



# A risk score to predict kidney survival in patients with autosomal recessive polycystic kidney disease at the age of two months

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**Autosomal recessive polycystic kidney disease (ARPKD) is a severe hepatorenal fibrocystic disorder. Its rareness and the variability of disease courses have been major obstacles for**

**the establishment of clinical trials on treatment of kidney disease in ARPKD. In this observational study we characterized kidney disease progression in a very large cohort of up to 658 patients with the clinical diagnosis of ARPKD and identified risk factors associated with rapid kidney disease progression. The estimated probability of kidney failure by the age of 20 years was 50.1% (95% confidence interval 42.2%–57.0%), with earlier kidney failure in specific subgroups. Mean yearly estimated glomerular filtration rate decline after the first year of life**

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was 1.3 ml/min per 1.73 m<sup>2</sup> during childhood and adolescence in the overall cohort, ranging from 0.5 to 2.2 ml/min per 1.73 m<sup>2</sup> in various subgroups. Furthermore, we developed prediction models for the relative risk of early kidney failure to be applied at the age of two months in daily clinical life. The finally chosen predictor set for a score based on a Cox model encompassed five factors: gestational age at oligo- or anhydramnios, gestational age at birth, functional genotype, serum creatinine (mg/dl) as well as documentation of arterial hypertension at the age of two months. The derived simple prognostic score showed good prediction performance, especially in the first three years of life. It reliably identified patients who are not at risk of early kidney failure and may be helpful to identify patients at risk of more rapid disease progression that could benefit from novel therapeutic interventions.

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## Lay Summary

Autosomal recessive polycystic kidney disease (ARPKD) is a disorder that typically presents very early in childhood. ARPKD frequently goes along with impairment of kidney function. However, the extent of impairment of kidney function and the age of a need for dialysis or kidney transplantation differ a lot between patients with ARPKD. It is currently hard to predict whether a patient with ARPKD will develop a mild or a more severe course of kidney disease. A reliable prediction would be helpful for the establishment of clinical trials and for counseling families. In this paper, we describe the clinical course of a large cohort of patients with ARPKD and identify risk markers. On the basis of this description, we develop a score that can be applied at the age of 2 months and which can help to differentiate patients at high risk of early and severe kidney disease from patients with a lower risk.

**A**utosomal recessive polycystic kidney disease (ARPKD) is a rare, but severe and early-onset systemic disorder typically presenting with clinical signs and symptoms due to the pathologic changes in the kidneys and the liver or the bile ducts. The disorder is mainly caused by variants in the *PKHD1* gene.<sup>1,2</sup> Kidney disease in ARPKD is characterized by the development of ubiquitous renal microcysts resulting in kidney enlargement and impairment of kidney function. Extensive clinical variability of the kidney phenotypes ranging from prenatally detected enlarged kidneys accompanied by oligo- or anhydramnios (OAH) and early kidney failure to milder phenotypes with stable courses into adulthood has been described.<sup>3–7</sup>

Current treatment of ARPKD remains symptomatic and is based on expert recommendations.<sup>8</sup> While kidney replacement therapy (KRT) in infants is technically feasible and associated with survival rates comparable to other disease entities,<sup>9</sup> dialysis in the first months of life remains a clinical challenge. The rareness of the disease and the clinical variability have impeded the predictability of clinical courses for a specific child in the setting of family counseling and the implementation of clinical trials.

Identifying patients who could have the greatest benefit from emerging therapeutic interventions early in life and identifying patients in comparable risk subgroups are of utmost importance to proceed in the search for novel therapeutic interventions for ARPKD.<sup>10</sup> Neonatal survivors with moderate to severe disease may profit most from early intervention. Potential candidates for selected clinical<sup>3,11–15</sup> or genetic risk markers<sup>3,7,16–19</sup> have been identified. These insights have led to the establishment of first phase 3 clinical trials,<sup>20</sup> but refinement of quantifiable risk scores is urgently needed.

Here, we characterize clinical courses of the kidney phenotype on the basis of a deeply phenotyped cohort of up to 658 patients. On the basis of these findings, we developed a scoring system indicating the relative risk of kidney survival in patients with ARPKD at the age of 2 months. This prognostic tool may help to identify infants who are at a relatively higher risk of rapid kidney disease progression compared to other infants in this population; thus, they are at major risk of kidney failure and may therefore predominantly qualify for early novel therapeutic intervention.

## METHODS

The analyzed cohort of 658 patients is derived from the international ARegPKD registry study. Details of the study approach and general inclusion criteria have been previously published.<sup>21</sup> In brief, ARegPKD is an international, multicenter, prospective and retrospective, observational study in both pediatric and adult patients with ARPKD. Inclusion criteria comprise the diagnosis of ARPKD by histology, molecular genetics, or clinical evaluation.<sup>22</sup> Diagnosis of other cystic kidney disorders represents an exclusion criterion. Clinical data covering various aspects of the ARPKD phenotype are entered in basic and follow-up visit data sets. Automated data entry checks and regular quality control accompany longitudinal data entries.

Informed consent was obtained from subjects and/or from a parent and/or legal guardian according to applicable local regulations. The study protocol was approved by the Ethics Committee of the Faculty of Medicine of Cologne University and the institutional review boards of participating sites. ARegPKD is in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Data analysis was performed on the ARegPKD data set available in November 2021.

Kidney survival was defined by the age of kidney failure, which was strictly defined as initiation of KRT (dialysis or

kidney transplantation). Estimated glomerular filtration rate (eGFR) was based on the Bedside Schwartz formula<sup>23</sup> for ages <1.0 year and on the full age spectrum formula<sup>24</sup> for all other ages. Categorization into chronic kidney disease stages was applied according to the Kidney Disease: Improving Global Outcomes classification. Arterial hypertension was defined as the standard deviation score of systolic blood pressure >2 or if any antihypertensive medication was documented.

For genetic analyses, all *PKHD1* variants reported by the participating centers were classified according to the revised criteria of the American College of Medical Genetics (ACMG).<sup>25</sup>

The genotypes were assigned to functional classes termed null variants (nonsense and frameshift variants, canonical splice-site variants, and whole gene deletions) or missense variants for variants classified as *uncertain significance* (ACMG class 3), *likely pathogenic* (ACMG class 4), and *pathogenic* (ACMG class 5). Patients with only a single variant of uncertain significance/likely pathogenic/pathogenic variant (“Single”) and those with any other combination (e.g., non-canonical splice variants or inframe indels; “Others”) were grouped independently. All other patients (no variant of uncertain significance/likely pathogenic/pathogenic *PKHD1* variants detected in *PKHD1* sequencing, no *PKHD1* sequencing) were grouped together. Patients with (likely) pathogenic variants in other polycystic kidney disease genes (such as *PKD1*, *PKD2*, *HNF1B*, *DZIP1L*, or *GANAB*) without relevant *PKHD1* variants were excluded from further analyses.

#### Statistical methods for description of clinical courses

Basic characteristics of the study population were described by median and first and third quartile for continuous variables and by absolute and relative frequencies for categorical variables. Kidney survival of the total cohort and within various strata was described by Kaplan-Meier estimates with pointwise 95% confidence intervals (CIs). Estimated GFR values with respect to age were visualized by scatter plots. Here, only values at ages >1 year and before the onset of KRT were considered to analyze eGFR of native kidneys. To consider information about the onset of KRT, eGFR values were set to 5 ml/min per 1.73 m<sup>2</sup> for patients once at the timepoint of the KRT onset. The mean eGFR age trajectories shown in the scatter plots were estimated by a linear mixed model to adjust for the dependence of multiple values of the same patient. Patient ID was included as random intercept as well as random slope for age. For the specific description of kidney function in the first 1.5 years of life, scatter plots of serum creatinine with respect to age were created. Furthermore, eGFR courses and serum creatinine courses were visualized for patients with at least 3 values spanning at least 0.5 years. Analogously to the description of eGFR values, serum creatinine values equivalent to eGFR values of 5 ml/min per 1.73 m<sup>2</sup> were added for patients at the timepoint of the onset of KRT.

#### Statistical methods for the development of prediction models

The development and validation of our prediction models was prespecified and described in a protocol presented in the [Supplementary Methods](#), also including more details of the applied methods. We only included data of patients who survived beyond the age of 2 months without kidney failure. The outcome of the prediction model was chosen to be a relative risk score of kidney survival. No sample size estimation was performed. Missing data were handled by multiple imputation. The data set of patients that survived beyond the age of 2 months without kidney failure was split randomly into a development data set and validation data set in a ratio of 3:1. This ratio was considered a reasonable trade-off between developing a well-performing prediction model and getting precise performance estimates. The data split was stratified by the most relevant variables to assure that known potential key variables affecting kidney function showed equal distribution between the data sets. The prediction models were developed on the development data set. The validation set remained blinded until the 2 final models were fixed. We considered 2 types of models: firstly, a Cox regression,<sup>26</sup> where the relative risk score is calculated by the linear predictor, and secondly, a random survival forest (RSF), a completely nonparametric machine learning method, where the relative risk score is the so-called “mortality.”<sup>27</sup> This approach enables us to assess whether the proportional hazard assumption of the Cox regression affects the prediction performance. Final prediction models were developed for both types, and their performances on the validation data set were evaluated and compared. A total of 15 potential early predictors were considered based on clinical experience and previous exploratory analyses. For simple use in clinical practice, we restricted the final model to have a maximum number of 5 predictors. During development, the performance of all possible predictor sets with a maximum of 5 predictors was estimated. For the Cox regression, this was done by 10-fold cross-validation. For the RSF, this was done using the out-of-bag predictions. The choice of the final predictor sets was based on the estimated performance as well as clinical considerations. For the Cox score, the final formula was transformed to integer values for convenient use in practice. Risk groups were created to facilitate interpretation of the risk score and were based on the distributions of the developed risk scores. The primary performance measure was Harrell’s c,<sup>28</sup> as it is an easily interpretable measure of discrimination. Based on the performances on the validation set, a recommendation was made on which of the 2 models to use in practice. Kaplan-Meier estimates within risk groups were calculated and pooled after multiple imputation. Pooling was only possible at ages where Kaplan-Meier estimates in all multiple imputed data sets were <1. Hence, some curves start at later ages. For more detailed information on statistical analysis methods, see the [Supplementary Methods](#). All analyses were performed in R (version 4.2; R Core Team, 2022).

**Table 1 | Characteristics of 658 patients from ARegPKD**

| Characteristics                                           | Value               |
|-----------------------------------------------------------|---------------------|
| <i>Basic characteristics, n (%) or median (Q1–Q3)</i>     |                     |
| Sex (n = 658)                                             |                     |
| Male                                                      | 343 (52.1)          |
| Female                                                    | 315 (47.9)          |
| Age at last visit (yr), (n = 606)                         | 9.5 (4.3–15.7)      |
| Follow-up time (yr), (n = 606)                            | 4.2 (0.8–9.2)       |
| CKD stage at last available visit (n = 596)               |                     |
| 1                                                         | 124 (20.8)          |
| 2                                                         | 116 (19.5)          |
| 3                                                         | 112 (18.8)          |
| 4                                                         | 48 (8.1)            |
| 5 without KRT                                             | 24 (4.0)            |
| 5 with KRT                                                | 172 (28.9)          |
| <i>Prenatal sonographic anomalies, n (%)</i>              |                     |
| Oligo- or anhydramnios (n = 547)                          |                     |
| No documentation                                          | 340 (62.2)          |
| ≥32 gw                                                    | 91 (16.6)           |
| 28–31 gw                                                  | 58 (10.6)           |
| ≤27 gw                                                    | 58 (10.6)           |
| Increased renal echogenicity (n = 498)                    |                     |
| No documentation                                          | 358 (71.9)          |
| ≥32 gw                                                    | 53 (10.6)           |
| 28–31 gw                                                  | 37 (7.4)            |
| ≤27 gw                                                    | 50 (10.0)           |
| Renal hyperplasia (n = 517)                               | 123 (23.8)          |
| Kidney cysts (n = 532)                                    | 146 (27.4)          |
| <i>Perinatal information, n (%) or median (Q1–Q3)</i>     |                     |
| Gestational age at birth (gw), (n = 496)                  | 38.0 (35.9–39.0)    |
| Prematurity (birth <37 gw), (n = 496)                     | 181 (36.5)          |
| Birth weight SDS (n = 444)                                | −0.05 (−0.7 to 0.6) |
| Apgar 10 min (n = 269)                                    | 9.0 (8.0–10.0)      |
| Poor postnatal adaptation (n = 580)                       | 137 (23.6)          |
| Stay on neonatal intensive care unit (n = 580)            | 160 (27.6)          |
| Pulmonary hypertension (n = 551)                          | 38 (6.9)            |
| Postnatal ventilation (n = 563)                           |                     |
| No documentation                                          | 433 (76.9)          |
| Continuous positive airway pressure                       | 44 (7.8)            |
| Conventional ventilation                                  | 44 (7.8)            |
| High-frequency oscillation ventilation                    | 42 (7.5)            |
| <i>Postnatal information, median (Q1–Q3)</i>              |                     |
| Maximal height-adjusted TKV within 18 mo (ml/m), (n = 81) | 385 (206–607)       |
| <i>Genetic results, n (%)</i>                             |                     |
| Functional genotype groups (n = 579)                      |                     |
| Null/null variant                                         | 24 (4.1)            |
| Missense/missense variant                                 | 132 (22.8)          |
| Null/missense variant                                     | 71 (12.3)           |
| Others                                                    | 35 (6.0)            |
| Single variant                                            | 38 (6.6)            |
| No <i>PKHD1</i> variant detected                          | 45 (7.8)            |
| No <i>PKHD1</i> test or insufficient data                 | 234 (40.4)          |

CKD, chronic kidney disease; KRT, kidney replacement therapy; SDS, standard deviation score; TKV, total kidney volume.  
Follow-up time is defined as an interval between first and last documented visits.

## RESULTS

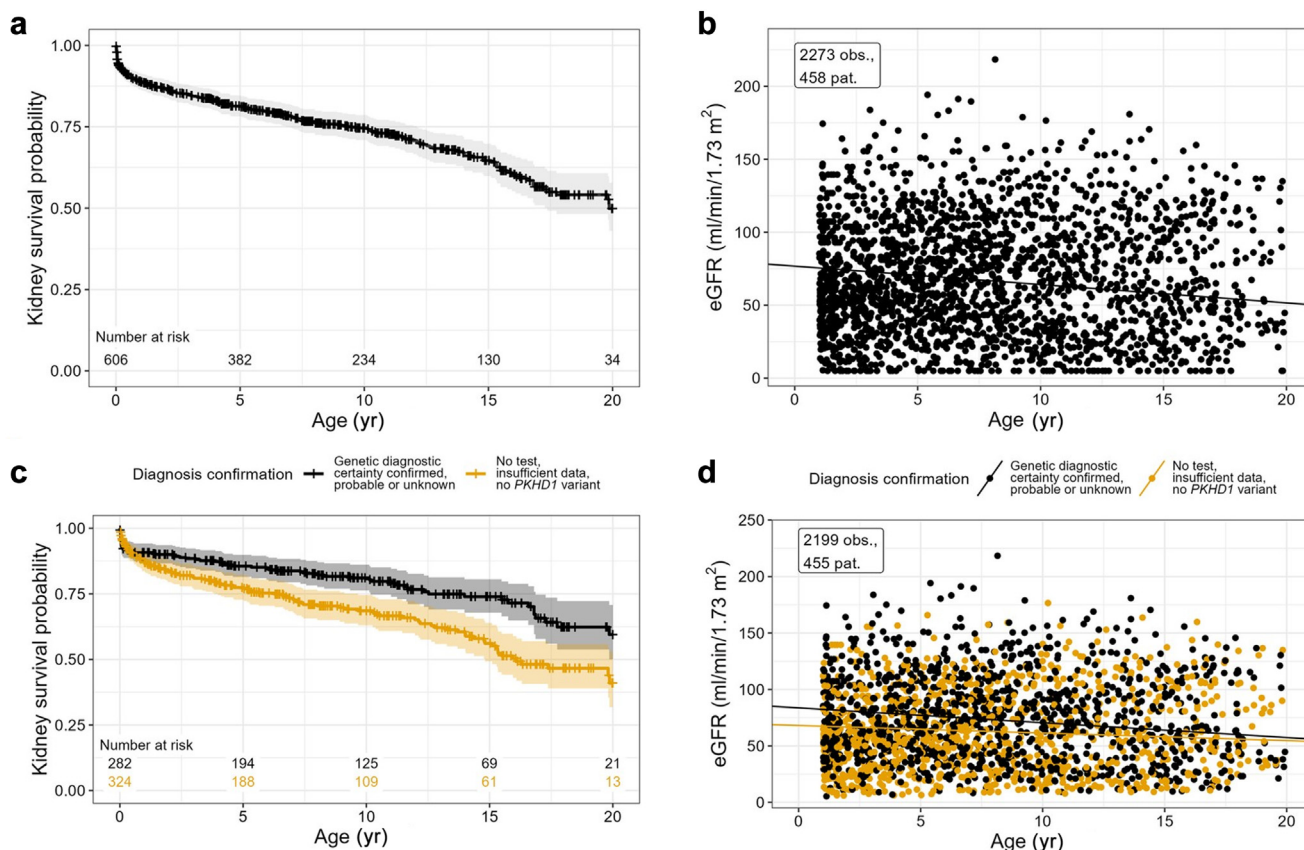
### Characterization of kidney disease courses in patients with ARPKD

**Patients.** Characteristics of 658 included patients are displayed in Table 1. Visits were documented for 606 patients.

**Clinical and genetic factors.** Kidney survival in the overall cohort was 74.6% (95% CI: 70.9%–78.6%) after 10 years (Figure 1a) without a relevant difference between females and males (Supplementary Figure S1A). Kidney survival after 10 years in the subcohort with kidney survival >2 months was 79.9% (95% CI: 76.3%–83.8%; Supplementary Figure S2A). The mean eGFR at the end of the first year of life in the subcohort with kidney survival >1.0 year was 75.5 ml/min per 1.73 m<sup>2</sup> (“native kidney eGFR”) with a mean yearly eGFR loss of 1.3 ml/min per 1.73 m<sup>2</sup> per year in the following years (Figure 1b). The courses (Supplementary Figure S1B) and distribution of single serum creatinine measurements (Supplementary Figure S1C) as well as eGFR courses within the first 18 months of life (Supplementary Figure S1D) revealed that many patients reached a plateau of eGFR in the first 6 months of life.

Ten-year kidney survival was 81.0% (95% CI: 76.3%–86.1%) in patients with detected *PKHD1* variants compared with 68.5% (95% CI: 63.0%–74.6%) in all other patients ( $P < 0.001$ ; Figure 1c). Patients with proof of *PKHD1* variants showed a trend toward higher mean native kidneys’ eGFR at the end of the first year of life (82.4 vs. 67.4 ml/min per 1.73 m<sup>2</sup>) and more pronounced mean yearly eGFR loss after the first year of life as compared to all other patients (1.3 vs. 0.7 ml/min per 1.73 m<sup>2</sup> per year; Figure 1d). Various additional subgroups stratified according to prenatal and perinatal factors showed remarkable differences: patients with very early (≤27 weeks) sonographic detection of OAH showed worse kidney survival (10-year kidney survival 32.2% [95% CI: 19.6%–52.9%]) than patients with early (28–31 weeks; 47.0% [95% CI: 33.1%–66.6%]) or late (≥32 weeks; 55.4% [95% CI: 42.9%–71.5%]) detection or without OAH (86.3% [95% CI: 82.2%–90.6%], log-rank  $P < 0.001$ ; Figure 2a). Similarly, the mean native kidney eGFR at the end of the first year trended to be lower in patients with early detection of OAH (54.1 in OAH ≤27 weeks vs. 55.7 in 28–31 weeks vs. 61.8 in ≥32 weeks vs. 83.6 ml/min per 1.73 m<sup>2</sup> if no OAH), and the mean yearly eGFR loss after the first year of life was higher in patients with early OAH compared to the no OAH group and the very early OAH group (2.2 in OAH 28–31 weeks and ≥32 weeks vs. 0.9 ml/min per 1.73 m<sup>2</sup> per year in OAH ≤27 weeks and in case of no OAH; Figure 2b).

Ten-year kidney survival was inferior in premature infants (gestational age <37 weeks; 47.9% [95% CI: 39.4%–58.3%]) compared with term infants (79.0% [95% CI: 73.9%–84.4%],  $P < 0.001$ ; Figure 2c). Accordingly, the mean native kidney eGFR at the end of the first year of life showed a trend to be lower in premature patients (61.6 vs. 74.4 ml/min per 1.73 m<sup>2</sup>), and the mean yearly eGFR loss after the first year of life was higher than that in the nonpremature control group (2.1 vs. 0.9 ml/min per 1.73 m<sup>2</sup> per year; Figure 2d).

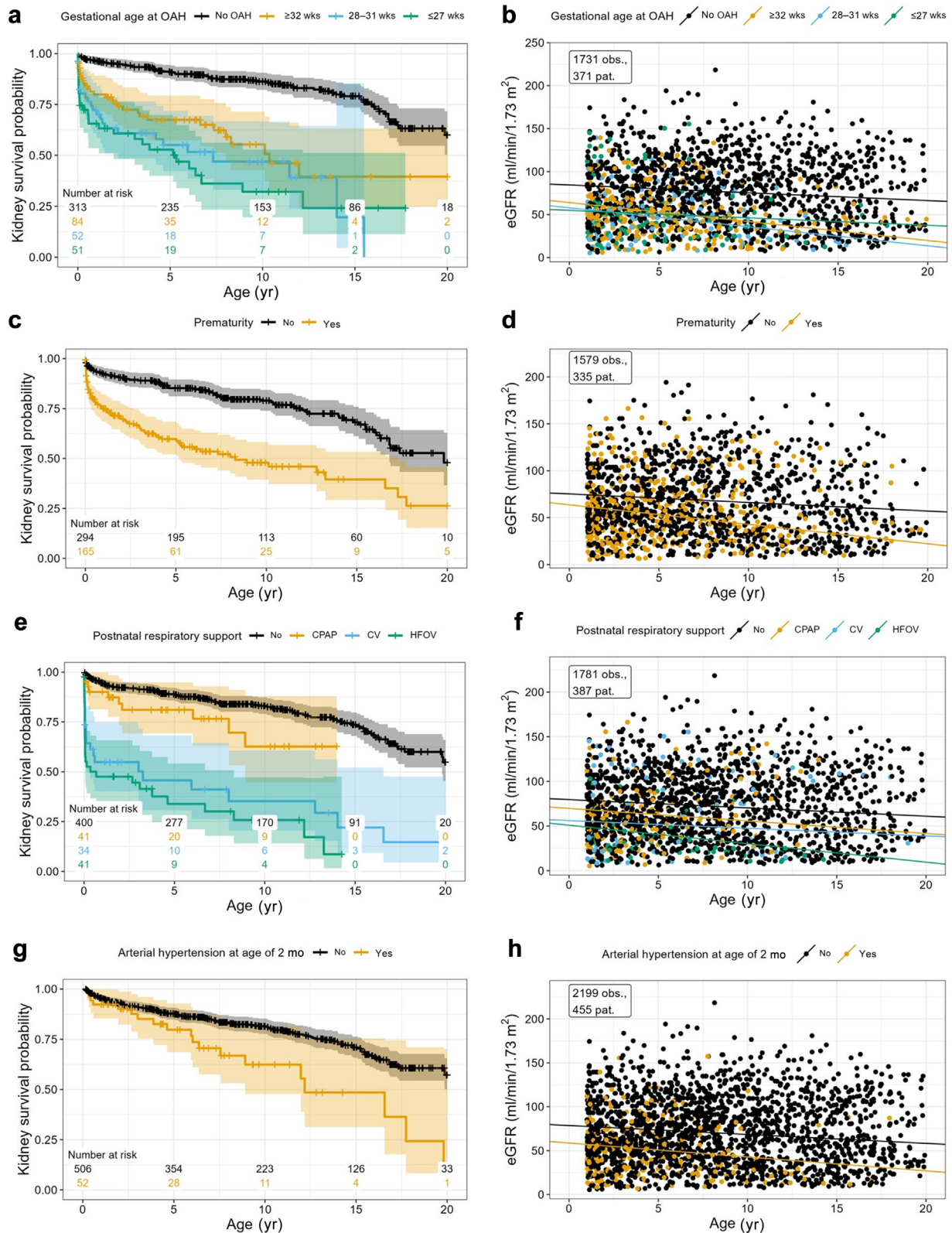


**Figure 1 | Kidney survival in the total cohort (a,c) and estimated glomerular filtration rate (eGFR) in the subcohort with kidney survival >1.0 year (b,d) in general (a,b) and stratified according to genetic results (c,d). obs., observations; pat., patients.**

Worse kidney survival was observed with increasing invasiveness of assisted breathing or ventilation: patients not requiring respiratory support in their postnatal phases showed 10-year kidney survival of 83.0% (95% CI: 79.0%–87.3%) compared with 62.7% (95% CI: 44.6%–87.9%) in infants with continuous positive airway pressure support, 35.2% (95% CI: 20.5%–60.6%) in conventionally ventilated infants, and 25.8% (95% CI: 14.1%–47.2%) in patients with high-frequency oscillation ventilation (log-rank  $P < 0.001$ ; [Figure 2e](#)). Again, patients without the need of respiratory support seemed to start with the highest mean native kidney eGFR at the end of the first year of life (78.7 ml/min per 1.73 m<sup>2</sup> in patients not requiring respiratory support vs. 68.4 ml/min per 1.73 m<sup>2</sup> in patients with continuous positive airway pressure vs. 55.3 ml/min per 1.73 m<sup>2</sup> in conventionally ventilated patients vs. 48.9 ml/min per 1.73 m<sup>2</sup> in patients with high-frequency oscillation ventilation) and trended to experience a smaller mean yearly eGFR loss after the first year of life compared to the group with continuous positive airway pressure and high-frequency oscillation ventilation (0.9 ml/min per 1.73 m<sup>2</sup> per year [no support] vs. 1.4 ml/min per 1.73 m<sup>2</sup> per year [continuous positive airway pressure] vs. 0.9 ml/min per 1.73 m<sup>2</sup> per year [conventional ventilation] vs. 2.1 ml/min per 1.73 m<sup>2</sup> per year [high-frequency oscillation ventilation]; [Figure 2f](#)). The subcohort of patients not receiving KRT until the age of 2 months

is preselected excluding the most severe cases resulting in better 10-year kidney survival. Still, trends in stratified subcohorts were comparable to the total cohort ([Supplementary Figure S2B–E](#)).

Overall, patients with a prenatal diagnosis of ARPKD experienced a worse 10-year kidney survival than patients with later diagnosis (46.5% [95% CI: 33.8%–64.1%] in prenatally diagnosed patients vs. 70.2% [95% CI: 64.7%–76.2%] in patients with diagnosis 0–1 year vs. 93.0% [95% CI: 88.6%–97.6%] in patients with a diagnosis >1 year; log-rank  $P < 0.001$ ; [Supplementary Figure S3A](#)). The prenatally diagnosed patients also showed the lowest mean native kidney eGFR at the end of the first year of life (66.7 [prenatal diagnosis] vs. 69.5 [diagnosis 0–1 year] vs. 89.3 [diagnosis >1 year] ml/min per 1.73 m<sup>2</sup>) and the highest mean yearly eGFR loss after the first year of life (2.2 vs. 1.3 vs. 0.6 ml/min per 1.73 m<sup>2</sup> per year; [Supplementary Figure S3B](#)). After stratification for genetic subgroups, kidney survival and mean yearly eGFR loss after the first year of life differed grossly (10-year kidney survival ranging from 46.3% up to 89.1% and mean yearly eGFR loss after the first year of life ranging from 0.5 up to 1.9 ml/min per 1.73 m<sup>2</sup> per year) between the groups, indicating the worst course in patients with biallelic *PKHD1* null variants (log-rank  $P < 0.001$  for kidney survival; [Supplementary Figure S3C and D](#)).



**Figure 2 | Kidney survival in the total cohort (a,c,e,g) and eGFR courses in the subcohort with kidney survival >1.0 year (b,d,f,h) stratified by gestational age at oligo- or anhydramnios (OAH; a,b), prematurity (c,d), type of postnatal respiratory support (e,f), or documentation of arterial hypertension until the age of 2 months (g,h). CPAP, continuous positive airway pressure; CV, conventional ventilation; eGFR, estimated glomerular filtration rate; HFOV, high-frequency oscillation ventilation; mo, months; obs., observations; pat., patients; wks, weeks.**

**Table 2 | Distribution of predictor variables in the subcohort of 558 patients with kidney survival  $\geq 2$  months and documented follow-up visits**

| Characteristics                                              | Value                 |
|--------------------------------------------------------------|-----------------------|
| <i>Basic characteristics, n (%)</i>                          |                       |
| Sex (n = 558)                                                |                       |
| Male                                                         | 289 (51.8)            |
| Female                                                       | 269 (48.2)            |
| <i>Prenatal sonographic anomalies, n (%)</i>                 |                       |
| Oligo- or anhydramnios (n = 456)                             |                       |
| No documentation                                             | 308 (67.5)            |
| $\geq 32$ gw                                                 | 72 (15.8)             |
| 28–31 gw                                                     | 40 (8.8)              |
| $\leq 27$ gw                                                 | 36 (7.9)              |
| Renal hyperplasia (n = 436)                                  | 80 (18.3)             |
| Kidney cysts (n = 446)                                       | 108 (24.2)            |
| <i>Perinatal information, n (%) or median (Q1–Q3)</i>        |                       |
| Gestational age at birth (n = 415)                           |                       |
| <34 gw                                                       | 42 (10.1)             |
| 34–36 gw                                                     | 96 (23.1)             |
| $\geq 37$ gw                                                 | 277 (66.7)            |
| Birth weight SDS (n = 367)                                   | −0.11 (−0.73 to 0.56) |
| Apgar 10 min (n = 215)                                       | 10.0 (8.5–10.0)       |
| Poor postnatal adaptation (n = 486)                          | 86 (17.7)             |
| Pulmonary hypertension (n = 467)                             | 18 (3.9)              |
| Postnatal ventilation (n = 468)                              |                       |
| No documentation                                             | 388 (82.9)            |
| Continuous positive airway pressure                          | 38 (8.1)              |
| Conventional ventilation                                     | 21 (4.5)              |
| High-frequency oscillation ventilation                       | 21 (4.5)              |
| <i>Postnatal information, n (%) or median (Q1–Q3)</i>        |                       |
| Maximal height-adjusted TKV within 2 months (ml/m), (n = 27) | 230 (137–443)         |
| Arterial hypertension at the age of 2 months (n = 558)       | 52 (9.3)              |
| Serum creatinine at the age of 2 months (mg/dl), (n = 89)    | 0.52 (0.36–0.70)      |
| <i>Genetic results, n (%)</i>                                |                       |
| Functional genotype groups (n = 500)                         |                       |
| Null/null variant                                            | 13 (2.6)              |
| Missense/missense variant                                    | 125 (25.0)            |
| Null/missense variant                                        | 57 (11.4)             |
| Others                                                       | 29 (5.8)              |
| Single variant                                               | 33 (6.6)              |
| No <i>PKHD1</i> variant detected                             | 40 (8.0)              |
| No <i>PKHD1</i> test or insufficient data                    | 203 (40.6)            |

SDS, standard deviation score; TKV, total kidney volume.

Patients who were diagnosed with arterial hypertension until the age of 2 months experienced worse 10-year kidney survival (62.4% [95% CI: 47.7%–81.5%] vs. 81.4% [95% CI: 77.7%–85.3%]; log-rank  $P < 0.001$ ; [Figure 2g](#)). The mean native kidney eGFR at the end of the first year was lower in patients with early arterial hypertension until the age of 2 months (57.1 vs. 77.6 ml/min per  $1.73 \text{ m}^2$ ), and the mean yearly eGFR loss after the first year of life was higher than in

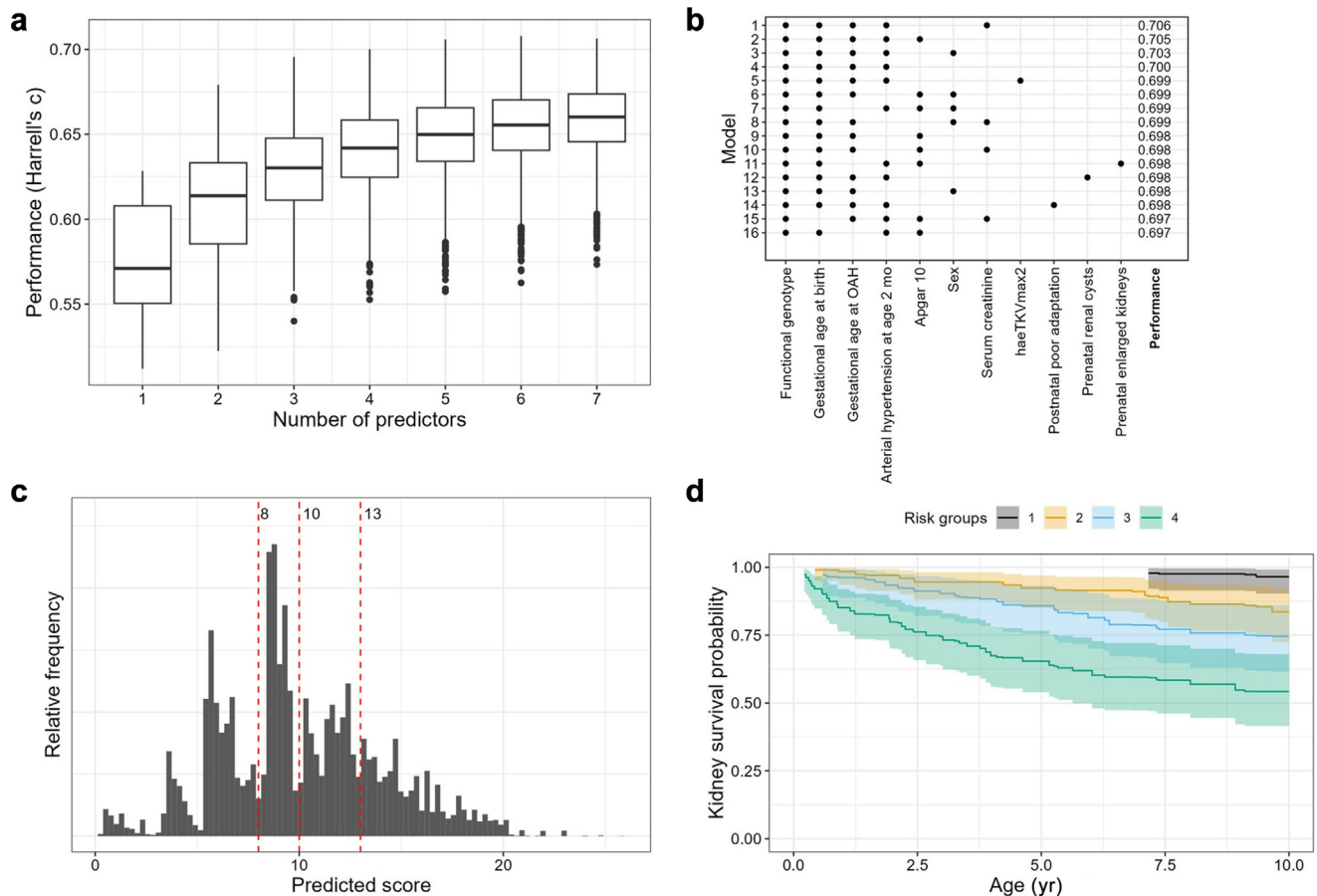
the nonhypertensive control group (1.6 vs. 1.0 ml/min per  $1.73 \text{ m}^2$  per year; [Figure 2h](#)).

### Prediction model for application at the age of 2 months

After identifying multiple associations of markers with kidney survival and eGFR, we next aimed to establish a prediction model. We reasoned that such a model should be applicable early during the disease course to identify patients at high or low risk of early requirement of KRT in the group of patients surviving the perinatal period. For the development of prediction models via the Cox model and RSF, 558 patients with kidney survival  $>2$  months and documentation of follow-up visits were identified ([Supplementary Figure S4A](#)). Details of this subcohort are displayed in [Table 2](#). The proportions of missing data were varying ([Supplementary Figure S4B](#)). After splitting into a development and validation data set, we confirmed that both kidney survival ([Supplementary Figure S4C](#)) and distribution of the most relevant variables ([Supplementary Figure S4D](#)) were very similar in both data sets.

### Cox score

In a next step, the selection of a predictor set for a Cox model with good prediction performance and feasible applicability in daily clinical life was pursued. During development, performances of different Cox scores were estimated on the development data set by cross-validation for all predictor sets with a maximum of 7 predictors. The best predictor sets with 5 predictors performed equally well as sets with more predictors ([Figure 3a](#)). Various combinations of maximal 5 predictors reached similar performances ([Figure 3b](#)). Functional genotype, gestational age at birth, and gestational age at OAH were found to be the most important predictors because they occur in almost all of the best models. In the interest of best performance and clinical applicability, we decided to choose the easily obtainable predictors gestational age at OAH, gestational age at birth, functional genotype, serum creatinine (mg/dl) at the age of 2 months, and documentation of arterial hypertension at the age of 2 months (model number 1 in [Figure 3b](#)). The corresponding formula for calculating the Cox score was transformed for convenient use in practice and is given in [Table 3](#). Weighed values of the individual 5 predictors are added up to give a final value of the Cox score. This includes the possibility that findings for genetics may not be available. The value of the Cox score can be assigned to 1 of 4 risk groups that were defined based on the distribution of the Cox score on the development data set ([Figure 3c](#)). They were defined by clear cutoff values of 8, 10, and 13 with the corresponding proportions of 29% (score  $\leq 8$ , risk group 1, lowest risk), 25% (score  $>8$  to  $\leq 10$ , risk group 2), 23% (score  $>10$  to  $\leq 13$ , risk group 3), and 23% (score  $>13$ , risk group 4, highest risk). Kidney survival in the development data set differed relevantly in the 4 assigned risk groups according to the Cox score with increasing risk of kidney failure with higher scores: 10-year kidney survival was 96.6% in risk group 1, 83.6% in risk group 2, 74.6% in risk group 3, and 54.3% in risk group 4 ([Figure 3d](#)).



**Figure 3 | Cox score performances and final Cox score during development.** Box plots of model performance (quantified by Harrell's c) with respect to the number of used predictors calculated during development on the development data set by cross-validation. One box contains performances of all possible predictor sets with the respective number of predictors (**a**). Predictor sets of the 16 best performing models according to Harrell's c (calculated on the development data set by cross-validation). The predictor set of model 1 was chosen for the final model (**b**). Distribution of predicted scores with the final Cox score in the development data set according to criteria in Table 3 with defined cutoff values of 8, 10, and 13 resulting in 4 risk groups (**c**). Kidney survival in the development data set stratified by the risk groups of the final Cox score. In some risk groups, pooling of Kaplan-Meier estimates was only possible at later ages (**d**). haeTKVmax2, highest documented height-adjusted estimated total kidney volume value within the first 2 months of life; mo, months; OAH, oligo- or anhydramnios.

After the score development in the development data set, we unblinded the validation data set and applied the Cox score to the patients in the validation data set to obtain an unbiased performance estimation. We observed a similar distribution of the Cox scores with a good performance (Figure 4a, Supplementary Figure S5A, Harrell's c 0.73, 95% CI: 0.57–0.89), especially in the first 3 years of life (Table 4, Supplementary Figure S5B and C). In the validation group, differentiation between risk groups 1 versus 2 and 3 versus 4 was not as clear as in the developmental data set (Figure 4b, Supplementary Table S1). A *post hoc* combined risk grouping of the final Cox score (1+2, 3+4) showed clear differentiation (Figure 4c). Remarkably, there were no observed events of KRT within the first 12 months of life in patients who were assigned to risk groups 1 and 2 in the validation data set. Events of KRT within the first 12 months of life were only observed in risk groups 3 and 4 (Figure 4d). All patients with an event in the first 36 months had a risk score that was above the median risk score of all patients at risk at the time of the

event. When only the classification into risk groups was used (and not the finer evaluation with the score), the performance (Harrell's c) of this approach on the validation data set was 0.70 (95% CI: 0.54–0.86). The final score was then applied in 7 patients who were registered in ARegPKD after the development of the scoring system: in the available follow-up data, there were no observed events of KRT within the first 12 months of life in patients who were assigned to risk groups 1 and 2 (Supplementary Table S2).

#### Random survival forest score

In addition to the Cox model, a completely nonparametric machine learning method, an RSF model was applied to the development data set.<sup>27</sup> The performance of the RSF score in the validation cohort was similar (Harrell's c 0.72, 95% CI: 0.55–0.88), but not superior to the Cox score (Supplementary Figure S6A–D). Similarly, there were also no observed events of KRT within the first 12 months of life in patients assigned to risk groups 1 and 2 in the validation data

**Table 3 | Calculation of the score according to the final Cox score using 5 predictors**

| Calculation of score                                                          |                    |
|-------------------------------------------------------------------------------|--------------------|
| Gestational age at OAH                                                        |                    |
| If no OAH                                                                     | add 0              |
| If GA at OAH ≥32 gw                                                           | add 2              |
| If GA at OAH ≤27 gw or 28–31 gw                                               | add 3              |
| Gestational age at birth                                                      |                    |
| If GA at birth ≥37 gw                                                         | add 0              |
| If GA at birth <37 gw                                                         | add 2              |
| Functional genotype                                                           |                    |
| If <i>PKHD1</i> variants classified in “others”                               | add 0              |
| If null/mis <i>PKHD1</i> variants                                             | add 2              |
| If mis/mis <i>PKHD1</i> variants                                              | add 3              |
| If null/null <i>PKHD1</i> variants                                            | add 4              |
| If single <i>PKHD1</i> variant                                                | add 4              |
| If no <i>PKHD1</i> test was performed or result of genetic testing is unknown | add 5              |
| If no <i>PKHD1</i> variant was detected in genetic <i>PKHD1</i> testing       | add 7              |
| Serum creatinine (mg/dl) at the age of 2 months                               | add value in mg/dl |
| Documentation of arterial hypertension at the age of 2 months                 |                    |
| If no arterial hypertension is documented until the age of 2 months           | add 0              |
| If arterial hypertension is documented until the age of 2 months              | add 3              |

GA, gestational age; OAH, oligo- or anhydramnios.

set (Supplementary Figure S6C). Summarizing, the RSF score yielded the same inferences and similar discrimination performance as the Cox score. As the RSF model is not superior and the Cox model offers easier manageability and applicability in clinical practice, we finally decided to focus on the application of the Cox score presented above.

DISCUSSION

In the current paper, we present data on the clinical course of kidney disease in patients with ARPKD and propose an easily applicable model for children at the age of 2 months to estimate the future relative risk of kidney failure.

ARPKD is a severe hepatorenal disorder. Newborns with the more severe phenotype may also have pulmonary hypoplasia, which may determine the prognosis concerning patient survival. Current treatment remains symptomatic and based on expert opinions. Clinical research on potential targeted therapies of kidney or liver disease has been hampered by the rareness of the disease and its clinical variability.

Kidney disease tends to present earlier in ARPKD than liver disease and poses the main clinical challenge in severely affected children surviving the perinatal period. While dialysis in the first year of life is feasible and safe with a remarkably improved outcome in terms of survival, it remains a clinical and socioeconomic challenge and a severe burden for the families.<sup>29,30</sup> Lower recipient weights are associated with more complications in kidney transplantation.<sup>31</sup> Most centers will offer kidney transplantation to children from a weight of 8 to

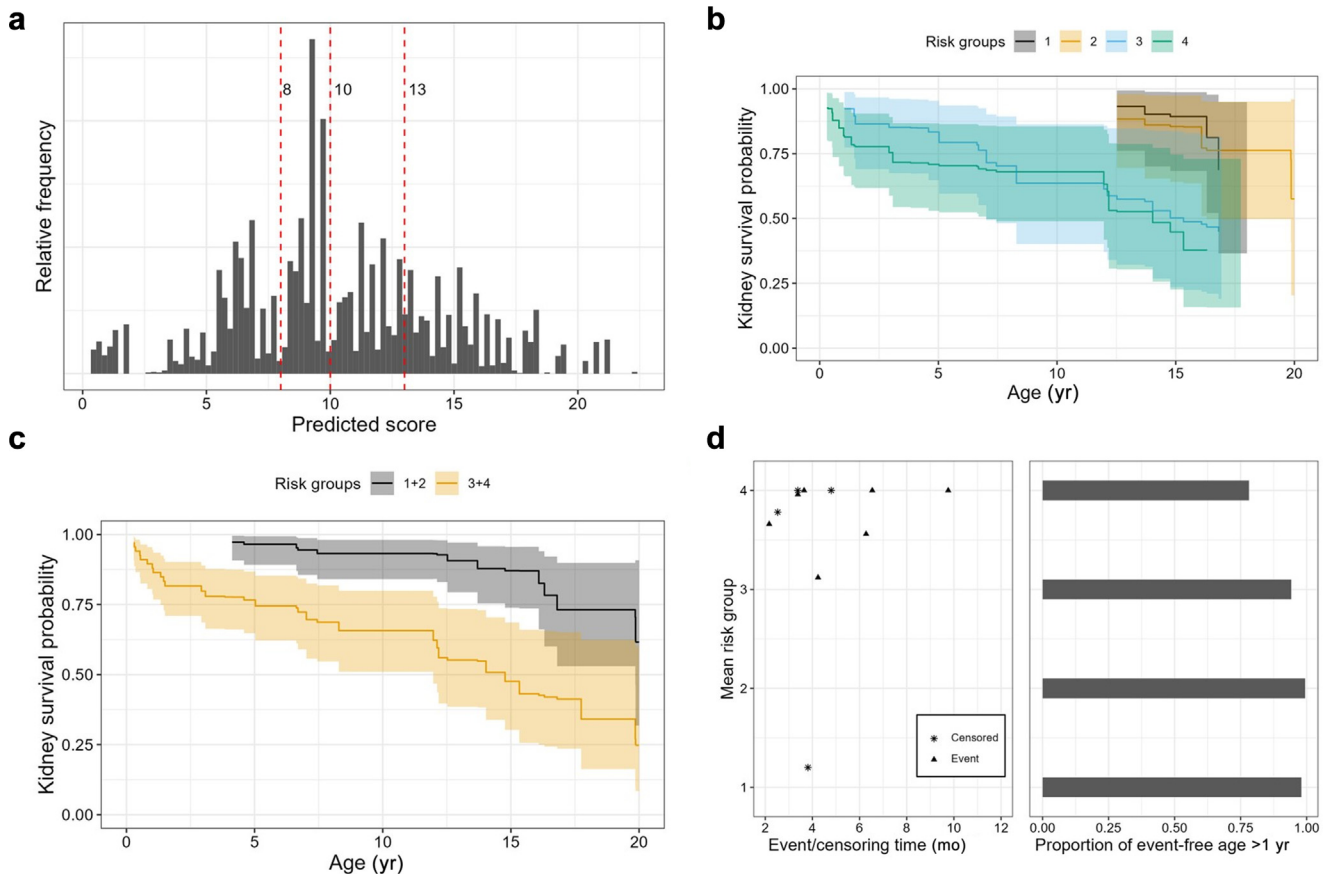
10 kg, which is typically reached by a healthy child at the end of the first year of life. Children with chronic kidney disease and especially children with kidney failure typically require longer to reach this weight.<sup>32</sup>

For children with ARPKD, survival after the perinatal period is very good, but previous studies have shown that some patients progress to kidney failure rapidly, partly because of the need of nephrectomies.<sup>3,4,12,33</sup> Clearly, patients surviving the perinatal period but showing rapid progression could have a relevant benefit from an early pharmacologic intervention and interventional trials for ARPKD.<sup>10</sup> This concept is mirrored by the criteria for first phase 3 clinical trials for ARPKD.<sup>20</sup> The group with the highest risk of kidney failure (i.e., KRT within the first 2 months of life) was not in the scope of our current approach.

Although first antenatal criteria have been identified that help to distinguish patients with a high risk of early need for dialysis,<sup>14</sup> there is thus still an urgent need for more precise prediction tools for clinical trials and to help clinicians when counseling families. Current knowledge does not allow clear prediction of the course of kidney disease in ARPKD, for example, whether a child will reach the weight required for pre-emptive transplantation. For clinical trials such a tool could help to identify comparable high-risk subgroups for randomized trials and to identify patients who could have a great benefit from therapeutic intervention. At the same time, unnecessary side effects of therapeutic intervention in those patients with a better short-term or even long-term prognosis could be avoided.

Our descriptive data validated and extended previous findings.<sup>4,13,33</sup> We have previously shown in a subcohort of patients with the clinical diagnosis of ARPKD and detection of at least 1 relevant *PKHD1* variant that kidney survival does not differ between groups of patients with different genetic confirmatory status with an ARPKD clinical diagnosis and *PKHD1* variants and identified associations of genetic subgroups with kidney survival.<sup>7</sup> In the current study, all individuals with a clinical diagnosis of ARPKD—with and without genetic workup—served as basis for the development of a prognostic score for kidney survival. Early clinical markers are clearly associated with different courses of kidney disease. Importantly, we define the yearly eGFR loss after the first year of life in this large cohort and in specific subcohorts. The data are consistent with previous findings in a smaller cohort<sup>34</sup> and suggest that the key determinants of kidney disease in ARPKD are developmental events that impede physiological development of kidney function antenatally and in the first year of life.

We followed the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) statement for reporting of studies developing, validating, or updating a prediction model.<sup>35</sup> We used easily obtainable clinical markers and also included the possibility that data may not be available for genetic findings (Table 3; Figure 5). The markers were



**Figure 4 | Graphical evaluation of the final Cox score on the validation data set.** Distribution of predicted scores with the final Cox score in the validation data set according to criteria in Table 3 with defined cutoff values of 8, 10, and 13 resulting in 4 risk groups (a). Kidney survival in the validation data set stratified by the risk groups of the final Cox score. In some risk groups, pooling of Kaplan-Meier estimates was only possible at later ages (b). Kidney survival in the validation data set stratified by *post hoc* combined risk groups of the final Cox score (1+2 and 3+4). Combination of risk groups was done due to similar kidney survival in groups 1+2 and 3+4 in the validation data set and was not prespecified (c). Ages at censoring or event of kidney replacement therapy in the validation data set in mean risk groups of the final Cox score. Mean risk groups were calculated over all multiple imputed data sets (d).

identified by 2 independent statistical approaches. The completely nonparametric machine learning method “random survival forest” did not perform better than a simpler score based on a Cox regression. This may not be very surprising, as the advantage of more complex machine learning methods primarily becomes apparent with larger data sets.

**Table 4 | Performance of the final Cox score on the validation data set by different measures**

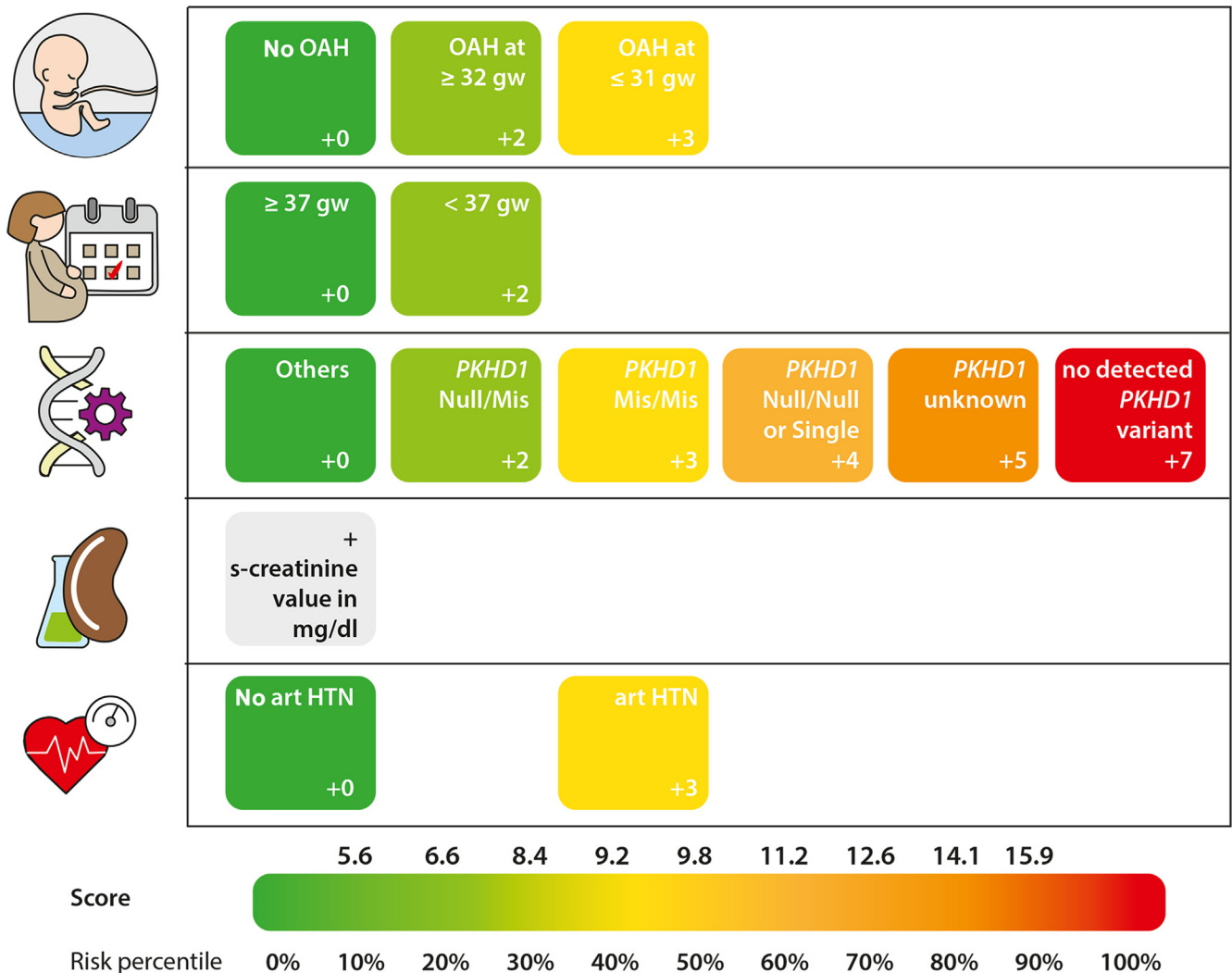
| Performance measure       | Value | 95% CI    |
|---------------------------|-------|-----------|
| Harrell's c               | 0.73  | 0.57–0.89 |
| Uno's C ( $\tau = 1$ yr)  | 0.84  | 0.75–0.94 |
| Uno's C ( $\tau = 3$ yr)  | 0.81  | 0.72–0.90 |
| Uno's C ( $\tau = 10$ yr) | 0.72  | 0.61–0.83 |
| Uno's C ( $\tau = 18$ yr) | 0.68  | 0.56–0.79 |
| Royston's D               | 1.12  | 0.50–1.74 |

CI, confidence interval.

Harrell's c is the primary performance measure. Uno's C is comparable to Harrell's c index but only concerns event times up to a certain follow-up time  $\tau$ . Royston's D can be interpreted as the log hazard ratio between the high- and low-risk group.

Our scoring approach is straightforward and can thus be applied in many centers. The scoring does not require a complicated calculation and gives clear-cut groups. Furthermore, we applied the developed score to an independent validation data set, obtaining an unbiased and reliable estimate of its prediction performance. This is critical for applying and interpreting the score in practice. Patients on a medium or high score percentile may have a particular benefit from inclusion in future clinical trials.

For daily clinical life, we added a categorization into risk groups to our score. The data from our validation cohort suggest that a pragmatic *post hoc* categorization into a combined “low-risk” subgroup (subgroups 1 and 2) and a combined “high-risk” subgroup (subgroups 3 and 4) may be helpful in clinical practice as events of KRT in the first 12 months of life were only observed in subgroups 3 and 4. The categorization into risk groups based on the score result may especially be helpful to identify patients who are at a very low risk of rapid progression to kidney failure early in life and can thus rely on current symptomatic treatment. Families of children assigned to risk group 1 or 2 may be informed that



**Figure 5 | Summarizing overview of the prognostic score indicating numbers to be summed up according to clinical and genetic presentation at the age of 2 months and indication of the risk percentiles according to the score.** art HTN, arterial hypertension; gw, gestational weeks; Mis, Missense; OAH, oligo- or anhydramnios.

the risk for the need of KRT within the first 12 months of life seems low. Children assigned to risk group 3 or 4 can be considered to be at major risk of early kidney failure.

From a genotype-phenotype point of view, it may seem surprising that patients with biallelic null variants in *PKHD1* do not receive the highest score in the genetic subsection and that patients without detection of variants in *PKHD1* receive a high score. It needs to be kept in mind that the score is based on real-world data and is intended to be widely applied to patients with the clinical diagnosis of ARPKD at the age of 2 months. Many patients with biallelic null variants in *PKHD1* will already have progressed to KRT at this age or will have passed away perinatally.<sup>7</sup> We have previously shown that non-*PKD1* subgroups of patients with ARPKD-mimicking phenotypes show worse kidney survival than patients with *PKHD1* variants explaining why molecular diagnosis of specific ARPKD-*PKHD1* subtypes may lead to a better score.<sup>36</sup>

A strength of our study is the international collaborative approach using longitudinal data of kidney disease in a large number of patients with ARPKD. To our knowledge, the presented cohort is by far the largest cohort of deeply characterized patients with ARPKD. The data represent real-world findings in multiple mainly European centers. We include a high percentage of patients with genetic analysis even though not all patients underwent genetic testing. Strategies and availability of genetic testing differ in participating centers from different countries. Patients with more rapid initial disease courses may have received more genetic workup. In patients without genetic testing or without proof of disease-causing *PKHD1* variants, we cannot exclude the possibility of phenocopies or currently unknown genetic causes of ARPKD.<sup>36</sup> Additional limitations encompass the variable number of informative cases per item, especially in variables within a short time frame. Furthermore, the number of patients per center and country vary, patients are mainly from

Europe with limited ethnical diversity, and there are differences in follow-up periods. There may have been selection biases as very severely affected children with early death may not have been included and less severely affected patients or patients with a predominant liver phenotype may have been under-represented due to the participation of many tertiary pediatric nephrology centers.

As ARPKD is a rare disease with substantial phenotypic variability, identification of an appropriate external cohort for validation is a major challenge. Our data are generated with internal validation for a cohort of patients mainly being treated in European centers. We also applied the score to a limited number of patients identified after the initial development and validation of the score with consistent results (Supplementary Table S2). Future work will have to validate the findings in independent health care settings and with more patients from non-European descent.

In summary, we deeply characterize the clinical course of kidney disease in childhood and adolescence with ARPKD. We characterize kidney survival in subcohorts and for the first time describe eGFR courses in a large cohort and in subcohorts of patients with ARPKD. Using these data, we establish a novel prediction tool for early kidney disease in ARPKD that can be widely used in the clinical setting and will help to identify patients for clinical trials on the basis of easily obtainable markers.

## APPENDIX

### Additional collaborators within ARegPKD consortium

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## DISCLOSURE

DH reports personal payments for various activities and research grants from Kyowa Kirin and Chiesi. FS reports consulting fees from Otsuka. MCL reports payments from Otsuka for advisory board activity as a representative of the University Hospital Cologne. All the other authors declared no competing interests.

## DATA STATEMENT

Clinical data sets of participating patients are not openly available, as the private nature in these data sets would potentially make individuals identifiable. Original data are available from the authors on reasonable request. The code for the Cox model without inclusion of clinical data can be found at <https://github.com/s-kilian/arpkd-kidney-survival>

**prediction.** Information on the random survival forest model containing clinical data can be provided on reasonable request.

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Supplementary material is available online at [www.kidney-international.org](http://www.kidney-international.org).

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