve issues with multicollinearity, only the single most important representative of each cluster was included in the Cox model. Here importance was assessed by comparison of the Akaike information criterion (AIC) of the respective models. Also based on assessment with the AIC, it was decided to use only the 10-minute Apgar score in the model and discard the measurements at 1 and 5 minutes. Model fit was assessed graphically via deviance residuals and revealed potential time dependencies of the coefficients for gestational age at birth, Apgar score, and assisted breathing or ventilation. This lack of fit was resolved by including simple interaction terms with time for each of these variables. Therefore, the estimated effect on the hazard ratio at any particular time t is given by the hazard ratio at time 0 (birth) multiplied

Table I. Patient characteristics and univariate analysis of prenatal, perinatal, and postnatal predictors of dialysis dependency within the first year of life

Characteristics	All cases (n = 385)	No dialysis in first year of life (n = 349)	Dialysis in first year of life (n = 36)	*P* Value
Prenatal information				
Oligohydramnios or anhydramnios, n/N (%)	107/318 (33.6)	77/284 (27.1)	30/34 (88.2)	<.001
Gestational age at diagnosis, wk (n = 96), mean (SD)	29.9 (5.1)	30.2 (5.3)	29.1 (4.6)	.20
Increased echogenicity, n/N (%)	78/291 (26.8)	60/267 (22.5)	18/24 (75.0)	<.001
Gestational age at diagnosis, wk (n = 72), mean (SD)	28.9 (5.0)	28.6 (5.3)	29.7 (4.1)	.55
Enlarged kidneys, n/N (%)	70/301 (23.3)	47/272 (17.3)	23/29 (79.3)	<.001
Renal cysts, n/N (%)	82/312 (26.3)	59/282 (20.9)	23/30 (76.7)	<.001
Amnioninfusion performed, n/N (%)	8/322 (2.5)	4/288 (1.4)	4/34 (11.8)	<.001
Perinatal information				
Vaginal delivery, n/N (%)	182/315 (57.8)	164/279 (58.8)	18/36 (50.0)	.007
Gestational age at birth, wk (n = 285), mean (SD)	37.5 (2.7)	37.7 (2.7)	36.1 (2.4)	<.001
Birth weight (n = 277), kg, mean (SD)	3.058 (0.657)	3.065 (0.644)	3.001 (0.757)	.92
(n = 250), SDS, mean (SD)	−0.1 (1.4)	−0.1 (1.5)	0.4 (1.3)	.003
Birth length (n = 203), cm, mean (SD)	49.9 (4.4)	50.0 (4.4)	48.8 (4.0)	.15
(n = 190), SDS, mean (SD)	−0.1 (1.3)	−0.1 (1.4)	−0.1 (1.1)	.87
Apgar 1 min (n = 176), mean (SD)	7.5 (2.4)	7.9 (2.1)	5.0 (2.5)	<.001
Apgar 5 min (n = 172), mean (SD)	8.4 (1.9)	8.7 (1.5)	6.3 (2.4)	<.001
Apgar 10 min (n = 157), mean (SD)	8.9 (1.4)	9.1 (1.3)	7.7 (1.6)	<.001
Admission to NICU, n/N (%)	83/336 (24.7)	60/300 (20.0)	23/36 (63.9)	<.001
Days on NICU (n = 73), mean (SD)	39 (68)	27 (32)	69 (113)	.003
Assisted breathing/ventilation, n/N (%)	78/333 (23.4)	54/297 (18.2)	24/36 (66.7)	<.001
Pharmacologic pulmonary maturation, n/N (%)	18/325 (5.5)	11/290 (3.8)	7/35 (20.0)	<.001
Postnatal information				
Poor adaptation, n/N (%)	75/338 (22.2)	54/302 (17.9)	21/36 (58.3)	<.001
Pulmonary hypertension, n/N (%)	23/323 (7.1)	13/291 (4.5)	10/32 (31.3)	<.001
Potter facies, n/N (%)	13/329 (4.0)	6/297 (2.0)	7/32 (21.9)	<.001
Genetic information				
Documentation of *PKHD1* testing, n/N (%)	169/385 (43.9)	150/349 (43.0)	19/36 (52.8)	
Truncating/truncating	10/169 (5.9)	6/150 (4.0)	4/19 (21.1)	
Truncating/missense	38/169 (22.5)	34/150 (22.7)	4/19 (21.1)	
Missense/missense	68/169 (40.2)	65/150 (43.3)	3/19 (15.8)	
One single mutation	16/169 (9.5)	13/150 (8.7)	3/19 (15.8)	
No mutation detection in case of *PKHD1* testing (n = 22) or insufficient data (n = 15)	37/169 (21.9)	32/150 (21.3)	5/19 (26.3)	
No documentation of *PKHD1* testing, n/N (%)	216/385 (56.1)	199/349 (57.0)	17/36 (47.2)	

NICU, neonatal intensive care unit.

by the time interaction effect (denoted by "* time" in Table II) to the power of *t*.

A logistic regression model was adopted for predictive modeling using the same imputed dataset as for the multivariate Cox model. The final model included the prenatal sonographic abnormalities oligohydramnios/anhydramnios, enlarged kidney size, and renal cysts and led to 8 prenatal sonographic phenotype groups—no abnormalities, enlarged kidneys, renal cysts, enlarged kidneys and renal cysts, oligohydramnios/anhydramnios only, oligohydramnios/anhydramnios and enlarged kidneys, oligohydramnios/anhydramnios and renal cysts, oligohydramnios/anhydramnios and enlarged kidneys and renal cysts—for which individual model-based risk predictions with confidence intervals were obtained. For the predictive modeling covering 36 months after birth, 25 patients were censored before the 36-month follow-up and thus were excluded from this specific modeling (n = 360).

Table II. Multivariate Cox model of prenatal, perinatal, and postnatal predictors of the need for renal replacement therapy within the first year of life

Variables	HR	95% CI	*P* value
Sex	0.925	0.462-1.850	.825
Oligohydramnios/anhydramnios	4.473	1.295-15.449	.018
Prenatal enlarged kidneys	3.177	1.087-9.282	.035
Vaginal delivery	1.271	0.584-2.765	.545
Gestational age at birth, wk	1.121	0.917-1.371	.265
Gestational age at birth * time	0.666	0.426-1.040	.074
Birth weight SDS	1.291	1.031-1.618	.026
Birth weight SDS * time	0.451	0.158-1.288	.137
Apgar 10 min	0.748	0.564-0.991	.043
Apgar 10 min * time	1.548	0.485-4.945	.460
Assisted breathing and/or ventilation	6.994	1.536-31.845	.012
Assisted breathing and/or ventilation * time	0.008	0.000-0.320	.010

Time interaction terms are denoted with "* time".

Results

Patient characteristics

Between July 2013 and May 2017, 420 patients treated at 58 centers in 18 mainly European countries (121 from Germany, 95 from Turkey, 67 from Poland, 27 from the United Kingdom, and 110 from other countries) were included in the ARegPKD registry study. Twelve patients were excluded due to failure to comply with the inclusion/exclusion criteria, and 23

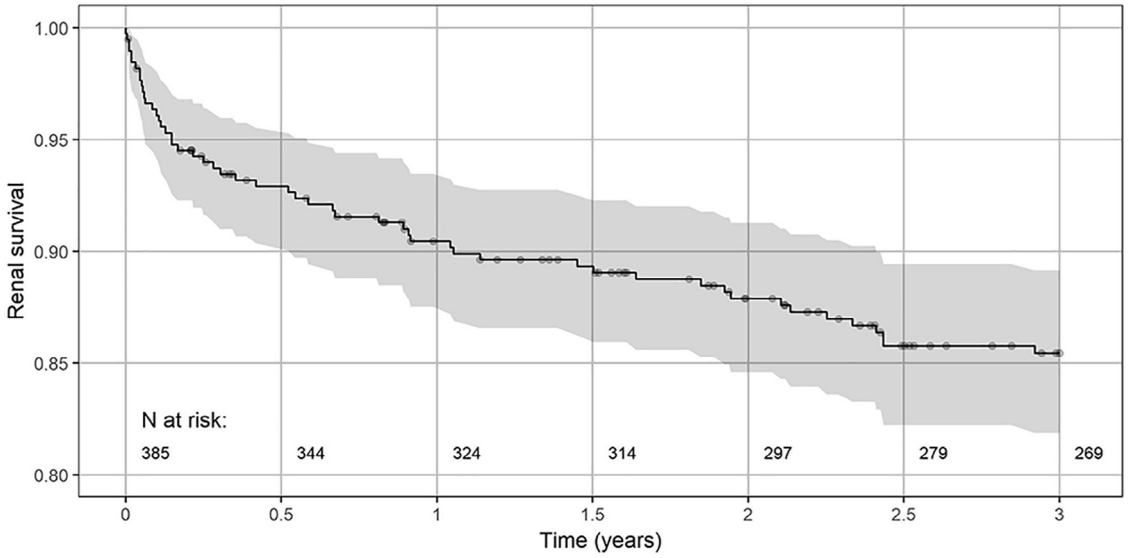

Figure 2. Renal survival within the first 3 years of life (Kaplan-Meier estimate and pointwise 95% CI).

patients were excluded due to a lack of postnatal follow-up. Three of these latter patients died within the first day of life due to respiratory failure in accordance with palliative management and 1 patient died 15 days after birth due to respiratory failure, following a complicated course without an attempt to start renal replacement therapy. Thus, the final analysis set comprised 385 patients (52.9% males) (**Figure 1**; available at www.jpeds.com).

Sufficient results of *PKHD1* testing were available for 154 of the 385 patients (40.0%). Relevant sequence changes were detected in 132 of these 154 patients (85.7%). *PKHD1* genotype information was lacking in 216 of the 385 patients (56.1%) and was insufficiently documented in 15 patients (3.9%). The endpoint of dialysis initiation in the first year of life was reached by 36 individuals (9.4%). No patient received a kidney transplant, and no other patients died before the onset of dialysis in the observation period. *PKHD1* genotype information was available for 19 of these 36 patients (52.8%). Four patients carried 2 (most likely biallelic) truncating mutations. Detailed information on prenatal, perinatal, and postnatal patient characteristics is provided in **Table I**. Dialysis was initiated at a median age of 7 weeks (range, 0-48 weeks), with the overall risk the greatest within the first 3 months of life (**Figure 2**). Thirty infants were started on peritoneal dialysis (PD) at a median age of 6 weeks (range, 0-47 weeks), 4 were started on hemodialysis (HD) at a median age of 8 weeks (range, 2-35 weeks), and 2 were started on continuous venovenous hemofiltration (CVVH) at 2 and 42 weeks of age (**Figure 3**; available at www.jpeds.com).

During the course of the initial dialysis treatment, 3 patients were switched from HD to PD, 2 patients were switched from PD to HD, and 1 patient was switched from PD to CVVH (**Figure 3**). Notably, 2 patients permanently discontinued dialysis due to persistent improvement of kidney function after 6 weeks and 6 months of dialysis respectively. Nine patients with initiation of dialysis in the first year of life later continued their first PD treatment until they received a kidney transplant at a median age of 2.1 (1.4-4.3) years. The first PD course is ongoing in 10 patients with a mean observational time of 1.5 years (0.2-11.1 years). Four of the patients on dialysis died (3 on PD, 1 on CVVH) at ages 4, 9, 24, and 27 weeks. One patient died after withdrawal of active treatment in accordance with the parent's wish. Two patients died due to persistent respiratory failure and 1 patient died due to sepsis.

Risk Factors for Early Dialysis Requirement

Pre-, peri- and postnatal factors. The requirement of early dialysis was associated with several prenatal, perinatal, and postnatal factors (**Table I**). These included the presence of oligohydramnios/anhydramnios and increased renal echogenicity on prenatal ultrasound, irrespective of the gestational age at diagnosis. Children who required dialysis had received amnioinfusions more frequently, although this measure was performed only in a very small fraction of patients in either group. Prenatal sonographic kidney enlargement and the presence of renal cysts were also associated with an increased likelihood of postnatal need for dialysis. Children who subsequently required dialysis within the first year of life were born at earlier gestational age with a higher corrected birth weight, were more likely to be delivered via cesarean section, and exhibited poorer postnatal adaptation with lower Apgar scores, more frequent admission to the neonatal intensive care unit and need for assisted breathing or mechanical ventilation, and an increased likelihood of pulmonary hypertension. Importantly, the vast majority of children did not require early dialysis.

Multivariate Risk Factor Analysis. According to multivariate Cox regression analysis, the presence of oligohydramnios/anhydramnios, enlarged kidneys, high birth weight, low 10-minute Apgar score, and the need for assisted breathing or

ventilation were independently associated with an increased risk of requiring dialysis within the first year of life (**Table II**). The description of genetic subgroups for identified risk factors is presented in **Table III** (available at www.jpeds.com). Kaplan-Meier renal survival analysis suggested that patients diagnosed clinically without genetic proof of ARPKD showed a comparable renal phenotype to those with genetically confirmed disease, with the potential exception of patients carrying biallelic truncating mutations. The biallelic state of the detected truncating mutations was confirmed by segregation analyses of all cases for which parental samples were available (n = 5). Patients with biallelic truncating mutations appear to be at special risk of severe courses, but the numbers in our study were small (**Figure 4**; available at www.jpeds.com). Time interaction terms were added to the model for covariates when the assumption of a time-invariant association with dialysis risk was considered problematic (ie, gestational age at birth, Apgar score, and postnatal assisted breathing/ventilation). Solving for the time *t* for which the time-dependent hazard ratio is 1 produces an estimate for the break-even point at which the covariate no longer modifies relative risk. If the interaction effect on the hazard ratio scale as given in **Table II** is <1, then the hazard ratio decreases over time, and if the interaction effect is >1, then the hazard ratio increases over time. Indeed, the increased dialysis risk associated with assisted breathing/ventilation persists only for the first 5 months after birth (**Table II**). The adverse effect of a low Apgar score does not persist beyond the first 8 months of life. The time dependency of these effects is consistent with the early drop in the overall renal survival curve (**Figure 2**).

Prenatal Prediction of Postnatal Dialysis Requirement

To further explore the usefulness of the identified prenatal risk factors for parental counseling, we compared the likelihood of dialysis requirement in different groups. Multiple statistical models of prediction were evaluated. The analysis of combinations of oligohydramnios/anhydramnios with isolated additional renal sonographic abnormalities yielded no lead risk feature (data not shown). The prenatal detection of increased renal echogenicity, kidney enlargement, and renal cysts were highly correlated. In the full model incorporating all available prenatal factors (ie, oligohydramnios/anhydramnios, increased renal echogenicity, enlarged kidneys, and renal cysts (AIC, 188.9; area under the curve [AUC], 84%)) hyperechogenicity did not contribute independently to the model-based predictions and thus was excluded. Fitting the reduced model incorporating oligohydramnios/anhydramnios, enlarged kidneys, and renal cysts resulted in a slightly better AIC (188.2) and only marginally worse AUC (83.7%). The receiver operator characteristics of these predictive models covering 12 and 36 months of life are depicted in **Figure 5** (available at www.jpeds.com). The final 3-parameter model achieved a similar receiver operating characteristic curve as the full model and substantially better prediction than a model accounting for oligohydramnios/anhydramnios only. Further reduction of the model complexity (enlarged kidneys only, renal cysts only, neither of both) resulted in substantially inferior model performance according to both AUC and AIC; therefore, we selected the model based on oligohydramnios/anhydramnios, enlarged kidneys, and renal cysts as a basis for predicting the probability of requiring dialysis within the first 12 months and the first 36 months after birth (**Table IV**). The estimated probabilities for early dialysis requirement (within 12 months) ranged from 1.5% (95% CI, 0.5%-4.1%) if no prenatal symptoms are present to 32.3% (95% CI, 22.2%-44.5%) if all 3 factors are detected. Adjusted odds ratio (aORs) for the 12-month model coefficients are 2.22 for kidney enlargement (95% CI, 0.53-9.19; $P = .276$), 2.27 for renal cysts (95% CI, 0.60-8.60, $P = .229$), and 6.21 for oligohydramnios/anhydramnios (95% CI, 1.77-21.81; $P = .005$). The estimated probabilities for requirement of renal replacement therapy within an extended time frame (36 months) are slightly higher, ranging from 1.7% (95% CI, 0.6%-4.7%) in the absence of prenatal symptoms to 34.8% (95% CI, 23.9%-47.5%) if all 3 factors were detected. In the extended observation period, 4 patients underwent preemptive kidney transplantation, including one patient who underwent combined liver and kidney transplantation. No other patients died before the onset of dialysis and kidney transplantation. aORs for the 36-month model coefficients were 2.04 for kidney enlargement (95% CI, 0.47-8.86; $P = .344$), 2.28 for renal cysts (95% CI, 0.59-8.87, $P = .237$),

Table IV. Model-based predicted probabilities for dialysis or renal replacement therapy within 12 and 36 months after birth

Prenatal symptoms	No. of dialysis cases within 12 mo after birth/ no. of observations	Probability of dialysis within 12 mo after birth (95% CI)	No. of cases with RRT within 36 mo after birth/ no. of observations	Probability of RRT within 36 mo after birth (95% CI)
No prenatal abnormalities	1.2/186.5	0.015 (0.005-0.041)	1.2/166.9	0.017 (0.006-0.047)
Enlarged kidneys	1.1/7.1	0.033 (0.006-0.155)	1.1/6.0	0.035 (0.006-0.170)
Renal cysts	0.2/18.6	0.034 (0.008-0.135)	0.2/16.5	0.039 (0.009-0.154)
Enlarged kidneys and renal cysts	2.6/17.2	0.071 (0.021-0.215)	2.6/15.2	0.076 (0.022-0.233)
OAH	4.2/32.6	0.087 (0.032-0.214)	4.2/26.6	0.103 (0.037-0.254)
OAH and enlarged kidneys	2.2/15.4	0.174 (0.055-0.431)	2.2/14.3	0.189 (0.059-0.463)
OAH and renal cysts	2.3/8.2	0.178 (0.047-0.486)	2.3/7.0	0.207 (0.054-0.546)
OAH and enlarged kidneys and renal cysts	22.3/74.4	0.323 (0.222-0.445)	22.3/69.5	0.348 (0.239-0.475)

OAH, oligohydramnios/anhydramnios; *RRT*, renal replacement therapy.
Observation numbers are not integers due to averaging of the imputed dataset.

and 6.50 for oligohydramnios/anhydramnios (95% CI, 1.78-23.68; $P = .005$).

Discussion

Prenatal suspicion of ARPKD imposes a major burden on affected parents and caregivers with respect to decision making regarding the continuation of pregnancy and postnatal management. Prenatal counseling is hampered by the poor predictability of the postnatal phenotype. An important aspect of parent counseling is the suspected need for renal replacement therapy in early infancy. The comprehensive data collection in the ARegPKD registry allowed us to identify important prenatal and perinatal risk factors associated with an adverse course of renal function and early need for dialysis.

Patient follow-up was excellent, and very few patients died in the perinatal or postnatal period, allowing a largely unbiased analysis of renal survival. Notably, the vast majority of patients included in the registry cohort did not require dialysis in the first year of life, including many in whom a severe renal phenotype was diagnosed on prenatal ultrasound. Dialysis, usually performed as PD, was efficient and tolerated well by most children. Only 4 children died while receiving dialysis, all from dialysis-unrelated causes. Thus, overall ARPKD was treatable with a good outcome in our cohort, even among severely affected children. Widely available PD may serve as a bridging therapy in nontertiary centers during initial stabilization before patients can be transferred to a tertiary center.

Although in clinical practice oligohydramnios/anhydramnios is assumed to indicate impaired renal function in utero, its relevance for predicting the postnatal renal phenotype in patients with ARPKD has not been established. The aim of the present study was to provide an evidence base for counseling affected families based on readily available prenatal, perinatal, and postnatal clinical risk markers. Here we show that although oligohydramnios/anhydramnios has some predictive value for the need for dialysis in infants with ARPKD, almost three-quarters of the children with reported reduced or absent amniotic fluid in our cohort did not require dialysis during the first year of life. In the multivariate model, kidney enlargement on prenatal ultrasound, a low Apgar score, and the need for assisted breathing or ventilation were identified as significant predictors of dialysis, independent of oligohydramnios/anhydramnios.

Although total kidney volume has been established as a surrogate measure for disease progression in autosomal dominant polycystic kidney disease, the role of renal enlargement in ARPKD is less clear. A recent study suggested a loose inverse correlation between total kidney volume and renal function in childhood that would be compatible with our present findings.[19] Yet, it also has been reported that ARPKD kidneys become smaller relative to body size during the course of the disease.[20] Neonatal ventilation has previously been identified as a strong predictor of mortality and earlier chronic renal insufficiency in ARPKD[6] and was found to be an independent risk predictor of dialysis in the first year of life in the present study. In line with a low Apgar score as another independent predictor, these findings suggest that neonatal respiratory insufficiency may negatively affect kidney function, for example, as an early second hit.

The observed time dependency of the hazard ratios of perinatal assisted breathing or ventilation as well as of Apgar score at 10 minutes implies that these negative long-term effects persist only within the first 5 or 8 months of life, respectively, matching the early drop in the overall renal survival curve with a sharp decline within the first 3 months after birth followed by a slow descent over the first years of life. This may either reflect the effects of secondary acute kidney injury within the first months of life or point to positive effects of renal maturation in ARPKD. The data suggest that even children requiring intensive support postnatally may avoid dialysis if they have been managed successfully during the first months of life.

In the multivariate analysis, neither gestational age at birth nor prematurity was found to be significantly associated with the need for dialysis within the first year of life. This finding may reflect general advances in the management of preterm infants and the fact that preterm or small-for-gestational-age children may be more likely to be delivered in centers with high-grade neonatology support. There was no independent association between the type of delivery and dialysis. Thus, from a renal standpoint, there is no indication for cesarean section in prenatally diagnosed ARPKD. We observed a significant association of birth weight SDS with onset of dialysis within the first year of life. This finding might be explained by the higher body weight attributable to very large kidneys in children with severe forms of ARPKD.

We developed a simple model to estimate the risk of early postnatal dialysis from prenatal sonographic indicators. The detection of kidney enlargement or renal cysts was each associated with a 3%-3.5% risk of needing dialysis if found in isolation, and the presence of both increased the risk to 7%. Oligohydramnios/anhydramnios was associated with a risk of dialysis approaching 9%, increasing to 32% in the presence of enlarged kidneys and renal cysts. These figures may be useful when counseling affected families; however, it is important to interpret our risk estimates in the proper context, understanding that these findings are derived from a cohort of patients in whom ARPKD was verified postnatally.

Major strengths of this study are the multinational approach covering a large cohort of well-phenotyped patients with ARPKD and the broad applicability of the identified clinical risk markers. Like all registry studies, ARegPKD has some limitations. We would expect some selection bias, because both severely affected infants with palliative treatment and severely affected deceased patients with and without dialysis might be underreported. Furthermore, the fraction of fetuses in which pregnancy was terminated due to oligohydramnios/anhydramnios and/or other sonographic findings was not reported by the investigators, and our data do not discriminate between oligohydramnios and anhydramnios. In addition, the ARegPKD consortium comprises mainly tertiary care centers, and patients with a milder phenotype not requiring renal replacement therapy might be preferentially treated at smaller centers not participating in our registry. Moreover, regional

differences in clinical practices may have affected the results in this multinational study. In addition, detailed perinatal information (eg, concerning the use of nephrotoxic medications) was unavailable. Finally, genetic confirmation of the clinical diagnosis was performed in less than one-half of the study population, precluding the use of genotype information for detailed genotype–phenotype correlation analysis and multivariate risk factor assessment. Of note, however, out of 10 patients with biallelic truncating *PKHD1* mutations, 4 patients required early dialysis. One of these patients was reported previously.[9] These data support the idea that even biallelic truncating *PKHD1* mutations might not preclude sufficient postnatal renal function even though they may be more frequently associated with a severe phenotype.[8,9]

The potential limitations are compensated for in part by the large number of patients with ARPKD with longitudinal clinical data available in the registry. Thus, our study provides important information on the likelihood of the need for dialysis in infants with ARPKD, which may be helpful for prenatal counseling regarding this serious disease presenting with a high phenotypic heterogeneity. ■

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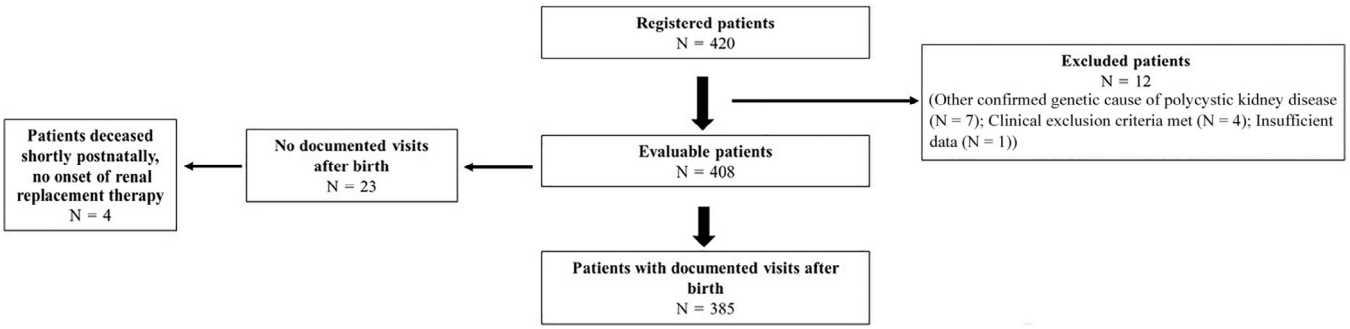

Figure 1. Flow chart of the patient selection process.

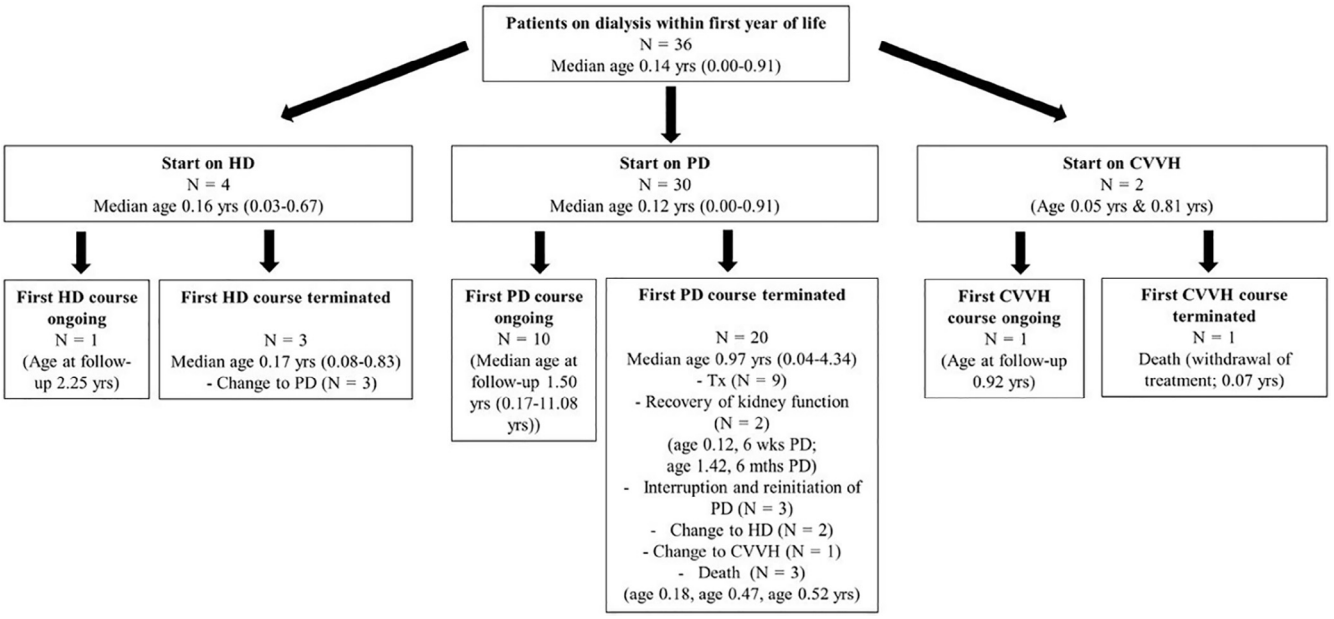

Figure 3. Dialysis modality and major characteristics in patients starting dialysis within the first year of life. *HD*, hemodialysis.

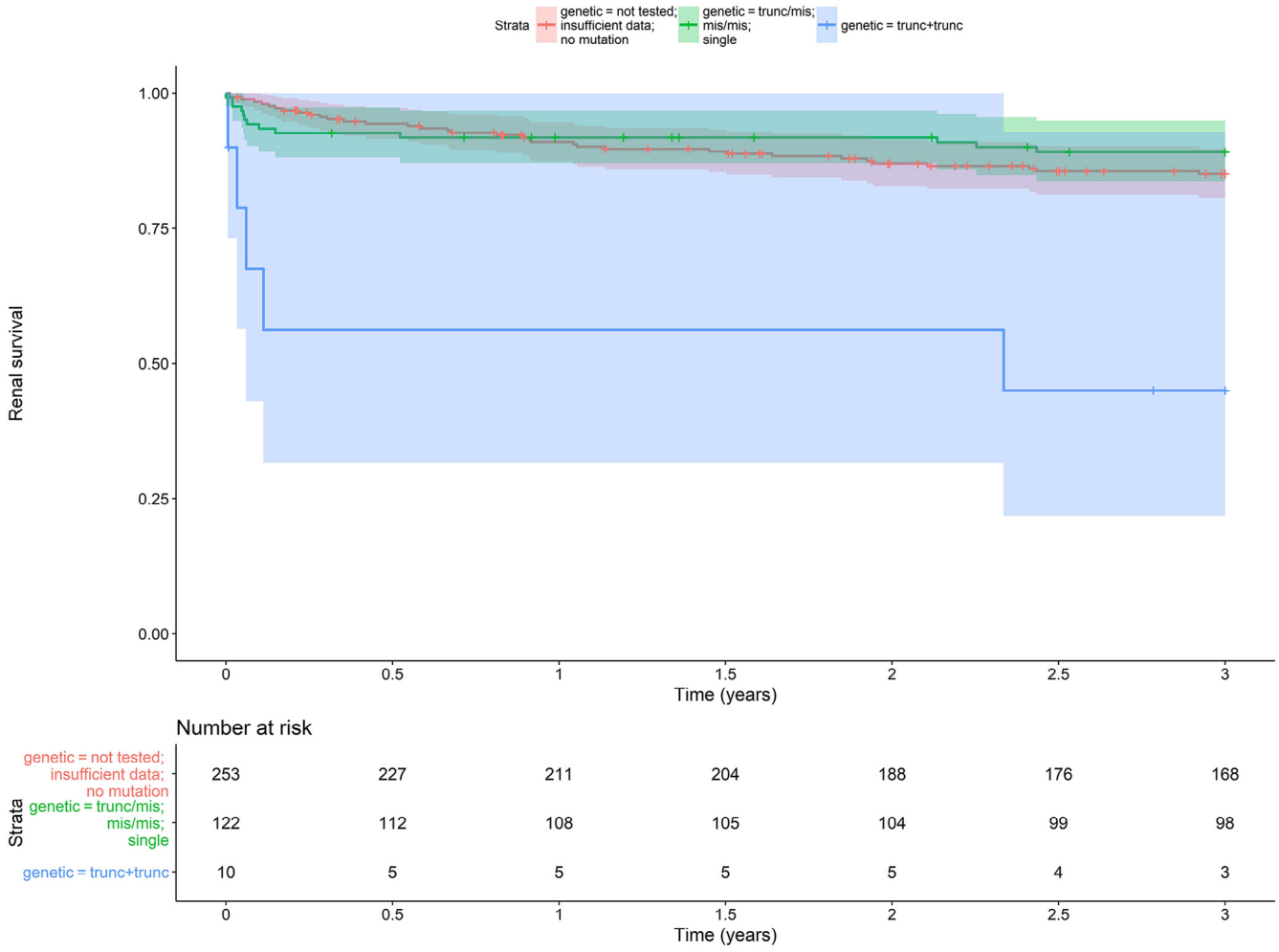

Figure 4. Kaplan-Meier estimate and pointwise 95% CI of renal survival within the first 3 years of life stratified according to genetic information. Red: no proof of *PKHD1* mutation (no documentation of *PKHD1* testing, n = 216; no mutation detection in cases of *PKHD1* testing, n = 22; insufficient data, n = 15); green: other confirmed mutations (truncating/missense, n = 38; missense/missense, n = 68; single mutation, n = 16); blue: two truncating mutations (n = 10). Patients with 2 truncating mutations appear to be at risk of severe courses, but with a large 95% CI.

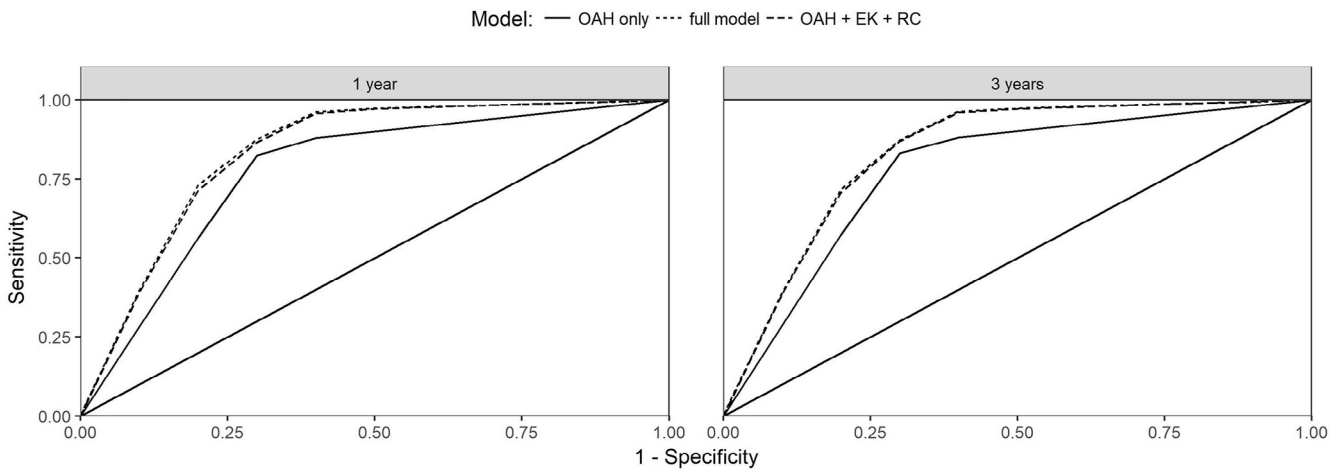

Figure 5. Receiver operating curve characteristics of the predictive models for onset of dialysis within 12 months (*left*) and 36 months (*right*) after birth (point estimate: OAH, oligohydramnios/anhydramnios; EK, enlarged kidneys; RC, renal cysts). The full model considers OAH, EK, RC, and renal parenchymal hyperechogenicity.

Table III. Description of genetic subgroups for identified risk factors

Variables	Total (n = 385)	*PKHD1* testing documented (n = 169)					No *PKHD1* testing documented (n = 216)
		Truncating/ truncating (n = 10)	Truncating/ missense (n = 38)	Missense/ missense (n = 68)	Single mutation (n = 16)	No mutation detection (n = 22) or insufficient data (n = 15)	
Oligohydramnios/ anhydramnios, n/N (%)	107/318 (33.6)	7/10 (70.0)	12/31 (38.7)	17/50 (34.0)	5/14 (35.7)	9/29 (31.0)	57/184 (31.0)
Prenatal increased echogenicity, n/N (%)	78/291 (26.8)	6/9 (66.7)	6/27 (22.2)	8/44 (18.2)	2/12 (16.7)	11/28 (39.3)	45/171 (26.3)
Prenatal enlarged kidneys, n/N (%)	70/301 (23.3)	5/9 (55.6)	7/27 (25.9)	13/49 (26.5)	4/14 (28.6)	8/26 (30.8)	33/176 (18.8)
Prenatal renal cysts, n/N (%)	82/312 (26.3)	5/9 (55.6)	5/29 (17.2)	14/53 (26.4)	3/13 (23.1)	10/28 (35.7)	45/180 (25.0)
Birth weight SDS (n = 250), mean (SD)	–0.1 (1.4)	0.7 (0.9)	.0 (0.9)	–0.4 (0.9)	0.4 (1.7)	0.1 (1.2)	–0.1 (1.7)
Apgar 10 min (n = 157), mean (SD)	8.9 (1.4)	6.0 (2.4)	9.1 (1.2)	9.2 (0.8)	8.4 (1.0)	9.4 (0.8)	9.0 (1.4)
Assisted breathing and/or ventilation, n/N (%)	78/333 (23.4)	7/9 (77.8)	7/30 (23.3)	12/57 (21.1)	5/15 (33.3)	6/32 (18.8)	41/190 (21.6)