

The impact of small kidneys

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Abstract

Background Small kidneys due to renal hypodysplasia (RHD) result from a decrease in nephron number. The objectives of this study were to identify clinical variables that determine long-term renal outcome in children with RHD and to define the role of kidney size as a predictor of developing end-stage renal disease (ESRD).

Methods This was a single-center retrospective cohort analysis. The primary outcome was development of ESRD. We identified 202 RHD cases, with 25 (12 %) reaching ESRD at mean age of 8.9 (± 6.6) years.

Results Children with RHD with a known genetic syndrome had the smallest kidneys while those with posterior urethral valves (PUV) had the largest kidneys at diagnosis. Cases with bilateral RHD were most likely to develop ESRD. Younger gestational age (OR 0.8, CI 0.69–0.99, $p=0.05$), smaller kidney size at diagnosis (OR 0.13, CI 0.03–0.47, $p=0.002$), lower best-estimated glomerular filtration rate (eGFR) (OR 0.74, CI 0.58–0.93, $p=0.01$), proteinuria (OR 1.03, CI 1.01–1.05, $p<0.001$) and high blood pressure (OR 1.02, CI 1.01–1.04, $p=0.01$) were associated with development of ESRD, while

kidney size at diagnosis was independently associated with ESRD (HR 0.03, CI 0.01–0.72, $p=0.043$).

Conclusions In children with RHD, kidney size at diagnosis predicts the likelihood of developing ESRD.

Keywords Renal hypodysplasia · Pediatric · Outcomes · End-stage renal disease

Introduction

Chronic kidney disease (CKD) is a serious health problem that has become an enormous medical burden worldwide. Up to 60–70 % of children with CKD have congenital anomalies of the kidney and urinary tract (CAKUT) [1, 2]. CAKUT is a group of heterogeneous diseases, with different causes, natural histories, and rates of progression. Children with small and/or dysplastic kidneys have a form of CAKUT collectively referred to as renal hypodysplasia (RHD) [3]. The NIH-funded Chronic Kidney Diseases in Children (CKiD) natural history study found that isolated RHD accounted for ~20 % of all CKD cases, while another 30–40 % have RHD in association with anomalies of the lower urinary tract [4].

RHD may be due to a congenital decrease in the normal number of nephrons, or to renal dysplasia due to abnormal kidney development. The causes of RHD are diverse, including mutations in genes that exclusively affect normal kidney development, genetic syndromes caused by gene mutations that affect the development of multiple organs, and exposure to nephrotoxic environmental factors during the critical phases of kidney development in utero. Genomic disorders have been identified in 23 % of RHD cases with multiple congenital malformations and in 15 % of individuals with isolated urinary tract anomalies [5].

Most children with CKD experience a progressive decline in kidney function over time. The different forms of CKD

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progress at different rates, with CKD due to glomerulonephritis progressing more rapidly than that caused by congenital anomalies of the kidney [6]. The rate of decline of kidney function among patients with RHD is highly variable and the factors that determine outcome are still poorly understood.

The primary objective of this study was therefore to define the clinical variables that determine long-term renal outcome in RHD, and in particular whether kidney size at the time of initial diagnosis predicts ESRD risk.

Patients and methods

This study was a retrospective cohort analysis approved by the Research Ethics Board of the University of British Columbia. The requirement for informed consent was waived as the data were obtained by a retrospective chart review and were de-identified.

Identification of cases

Eligible cases with the ICD-9 diagnoses of renal dysplasia or RHD were identified from the British Columbia Children's Hospital (BCCH) Nephrology Clinic datasets from 1983–2013. Inclusion criteria for this study were: (1) age at diagnosis between 0 and 18 years, (2) postnatal diagnosis of RHD by ultrasound scan, where RHD was defined as a unilateral or bilateral renal length or parenchymal volume <5th percentile for body length or weight, respectively. Absolute renal measurements were obtained from the ultrasound reports or from the actual scan, if not reported. Renal parenchymal volume was calculated using the formula $mid\text{-transverse length} \times width \times depth \times 0.523$ as an estimation of the volume of an ellipsoid [7]. The length and volume data were compared to published renal length/body height and volume/body weight nomograms [7–9]. Contralateral compensatory renal growth (CRG) was defined as a renal length or volume >95th percentile for body length or weight, respectively. Renal measurements were obtained at each renal ultrasound. If multiple ultrasounds were performed in a case, the time at which RHD or RHD and CRG was first noted was designated the time of diagnosis. Exclusion criteria included patients with multicystic dysplastic kidney disease, a solitary kidney (renal agenesis), and cases where clinical data or kidney ultrasounds were unavailable.

The outcome of children with CAKUT with and without RHD has been difficult to ascertain because of the clinical and genetic heterogeneity of the group. To minimize the effects of heterogeneity and to determine other clinical features that are associated with poor outcomes, the study cases were classified using a modified RHD/CAKUT stratification method that has been previously published [5]. Cases with *isolated RHD* had at least one small kidney in the absence of any other

discernible clinical anomalies; those with *RHD and PUV* had at least one small kidney in the presence of bladder outlet obstruction due to posterior urethral valves (PUV) but no other anomalies outside the urinary tract; cases with *RHD and other urogenital anomalies* had at least one small kidney with associated other lower urinary tract anomalies but without PUV; *RHD and extra-urogenital anomalies* cases had at least one small kidney in the absence of any other urinary tract anomalies but with identified anomalies outside the urinary tract; and cases with *RHD and genetic syndromes* had at least one small kidney as part of a defined genetic syndrome which had been diagnosed by clinical features and/or through genetic testing.

To determine the influence of kidney size on outcome, we also classified cases as having *bilateral RHD* when both kidneys measured below the 5th percentile for volume, *unilateral RHD* when one kidney measured below the 5th percentile for volume and the contralateral kidney measured between the 5th and 95th percentile, and *unilateral RHD and CRG* when one kidney measured below the 5th percentile for volume and the contralateral kidney measured above the 95th percentile. To further reduce the heterogeneity within each group, we also separated the cases with PUV from the *bilateral*, *unilateral*, and *unilateral and CRG* groups for the analyses.

Data collection

Patient data were obtained from clinical records and managed using the Research Electronic Data Capture (REDCap) data management system hosted at the Child and Family Research Institute [10]. Clinical biomarkers included gestational age, birth weight, age at diagnosis, and duration of follow-up. Renal function biomarkers included estimated glomerular filtration rate (eGFR), measured GFR (mGFR), and best-recorded eGFR (eGFR^{best}) and mGFR (mGFR^{best}). Serum creatinine levels have been measured enzymatically at our institution since 1987, and are presently analyzed with the Vitros E-950/250 (Ortho Clinical Diagnostics, Janssen-Ortho, Inc). In our laboratory, the IDMS-referenced creatinine measurement was lower than previously reported enzymatic creatinine levels. Therefore our laboratory developed a formula to convert pre-2006 levels to IDMS-referenced creatinine: $standardized [IDMS\text{-referenced}] creatinine = (uncorrected Vitros creatinine - 9.588) / 1.0342$. For children older than 1 year of age, eGFR was calculated using the modified Schwartz formula $36.5 \times height / serum\ creatinine (umol/l)$ (or $k=0.41$, using mg/dl for serum creatinine concentration units), as previously described [11]. For children less than 1 year of age, a modified eGFR formula was used, with the k value adjusted for term ($k=0.45$, using mg/dl for serum creatinine concentration) and preterm ($k=0.33$) infants, as published [12, 13]. mGFR was determined using a two-point single injection of

^{99m}Tc -diethylenetriaminepentaacetic acid [14]. CKD was defined as an eGFR of less than 60 ml/min/1.73 m².

Recognizing the drawbacks and challenges of collecting multiple measurements over time in a retrospective review, blood pressure (BP) and proteinuria were quantified and expressed as “percentage load”, defined as the total number of abnormal measurements divided by the total number of measurements per case. High BP was defined as a systolic and/or diastolic BP >95th percentile for sex and age [15, 16]. The majority of BP measurements were performed as single measurements done by either oscillometry or by auscultation. Proteinuria was defined as a random urine protein >0.25 g/l, as determined by the Bayer/Siemens 2000 analyzer (Siemens Healthcare Diagnostics Ltd). These “load” methods have not been validated but were derived expressly for the purposes of this study. A limitation of this retrospective collection of BP and proteinuria data is that they were not always collected the same way, at the same time, and in a standardized fashion.

The size of both kidneys was calculated to estimate total kidney mass. A renal hypodysplasia index (RHDI) was developed using renal lengths (RHDI^{length}) and renal volumes (RHDI^{volume}). RHDI^{length} was defined as the average of the lengths of both kidneys (cm) divided by body length (cm) at the time of the assessment. Given the potential confounding effect of hydronephrosis on kidney length, kidney volume was also calculated using the three planar measurements of kidney tissue (see above). The kidney volume therefore estimated the actual renal parenchymal mass, irrespective of the degree of hydronephrosis. RHDI^{volume} was defined as the average of the volumes of both kidneys (cm³) divided by body weight (kg).

Definition of outcomes

The development of ESRD (initiation of dialysis or a pre-emptive renal transplantation) was defined as the primary outcome. The secondary outcome was development of CKD (eGFR 15–59 ml/min/1.73 m²).

Statistical analyses

Normally distributed data were expressed as means and standard deviation (SD), non-normally distributed data as medians and interquartile range (IQR), and categorical variables as proportions. Differences between the groups were analyzed by two-sided Student's *t* tests, Mann–Whitney and Kruskal–Wallis tests for significance, and by Chi-square tests where appropriate, with $p < 0.05$ as the threshold for statistical significance.

Kaplan–Meier analysis was used to determine the ESRD-free survival according to CAKUT/RHD category, and according to whether the RHD was bilateral, unilateral, or unilateral with CRG. Statistical significance was defined as a log-rank value <0.05.

Univariate logistic regression was used to identify clinical variables associated with ESRD and CKD. Multivariate Cox regression analysis was performed to determine which variables were independently associated with the primary outcome of ESRD using those variables that were significantly different between the ESRD and non-ESRD groups and that were associated with ESRD using bivariate analyses. All statistical analyses were performed using SPSS software, version 22 (SPSS Inc., Chicago, IL, USA).

Results

Identification of cases

A total of 202 cases of RHD were selected from the initial group of 429 RHD-coded patients (Supplemental Figure 1). This cohort included 39 cases with *isolated RHD* (19 % of the cohort), 62 cases with *RHD and PUV* (31 % of the cohort), 50 with *RHD and other urogenital anomalies* (25 % of the cohort), including vesicoureteral reflux ($n=33$), hydronephrosis ($n=38$) and ureteric anomalies ($n=14$), 27 cases with *RHD and extra-urogenital anomalies* (13 % of the cohort) and 24 cases (12 % of the cohort) with *RHD and genetic syndromes* (Table 1 and Supplemental Table 1).

Clinical characteristics

The clinical characteristics of the groups are summarized in Tables 1 and 2. The mean gestational age (GA) for the cohort was 37.8 (3.3) [mean (SD)] weeks with a mean birth weight of 3.1 (0.7) kg. The RHD group with urogenital anomalies other than PUV was significantly older and larger at birth than the other RHD groups (Table 1), while the *bilateral RHD* group was significantly younger at birth than the *unilateral, unilateral and CRG*, and *PUV* groups (Table 2). The majority of patients were males (71 %), reflecting the incidence of PUV, which is a disorder of males. The mean age at follow-up and follow-up duration for the entire cohort were 10.1 (5.9) and 5.5 (4.7) years, respectively. The PUV group was significantly younger at diagnosis and had a significantly longer follow-up period when compared to the other RHD groups, both when categorized according to the CAKUT classification (Table 1) and when categorized according to kidney size (Table 2).

Renal hypodysplasia index

RHDI^{volume} correlated well with RHDI^{length} in cases without hydronephrosis. In cases with hydronephrosis, the renal length overestimated the renal parenchymal volume (Fig. 1); therefore, further analyses in this report use RHDI^{volume} at diagnosis. RHDI^{volume} also decreased slightly, yet significantly, as the age at diagnosis increased ($r=-0.39$, $p < 0.001$) (Fig. 2).

Table 1 RHD clinical phenotypes based on congenital anomalies of the kidney and urinary tract (CAKUT) classification ($n=202$)

| | Isolated RHD | RHD and PUV | RHD and other urogenital anomalies | RHD and extra-urogenital anomalies | RHD and genetic syndrome |
|--|--------------|-------------|------------------------------------|------------------------------------|--------------------------|
| Cases, n (%) | 39 (19 %) | 62 (31 %) | 50 (25 %) | 27 (13 %) | 24 (12 %) |
| GA, weeks | 37.1 (4.2) | 37.3 (2.2) | 39.2 (3.0)* | 37.0 (4.4) | 38.8 (2.4) |
| BW, kg | 2.9 (.9) | 3.2 (.6) | 3.3 (.6)* | 2.7 (.9) | 3.1 (.4) |
| Sex, male | 21/39 | 62/62+ | 34/50 | 14/27 | 13/24 |
| Age at diagnosis, years | 7.6 (5.2) | 3.8 (4.6)* | 4.7 (5.4) | 4.5 (4.4) | 7.4 (5.6) |
| Length of follow-up, years | 3.4 (2.9) | 8.3 (5.7)* | 5.2 (4.2) | 4.1 (2.4) | 5.2 (4.8) |
| Age at follow-up, years | 11.0 (5.8) | 9.7 (6.0) | 10.0 (6.2) | 8.6 (5.4) | 11.7 (5.3) |
| RHDI ^{volume} at diagnosis | 1.7 (.7) | 2.0 (.7) | 2.0 (.8) | 1.8 (1.0) | 1.5 (.5)* |
| eGFR ^{best} (ml/min/1.73 m ²) | 81 (35) | 73 (35) | 70 (36) | 78 (36) | 70 (35) |
| mGFR ^{best} (ml/min/1.73 m ²) | 79 (36) | 87 (38) | 75 (32) | 85 (21) | 70 (32) |
| CKD | 10/39 | 27/62 | 17/50 | 8/27 | 12/24 |
| ESRD | 3/39 | 12/62 | 7/50 | 1/27 | 2/24 |

Values for GA, BW, age, RHDI, and GFR are mean (SD)

Significant differences among groups by *ANOVA and + Chi-square analysis

GA gestational age; BW birth weight; RHD renal hypodysplasia; PUV posterior urethral valves; RHDI renal hypodysplasia index; eGFR estimated glomerular filtration rate; mGFR measured glomerular filtration rate; CKD chronic kidney disease; ESRD end-stage renal disease

When the cohort was stratified as RHD and PUV, bilateral RHD, unilateral RHD, or unilateral RHD associated with CRG, the increased number of cases with CRG rather than the specific RHD category accounted for the higher RHDI in the younger age group (Fig. 2).

When the RHDI^{volume} at diagnosis was compared across the CAKUT/RHD diagnostic categories, the RHD group with genetic syndromes had significantly smaller kidneys (ANOVA $p=0.027$) (Table 1). Not surprisingly the RHDI

was lowest in cases with bilateral RHD and highest in RHD with contralateral CRG (ANOVA, $p<0.001$) (Table 2).

Correlation of kidney size with kidney function

The eGFR^{best} was calculated for each case using the lowest serum creatinine values obtained during the course of follow-up. eGFR^{best} correlated well with corresponding mGFR^{best} values for individual patients ($r=0.70$, $p<0.001$) and among

Table 2 RHD clinical phenotypes based on kidney size ($n=202$)

| | PUV | Bilateral | Unilateral | Unilateral and CRG | Total |
|--|-------------|-------------|------------|--------------------|------------|
| Cases (%) | 62 | 44 | 72 | 24 | 202 |
| GA, weeks | 37.3 (2.2) | 36.8 (3.9)* | 38.2 (3.8) | 39.7 (2.6) | 37.8 (3.3) |
| BW, kg | 3.2 (0.6) | 2.9 (0.7) | 3.0 (0.8) | 3.3 (0.7) | 3.1 (0.7) |
| Sex, male | 62 (100)+ | 27 (61) | 39 (54) | 16 (67) | 144 (71) |
| Age at diagnosis, years | 3.8 (4.6)* | 5.6 (5.7) | 6.5 (5.2) | 4.9 (5.1) | 5.3 (5.2) |
| Length of follow-up, years | 8.3 (5.7) * | 3.8 (3.5) | 4.7 (4.1) | 5.0 (3.2) | 5.5 (4.7) |
| Age at follow-up, years | 9.7 (6.0) | 9.5 (6.0) | 11.0 (5.6) | 9.8 (6.4) | 10.1 (5.9) |
| RHDI ^{volume} at diagnosis | 2.0 (0.7) | 1.1 (0.4)* | 1.9 (0.5) | 2.9 (0.9) | 1.9 (0.8) |
| eGFR ^{best} (ml/min/1.73 m ²) | 73 (35) | 57 (34)* | 82 (32) | 95 (34) | 74 (36) |
| mGFR ^{best} (ml/min/1.73 m ²) | 87 (38) | 61 (31)* | 81(26) | 99 (32) | 80 (33) |
| CKD (%) | 27 (45) | 27 (61)+ | 17 (30) | 3 (16) | 74 (37) |
| ESRD (%) | 12 (19) | 9 (21)+ | 4 (6) | 0 (0) | 25 (12) |

Values for GA, BW, age, RHDI, and GFR are mean (SD)

Significant differences among groups by *ANOVA, +Chi-square analysis

PUV posterior urethral valves; CRG compensatory renal growth; GA gestational age; BW birth weight; RHDI renal hypodysplasia index; eGFR estimated glomerular filtration rate; mGFR measured glomerular filtration rate; CKD chronic kidney disease; ESRD end-stage renal disease

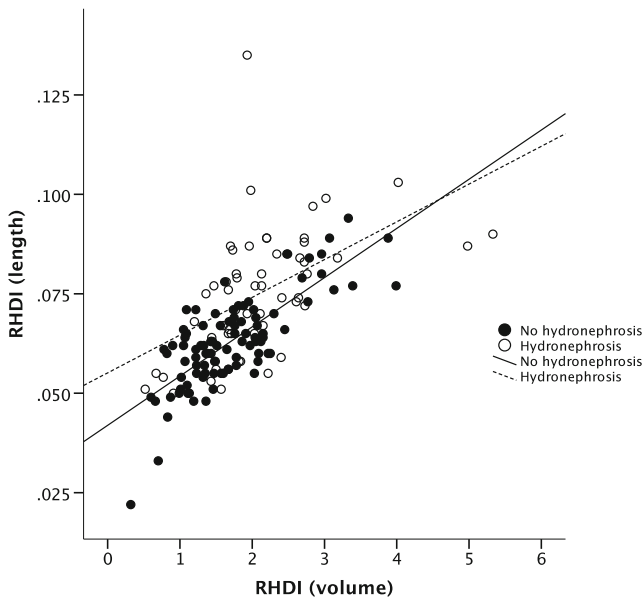


Fig. 1 Kidney parenchymal volumes in renal hypodysplasia (RHD). Scatter plot of the correlation of renal parenchymal volumes (RHDl^{volume}) (see Methods for details of calculation) and renal lengths (RHDl^{length}) for all kidneys from all cases in the cohort. For the entire cohort, kidney parenchymal volume correlates significantly with kidney lengths ($r = 0.67, p < 0.001$). However, the regression line for the hydronephrosis group ($r = 0.52, p < 0.001$) lies above that for the group without hydronephrosis ($r = 0.78, p < 0.001$), suggesting that kidney lengths in cases with hydronephrosis (*open circles*) overestimated kidney parenchymal volumes

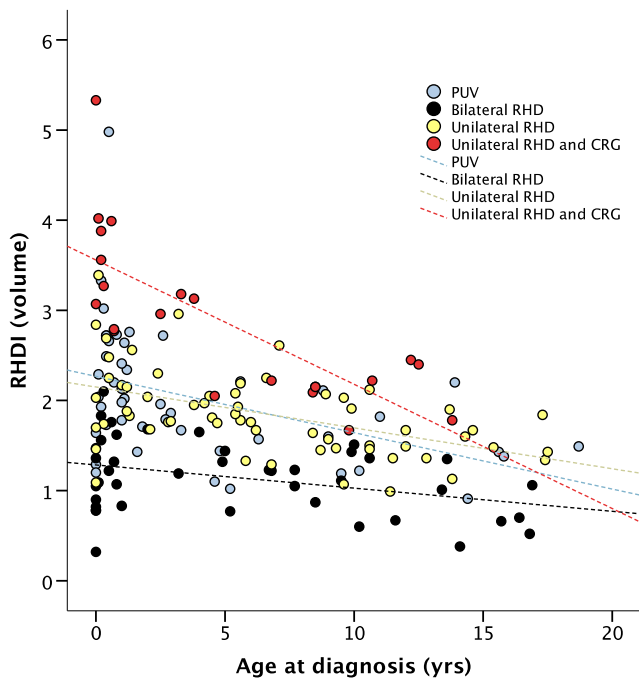


Fig. 2 RHDl^{volume} decreases with age at diagnosis. RHDl^{volume} for each case at the time of diagnosis stratified according to whether the RHD was associated with PUV, bilateral, unilateral, or unilateral associated with CRG. RHDl^{volume} decreases as the age at diagnosis increases; explained in part by the increased proportion of cases with CRG in the younger cases ($r = -0.39, p < 0.001$). RHD renal hypodysplasia, PUV posterior urethral valves, CRG compensatory renal growth

groups (Tables 1 and 2). The eGFR^{best} and mGFR^{best} for the whole cohort were 74 (36) and 80 (33) ml/min/1.73 m², respectively. There were no significant differences in the eGFR^{best} or mGFR^{best} among the RHD/CAKUT sub-groups, and all mean values were <90 ml/min/1.73 m², classified as

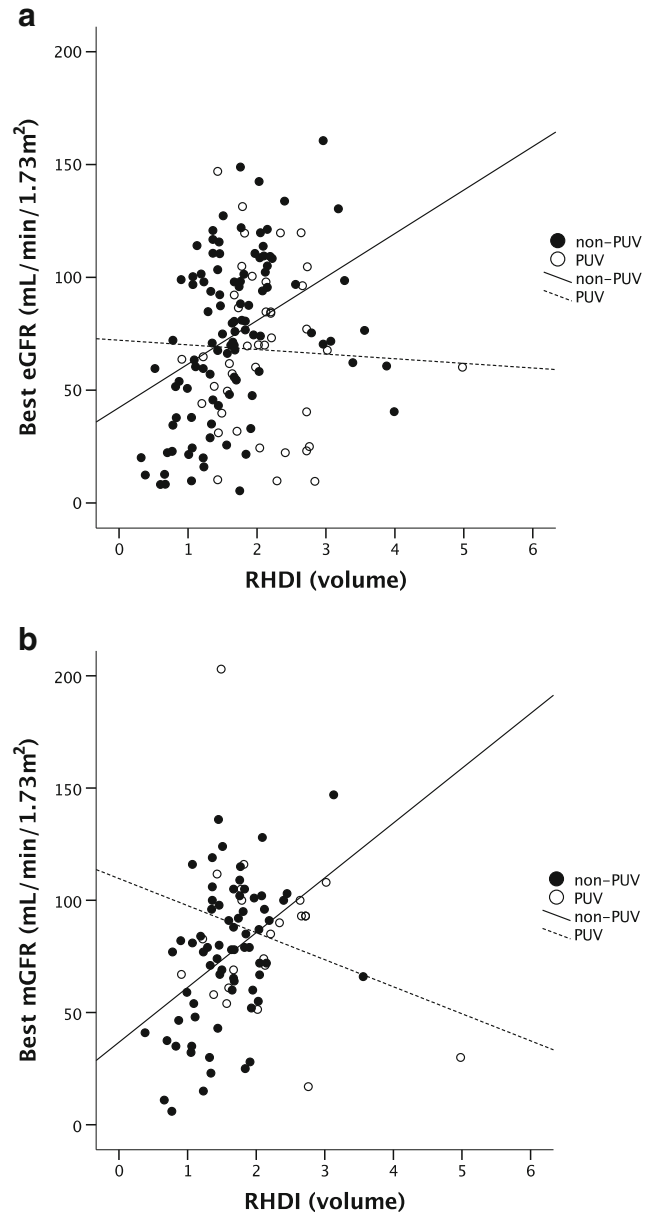
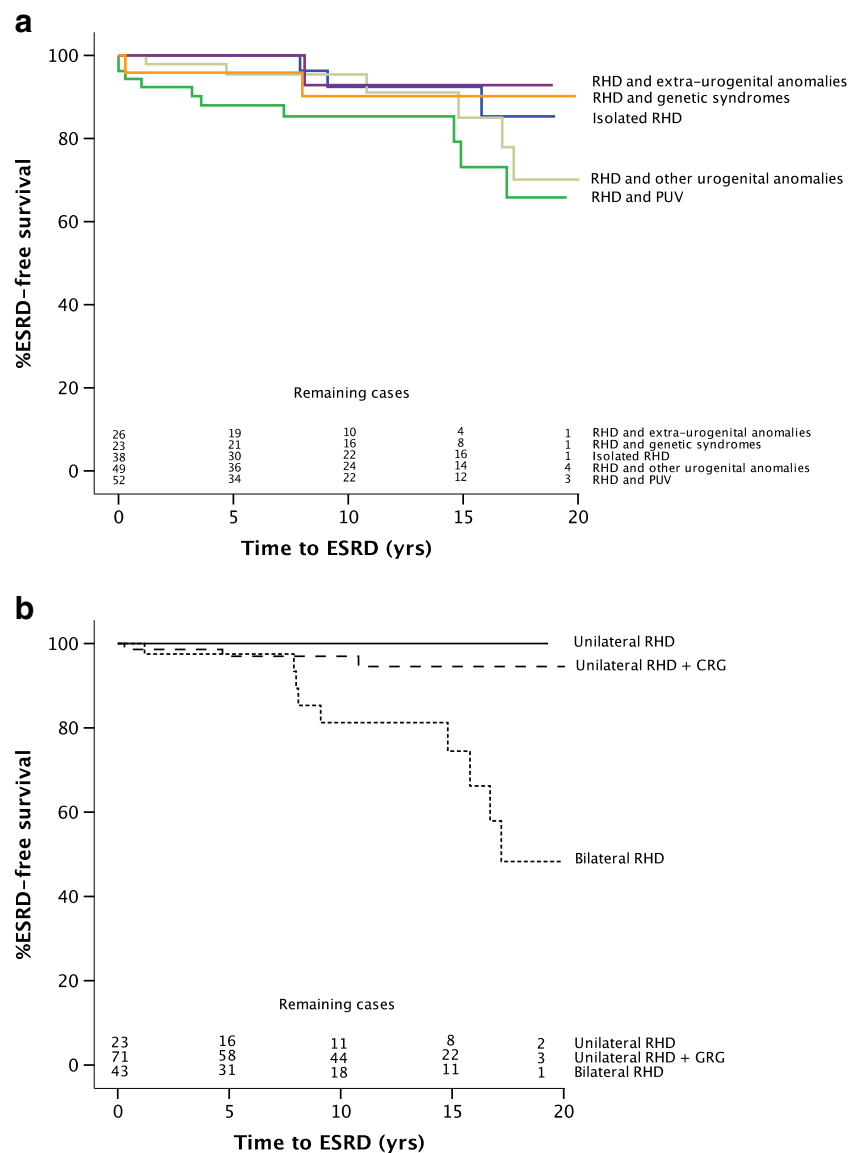


Fig. 3 Correlation of RHDl^{volume} and GFR. **a** RHDl^{volume} at diagnosis for the whole cohort demonstrated a weak significant correlation with the eGFR^{best} (see text). However, when the cases were grouped into those without PUV (non-PUV) and those with PUV (PUV), there was a significant correlation between RHDl^{volume} and eGFR^{best} in the non-PUV group ($r = 0.39, p < 0.001$), but not in the PUV group ($r = -0.04, p = 0.80$). **b** RHDl^{volume} at diagnosis for the whole cohort did not correlate with the mGFR^{best} (see text). However, when the cases were grouped into those without PUV (non-PUV) and those with PUV (PUV), there was a significant correlation between RHDl^{volume} and mGFR^{best} in the non-PUV group ($r = 0.43, p < 0.001$), but not in the PUV group ($r = -0.28, p = 0.20$). RHD renal hypodysplasia, PUV posterior urethral valves, GFR glomerular filtration rate

CKD stage 2 (Table 1). As a group, cases with *bilateral RHD* had significantly lower $eGFR^{best}$ and $mGFR^{best}$ than the other three groups ($p < 0.001$, ANOVA) (Table 2), suggesting a relationship between kidney size and function.

We next studied the relationship of renal size ($RHDI^{volume}$) and renal function. For individual cases in the entire cohort, $RHDI^{volume}$ correlated modestly with $eGFR^{best}$ ($r = 0.24$, $p = 0.004$) but not with $mGFR^{best}$ ($r = 0.19$, $p = 0.06$). However when the cohort was divided into groups without PUV (non-PUV) and with PUV (PUV), $RHDI^{volume}$ correlated well with $eGFR^{best}$ and $mGFR^{best}$ in the non-PUV group ($r = 0.39$, $p < 0.001$ and $r = 0.43$, $p < 0.001$ respectively), but not in the PUV group ($r = -0.04$, $p = 0.80$ and $r = -0.28$, $p = 0.20$, respectively), suggesting the possibility of a confounding effect of obstructive dysplasia on the correlation of renal parenchymal mass and kidney function (Fig. 3a, b).

Fig. 4 End-stage renal disease-free survival. **a** When the RHD cohort was categorized by CAKUT/RHD groups, there were no significant differences in ESRD-free survival to 19 years of age. **b** When the RHD cohort was categorized by unilateral or bilateral RHD (with cases of PUV excluded), cases with bilateral RHD had significantly worse ESRD-free survival by 19 years of age (log rank $p < 0.001$). Kaplan–Meier analysis was used to determine the ESRD-free survival for the entire study cohort, and Cox regression analysis to compare outcomes when the cases were stratified by RHD sub-groups *RHD* renal hypodysplasia, *CAKUT* congenital anomalies of the kidney and urinary tract, *PUV* posterior urethral valves, *ESRD* end-stage renal disease



Within the entire RHD cohort, 12 and 41 % went on to develop ESRD and CKD, respectively. Among the five RHD/CAKUT sub-groups the percentages of cases that developed ESRD or CKD was similar (Table 1). However, the risk of developing ESRD (21 %) and CKD (61 %) was significantly higher among cases with *bilateral RHD* compared to the other groups over the period of follow-up (Table 2).

Modifiable characteristics

Proteinuria and hypertension are independent predictors of poor outcome in a number of different kidney diseases [17, 18] and are potentially modifiable. The percentage loads for proteinuria and high blood pressure for the whole cohort were 25 and 21 %, respectively, with no significant differences among the RHD groups categorized according to CAKUT classification. However, the cases with *bilateral RHD* had a

Table 3 Univariate logistic regression

| | ESRD | | CKD | |
|--|------------------|--------|------------------|--------|
| | OR (95 % CI) | P | OR (95 % CI) | P |
| GA | 0.83 (0.69–0.99) | 0.05 | 0.94 (0.84–1.06) | 0.33 |
| BW | 0.71 (0.24–2.08) | 0.52 | 0.59 (0.30–1.16) | 0.13 |
| Age at diagnosis | 1.14 (1.03–1.27) | 0.02 | 1.09 (1.02–1.17) | 0.01 |
| RHDI ^{volume} | 0.13 (0.03–0.47) | 0.002 | 0.26 (0.12–0.56) | 0.001 |
| eGFR ^{best} (ml/min/1.73 m ²) | 0.74 (0.58–0.93) | 0.01 | 0.86 (0.81–0.92) | <0.001 |
| mGFR ^{best} (ml/min/1.73 m ²) | 0.87 (0.79–0.96) | 0.01 | 0.89 (0.84–0.94) | <0.001 |
| Proteinuria* | 1.03 (1.01–1.05) | <0.001 | 1.05 (1.03–1.06) | <0.001 |
| High blood pressure* | 1.02 (1.01–1.04) | 0.01 | 1.01 (1.00–1.02) | 0.20 |

*load

GA gestational age; BW birth weight; RHDI renal hypodysplasia index; eGFR estimated glomerular filtration rate; mGFR measured glomerular filtration rate; CKD chronic kidney disease; ESRD end-stage renal disease; OR odds ratio; CI confidence interval

significantly increased proteinuria load (48 %) compared to the other groups ($p < 0.05$, Kruskal–Wallis test).

ESRD-free survival

By 19 years of age, 76 % of the RHD cohort was ESRD-free. However, CKD progressed at different rates among the different RHD CAKUT groups. In the RHD and PUV group, 66 % of the cases were ESRD-free at 19 years of age. Among the other sub-groups, 85 % of isolated RHD, 70 % of RHD and other urogenital anomalies, 93 % of RHD and extra-urogenital anomalies and 90 % of RHD and defined genetic syndromes cases were ESRD-free at 19 years of age (Fig. 4a). When stratified according to bilateral RHD, unilateral RHD, or unilateral RHD with CRG (and not including the PUV cases), 48, 96, and 100 % of cases were ESRD-free at 19 years of age, respectively (log rank $p = 0.001$) (Fig. 4b).

Regression analyses

After excluding cases with PUV, by univariate logistic regression analysis, RHDI^{volume}, eGFR^{best}, mGFR^{best}, and proteinuria were significantly associated with both the primary and secondary outcomes of ESRD and CKD, respectively (Table 3). Cases with larger kidneys at diagnosis were less likely to develop ESRD or CKD (OR 0.13 and 0.26, respectively). Cases with a higher eGFR^{best} were also less likely to develop ESRD or CKD (OR 0.74 and 0.86, respectively). Cases with proteinuria, on the other hand, were more likely to develop both outcomes (OR 1.03 for ESRD, 1.05 for CKD). Younger gestational age and high blood pressure were also associated with the development of ESRD in our cohort (Table 3). In the PUV group alone, only eGFR^{best} was associated with ESRD (OR 0.90, CI 0.84–0.96) and CKD (OR 0.95, CI 0.93–0.98), and proteinuria with CKD (OR 1.04, CI 1.01–1.06).

Based on the univariate analysis, we included gestational age, RHDI^{volume}, eGFR^{best}, proteinuria and high blood pressure load in a multivariate Cox regression model. Only RHDI^{volume} was independently associated with the development of ESRD in our RHD cases, with a HR of 0.03 (Table 4).

Discussion

Nephron number at birth is an important determinant of long-term kidney outcome. A reduction in nephron number results in glomerular hyperfiltration, glomerular hypertrophy, progressive glomerular scarring and interstitial fibrosis, and is a risk factor for the development of CKD and ESRD [19–23]. RHD is an important cause of CKD with a highly variable prognosis. It is associated with a decrease in nephron endowment, manifests as one or two small kidneys, and is a well-recognized cause of CKD in children. There are several known and many unknown causes of human RHD and CAKUT. In some cases, RHD is an isolated anomaly, while in others it is associated with urogenital anomalies, with anomalies in other organ systems and with defined genetic syndromes.

Table 4 Multivariate Cox regression analysis

| | HR (95 % CI) | P |
|------------------------|------------------|------|
| GA | 0.82 (0.61–1.09) | 0.17 |
| RHDI ^{volume} | 0.03 (0.01–0.72) | 0.03 |
| Proteinuria* | 1.00 (0.97–1.03) | 0.95 |
| High blood pressure* | 1.00 (0.95–1.06) | 0.98 |

*load

GA gestational age; RHDI renal hypodysplasia index; HR hazard ratio; CI confidence interval

Five distinct RHD/CAKUT clinical sub-categories were used to analyze renal outcomes in our heterogeneous pediatric patient cohort. The patients in each sub-group had an abnormally low mean GFR value (less than 90 ml/min/1.73 m², measured as eGFR or mGFR), placing them in CKD category 2 or higher. However, there were no differences among the five sub-groups in the proportions of cases that developed CKD or ESRD, nor were there significant differences in the kidney survival curves for each group. Therefore, the specific CAKUT/RHD clinical category was not a good predictor of kidney outcome.

Our data highlight that RHD is not a benign condition, with 37 % of the cohort developing CKD (defined as an eGFR <60 ml/min/1.73 m²) and 12 % progressing to ESRD. These results are consistent with previous publications of long-term follow-up of cases of CAKUT, solitary functioning kidneys (SFK) and unilateral multicystic dysplastic kidneys (MCDK), with ESRD in 19 % of cases of CAKUT followed for greater than 30 years [3], signs of renal injury in up to 32 % and CKD in up to 4 % of cases with SFK [24, 25], and CKD in approximately 10 % of cases with MCDK [26].

We next evaluated the utility of kidney length and calculated volume measurements as surrogate estimates of nephron number and predictors of renal outcomes in pediatric RHD. Patients from all five clinical sub-categories were combined and classified on the basis of whether they had PUV, unilateral disease, bilateral disease, or unilateral disease with compensatory hypertrophy in the contralateral kidney. Among those with bilateral RHD and significantly smaller kidneys at diagnosis (as measured by RHD^{volume}), a significantly higher proportion developed CKD (61 %) and ESRD (21 %). Furthermore, our data suggest a “nephron-mass” dose-response relationship. While small kidney size, along with decreased gestational age, a low eGFR^{best} and the presence of proteinuria were individually associated with CKD and ESRD in our RHD cohort, only small kidney size (RHD^{volume}) was independently associated with ESRD in a multivariate model.

Cases of RHD associated with PUV deserve special consideration as an exception to this generalized association. Notably, the PUV group failed to demonstrate any significant correlation between kidney size, renal function, and long-term outcome. These data are consistent with findings in experimental models that demonstrate that, in addition to reducing nephron number, congenital urinary tract obstruction causes kidney dysplasia and fibrosis that contribute to the poor long-term outcome [27, 28]. Although the degree of loss of functional kidney parenchymal mass has been shown to correlate with development of ESRD in boys with PUV [29], the findings in this study highlight that the relationship between kidney size and renal function in boys with PUV is complex and requires further study.

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