Title
Primary causes of kidney disease and mortality in dialysis-dependent children.

Journal
Pediatric Nephrology, 35(5)

Authors
Okuda, Yusuke
Soohoo, Melissa
Ishikura, Kenji
et al.

Publication Date
2020-05-01

DOI
10.1007/s00467-019-04457-7

Peer reviewed

HHS Public Access

Author manuscript

Pediatr Nephrol. Author manuscript; available in PMC 2022 February 25.

Published in final edited form as:

Pediatr Nephrol. 2020 May ; 35(5): 851–860. doi:10.1007/s00467-019-04457-7.

Primary causes of kidney disease and mortality in dialysis-dependent children

Yusuke Okuda[1,2], **Melissa Soohoo**[1], **Kenji Ishikura**[2], **Ying Tang**[1], **Yoshitsugu Obi**[1], **Marciana Laster**[3,4], **Connie M. Rhee**[1], **Elani Streja**[1], **Kamyar Kalantar-Zadeh**[1]

[1]Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California Irvine, School of Medicine, Orange, CA

[2]Department of Pediatrics, Kitasato University School of Medicine, Kanagawa, Japan

[3]David Geffen School of Medicine at UCLA, Los Angeles, CA

[4]Division of Pediatric Nephrology, Mattel Children's Hospital at UCLA, Los Angeles, CA

Abstract

Background: Congenital anomalies of the kidney and urinary tract (CAKUT) is associated with slower progression to end-stage renal disease (ESRD) pre dialysis. However, little is known about associated mortality risks after transitioning to dialysis.

Methods: This retrospective cohort study of 0–21 year-old incident dialysis patients from the United States Renal Data System starting dialysis between 1995–2016, examined the association of CAKUT vs. non-CAKUT with all-cause mortality, using Cox regression adjusted for case-mix variables. We examined mortality risk associated with 14 non-CAKUT vs. CAKUT ESRD etiologies.

Results: Among 25,761 patients, median (interquartile range) age was 17 (11–19) years, and 4,780 (19%) had CAKUT. CAKUT was associated with lower mortality, with adjusted hazard ratio (aHR) 0.72 (95%CI, 0.64–0.81) (reference: non-CAKUT). In age-stratified analyses, CAKUT vs. non-CAKUT aHRs (95%CI) were 0.66 (0.54–0.80), 0.56 (0.39–0.80), 0.66 (0.50–0.86) and 0.97 (0.80–1.18) among patients <6, 6-<13, 13-<18, and ≥18 years at dialysis

Address correspondence to: Kamyar Kalantar-Zadeh, MD, MPH, PhD, Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California Irvine, School of Medicine 101 The City Drive South, City Tower, Suite 400, Orange, CA 92868, USA. Tel: 714-456-5142 Fax: 714-456-6034, kkz@uci.edu.

Conflict of Interest

K.K.-Z. has received honoraria and/or support from Abbott, Abbvie, Alexion, Amgen, American Society of Nephrology, Astra-Zeneca, AVEO Oncology, Chugai, DaVita, Fresenius, Genentech, Haymarket Media, Hofstra Medical School, International Federation of Kidney Foundations, International Society of Hemodialysis, International Society of Renal Nutrition and Metabolism, Japanese Society of Dialysis Therapy, Hospira, Kabi, Keryx, Novartis, National Institutes of Health, National Kidney Foundation, OPKO, Pfizer, Relypsa, Resverlogix, Sandoz, Sanofi, Shire, Vifor, UpToDate, and ZSPharma.

Compliance with Ethical Standards

This study was approved by the Institutional Review Board of University of California Irvine with waiver of informed consent because the USRDS contains only deidentified information.

initiation, respectively. Among non-CAKUT ESRD etiologies, mortality associated with primary glomerulonephritis (aHR, 0.93; 95%CI 0.80–1.09) and focal segmental glomerulosclerosis (aHR, 0.89; 95%CI, 0.75–1.04) were comparable or slightly lower compared to CAKUT, whereas most other primary causes associated with higher mortality risk. While CAKUT group had lower mortality risk compared to non-CAKUT group patients with eGFR ≥5 mL/min/1.73m^2, CAKUT was significantly associated with higher mortality in patients with eGFR <5 mL/min/1.73m^2.

Conclusions: CAKUT is associated with lower mortality among children <18 years, but showed comparable mortality with non-CAKUT among patients ≥18 years old. ESRD etiology should be considered in risk assessment for children on dialysis.

Keywords

CAKUT; cause of end-stage renal disease; estimated glomerular filtration rate; propensity score matching; competing risk

Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) is a leading cause of chronic kidney disease (CKD) in children [1]. Although underlying causes of CKD in childhood, including CAKUT, are substantially different from those in adults, they are associated with CKD progression to end-stage renal disease (ESRD) in children [2] as well as in adults [3]. Even mild kidney abnormalities or injury in childhood may heighten risk of ESRD in adulthood [4].

Patients with CAKUT experience a relatively slower progression to ESRD than those with glomerulonephritis (GN) [2, 5, 6]. Rates of progression to ESRD also differ according the various causes of CAKUT, i.e. solitary kidney or smaller kidney are associated with a higher risk of ESRD compared to other forms of CAKUT [7, 8]. These observations highlight the importance of the underlying etiologies of kidney disease amongst pediatric CKD patients, with a central focus on CAKUT. Particular interest, however, has been placed on the progression to ESRD among pre-dialysis patients, and thus the knowledge of prognosis after ESRD transition is limited. In a study from the European ERA-EDTA registry of both pediatric and adult patients with ESRD including 4,765 CAKUT patients, CAKUT had favorable outcomes compared to those with non-CAKUT etiologies [9]. Yet as the median age of ESRD onset was 31 years old in this cohort, the information on children with ESRD is limited. A smaller study of 1,063 infants from the European ESPN/ERA-EDTA registry also showed non-CAKUT as a predictor of higher mortality compared to CAKUT after transition to dialysis [10]. However, the relationship between the cause of ESRD, particularly CAKUT, and mortality in children with ESRD remains unclear and understudied. Therefore, we conducted a retrospective cohort study of children and young adults on dialysis using data from the United States Renal Data System (USRDS) to evaluate mortality risk among patients with CAKUT vs. non-CAKUT causes of ESRD.

Methods

Study population and data sources

A total of 30,034 patients who were 21 years old or younger (range 0–21 years) and initiated dialysis between April 1, 1995 and April 30, 2016 were identified from the USRDS database. We excluded 838 patients who received <60 days of dialysis, 3,143 patients who received a kidney transplantation prior to dialysis initiation, and 292 patients with missing data on the cause of ESRD. Our final analytical cohort was comprised of 25,761 patients (Supplemental Fig. 1). Patients were followed from the time of dialysis initiation and were censored for transplantation, loss to follow-up, discontinuation of dialysis, or the end of follow-up (June 30, 2016), whichever occurred first.

Information on death, transplantation, age at initiation of dialysis, sex, race, ethnicity, initial dialysis modality, comorbidities, height, and serum creatinine (sCr) was obtained from the USRDS Patients file (PATIENTS), the Treatment History file (RXHIST), the Medical Evidence file (MEDEVID) which contains data from the Centers for Medicare and Medicaid Services Medical Evidence form (CMS 2728), and the Transplant file (TX).

We calculated estimated glomerular filtration rates (eGFRs) using the Schwartz formulas for children younger than 20 years old [11, 12] and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for patients aged 20 to 21 years old [13]. Height and sCr used to calculate eGFR were extracted from MEDEVID at ESRD onset. Data for sCr were restricted to those obtained within three months of dialysis initiation to calculate eGFR.

Primary cause of ESRD

We determined the primary cause of ESRD using data from the PATIENTS and MEDEVID files. Codes for primary disease were based on International Classification of Diseases, Ninth and Tenth Editions, Clinical Modification (ICD-9-CM and ICD-10-CM). We then categorized cause of ESRD into CAKUT and non-CAKUT. CAKUT consisted of congenital obstructive uropathies, renal hypoplasia/dysplasia/oligonephronia, prune belly syndrome, and chronic pyelonephritis/reflux nephropathy (Supplemental Table 1).

Statistical analysis

Baseline characteristics at the time of dialysis initiation for patients with CAKUT and non-CAKUT etiologies of ESRD were expressed as median (interquartile range) values and number (proportions) as appropriate. Differences in baseline characteristics between patients with CAKUT and non-CAKUT etiologies, as well as included and excluded patients, were compared with standardized differences, of which 80%, 50%, and 20% were considered large, medium, and small differences, respectively, and ≥10% was defined as meaningful imbalance, due to the large sample size of this study [14].

The primary outcome was all-cause mortality. Survival rates were estimated by the Kaplan-Meier method. Cox regressions were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). We examined the risk of CAKUT vs. non-CAKUT with mortality in unadjusted and case mix-adjusted models. Covariates in the case mix-adjusted model

included age at dialysis initiation, sex, race (White, Black, or Other Races), ethnicity (Hispanic or Non-Hispanic), Medicaid coverage as an indicator of socioeconomic status, initial dialysis modality (hemodialysis (HD), peritoneal dialysis (PD), or unknown), the year in which dialysis started, and five comorbidities (hypertension, heart disease, non-renal anomaly, malignancy, and diabetes).

We performed a number of sensitivity analyses to test the robustness of our results. We did a time-dependent Cox regression with transplantation as a time-varying covariate in order to examine mortality across both dialysis and transplantation. In this analysis, patients were not censored for transplantation and were followed up until death, loss to follow-up, discontinuation of dialysis, or the end of follow-up period. Associations with cause-specific mortality were also examined, which included cardiovascular- and infection-related death. We estimated mortality risk across various age strata (i.e. <6 years old, 6–<13 years old, 13–<18 years old, and ≥18 years old). Because the likelihood of receiving transplantation might impact mortality risk by age, we additionally estimated death-censored time to transplantation across age strata (i.e. <18 and ≥18 years old). We also compared the mortality risk across specific non-CAKUT vs. CAKUT causes of ESRD in the overall cohort, as well as stratified by age (i.e. <18 and ≥18 years old). Non-CAKUT causes of ESRD were categorized as primary GN, focal segmental glomerulosclerosis (FSGS), secondary GN, hypertensive nephropathy (HTN), Alport syndrome, congenital nephrotic syndrome (CNS), hemolytic uremic syndrome (HUS), diabetic nephropathy, tubular necrosis, chronic tubulointerstitial nephritis (TIN), drug-induced nephropathy, autosomal dominant polycystic kidney disease (ADPKD), autosomal recessive polycystic kidney disease (ARPKD), medullary cystic kidney disease (MCKD)/nephronophthisis (NPHP), and other/uncertain (Supplementary Table S1). Furthermore, we divided the CAKUT group into obstructive uropathies and other CAKUT, and examined the association of obstructive uropathies (vs. other CAKUT) with mortality among CAKUT patients. Sensitivity analyses also included propensity score (PS)-matched analysis, using matching within the caliper of 0.2 of the standard deviation of the logit (PS) [15], which was calculated based on case mix variables. Moreover, we treated transplantation as a competing risk, and used the Fine and Gray model to estimate the subhazard ratios in the overall, the PS-matched, and age-stratified analysis [16].

We also examined potential effect modification of the association of CAKUT vs. non-CAKUT with mortality by case-mix variables by including interaction terms within Cox regression models. As eGFR at dialysis initiation may be associated with clinical outcomes [17–20] and is related with primary cause of ESRD [2], we also assessed for potential effect modification by eGFR at dialysis initiation. Then, we performed subgroup analysis by case mix variables and four eGFR strata; <5 mL/min/1.73m^2, 5–<10 mL/min/1.73m^2, 10–15 mL/min/1.73m^2, ≥15 mL/min/1.73m^2. Additionally, mortality risk associated with CAKUT (vs. non-CAKUT) across continuous eGFR was examined using a restricted cubic spline function with four knots placed at the 5th, 35th, 65th and 95th percentile of the eGFR distribution. Median time lag between first dialysis date and date of sCr obtained, which was used to calculate eGFR, was −1 (interquartile range: −6 to 0) days. eGFR was missing in 1,123 patients, and complete case analyses for eGFR analyses were performed in the

24,638 patients with eGFR data. All other analyses did not have missing data. Analyses were performed using STATA MP, version 13.1 (Stata Corp, College Station, TX).

Results

Patients characteristics

Among 25,761 included patients, 4,780 (19%) were categorized as having CAKUT as the primary cause of ESRD (Supplemental Fig. 1). Compared to patients with non-CAKUT etiologies of ESRD, those with CAKUT were younger, and were more likely to be male, white, have Medicaid coverage, to have a non-renal anomaly; were less likely to start dialysis with HD and have hypertension and diabetes (Table 1). In the PS-matched cohort of 8,902 matched patients (4,451 in each group), there were no apparent differences between the CAKUT and non-CAKUT groups (Supplemental Table 2). When stratified by age group, CAKUT, primary GN, FSGS and secondary GN accounted for over half of the primary causes of ESRD. Proportions of CAKUT were lower with advancing age, whereas the prevalence of primary GN, FSGS and secondary GN was higher with advancing age (Table 2). Across patients initiating dialysis over 1995 to 2016, the proportion of these four major primary causes of ESRD were almost constant over time, suggesting an absence of a secular trend, with the exception of a decreasing trend in primary GN ($P_{trend} < 0.001$) (Supplemental Fig. 2).

Mortality in CAKUT vs. non-CAKUT causes of ESRD

A total of 3,069 deaths were observed during a total follow-up period of 75,635 patient-years. The overall crude mortality rate was 41 per 1,000 patient-years, and age-specific mortality was 82, 31, 31 and 40 per 1,000 patient-years in those <6 years, 6– <13 years, 13–<18 years and ≥18 years of age, respectively. The mortality rate was 34 and 42 per 1,000 patient-years in patients with CAKUT and non-CAKUT causes of ESRD, respectively. Information on cause of death was available in 2,819 patients (92%). Cardiovascular disease (39%) and infection (15%) were the leading causes (Supplemental Table 3). Cardiovascular disease-related death was higher in the non-CAKUT group, while that of infection was higher in the CAKUT group.

Overall survival rate was better in the CAKUT group (Supplemental Fig. 3). The overall HRs in the CAKUT group were 0.82 (95%CI, 0.74 – 0.91) and 0.72 (95%CI, 0.64 – 0.81) in unadjusted and case mix-adjusted models, respectively (reference: non-CAKUT group). A consistent result was observed in the PS-matched cohort (HR, 0.73; 95%CI 0.63 – 0.84; reference: non-CAKUT group) (Fig. 1). In the time-dependent analysis, the case mix-adjusted HR was 0.78 (95%CI, 0.71 – 0.86). CAKUT was associated with low risk for cardiovascular and infection-related death, where the case mix-adjusted HRs were 0.69 (95%CI, 0.57 – 0.84) and 0.81 (95%CI, 0.62 – 1.06), respectively. This association was not modified by sex, race, ethnicity, use of Medicaid, or initial dialysis modality ($P_{interaction} > 0.10$ for all), and mortality in CAKUT patients was lower in all subgroups (Fig. 2). In age-stratified analysis, patients with CAKUT showed consistently better survival than non-CAKUT patients except for those ≥18 years old (Fig. 3). The case mix-adjusted HRs in CAKUT patients were 0.66 (95%CI, 0.54 – 0.80), 0.56 (95%CI, 0.39 – 0.80), 0.66

(95%CI, 0.50 – 0.86), 0.97 (95%CI, 0.80 – 1.18) in those <6 years, 6–<13 years, 13–<18 years and ≥18 years, respectively (Fig. 4). The case mix-adjusted HRs for transplantation (likelihood of receiving transplantation) in the CAKUT group were 1.01 (95%CI, 0.96–1.05) and 0.93 (95%CI, 0.84–1.02) among patients <18 and ≥18 years old, respectively (reference: non-CAKUT group). When patients were stratified based on case-mix variables, mortality in CAKUT patients was lower in all subgroups among patients <18 years old, whereas the association between CAKUT and mortality in patients ≥18 years old varied across subgroups (Supplemental Fig. 4). The results from competing risk models showed similar mortality to those from the analyses with censoring at transplantation (Supplemental Table 3).

Mortality risk of specific causes of ESRD among non-CAKUT etiologies

Among major specific causes of ESRD in the non-CAKUT group, secondary GN had higher mortality risk (case mix-adjusted HR, 2.00; 95%CI, 1.73 – 2.30), while primary GN and FSGS had comparable or slightly lower mortality risk compared to CAKUT causes; the case mix-adjusted HRs were 0.93 (0.80 – 1.09) and 0.89 (0.75 – 1.04) in patients with primary GN and FSGS, respectively. Most of the others also had high mortality risk, and Alport syndrome, HUS and MCKD/NPHP had lower mortality risk (Fig. 5). Similar associations were observed in patients <18 years old; on the other hand, in those ≥18 years old, mortality was lower in many non-CAKUT causes, i.e. primary GN, FSGS, HTN, Alport syndrome, HUS, chronic TIN, ARPKD and ADPKD (Supplemental Fig. 5).

Among 4,780 CAKUT patients, obstructive uropathies were associated with lower mortality risk, where the case mix-adjusted HR was 0.79 (95%CI, 0.63 – 0.98) (reference: other CAKUT).

Mortality according to eGFR at dialysis initiation

eGFR at dialysis initiation was an effect modifier of the association between cause of ESRD and mortality ($P_{\text{interaction}} < 0.001$). The CAKUT group had lower mortality risk compared to the non-CAKUT group in eGFR groups ≥5 mL/min/1.73m^2, which was consistent with our overall analysis. Contrary to these observations, CAKUT was significantly associated with higher mortality in both unadjusted and case-mix adjusted models among patients with eGFR <5 mL/min/1.73m^2 (Fig. 6). This association was robust in using restricted cubic splines (Supplemental Fig. 6). Upon further stratifying eGFR and age into eight groups, we found that CAKUT had the highest mortality risk among patients ≥18 years old with eGFR <5 mL/min/1.73m^2 (Supplemental Table 4).

Discussion

In a contemporary cohort of 25,761 young ESRD patients, CAKUT as a primary cause of ESRD was associated with lower mortality risk compared to non-CAKUT. This association was consistent in subgroup analyses of patients younger than 18 years old, and across strata of sex, race, ethnicity, Medicaid coverage and initial dialysis modality. When non-CAKUT causes of ESRD were categorized into specific etiologies, primary GN and FSGS had comparable or slightly lower mortality risk compared to CAKUT. Most of the other

primary causes had higher mortality risk, except for Alport syndrome, HUS and MCKD/NPHP. Similar trends were observed in patients younger than 18 years old by age-stratified analysis. The associations of CAKUT and non-CAKUT causes of ESRD with mortality were modified by eGFR at dialysis initiation, and higher mortality in CAKUT was observed in those with eGFR <5 mL/min/1.73m^2, especially among patients ≥18 years old.

In our study, patients in whom CAKUT was the primary cause of ESRD had a favorable outcome compared to those with non-CAKUT causes. This association was robust in the PS-matched analyses. After taking into account mortality across both dialysis and transplantation, CAKUT had a lower mortality risk. In a previous study, which assessed patient survival in children and primarily adults, the survival of patients with ESRD on renal replacement therapy due to CAKUT was slightly better than that of age-matched patients with non-CAKUT [9]. In studies of 1,063, 87, and 23,401 children, respectively, CAKUT causes of ESRD were associated with lower risk of mortality than non-CAKUT causes in patients on dialysis, albeit CAKUT causes were not the main exposure [10, 21, 22]. Strengths of the present study include examination of the entire age range of children and young adults, primary focus upon CAKUT, and the large sample size, which allowed for analyses across age-strata and specific causes of ESRD. Primary cause of ESRD and mortality in children with ESRD varied across age [23–27] which was also observed in our cohort, where mortality was remarkably high in patients younger than 6 years old. Thus, ESRD etiology is an important consideration in overall as well as age-related mortality.

CAKUT was associated with lower mortality risk in patients <18 years old, while similar mortality was observed in patients ≥18 years old. The result of time to transplantation analysis indicated that the similar mortality risk might be attributed in part to low likelihood of receiving transplantation in young adult patients with CAKUT, though the effect size was small. Moreover, mortality according to specific etiologies of ESRD may be different between patients <18 years old and those ≥18 years old. Many non-CAKUT diseases including CNS and ARPKD were associated with higher mortality compared to CAKUT, whereas primary GN and FSGS, which were the most common primary causes, had similar mortality to CAKUT. Although only limited data are available for mortality of those specific primary causes in children and young adults [28–33], our results were mostly consistent with these studies, including favorable outcomes in Alport syndrome. Lower mortality in CAKUT may be due to high urine output, which is typical in CAKUT [34] and which itself is associated with lower mortality [35]. Other factors may also contribute to lower mortality in CAKUT, including lower likelihood of associated conditions and lack of systemic inflammatory disease.

Our results indicate that eGFR may be an effect modifier for the association of primary ESRD causes with mortality. Considering that the onset of CKD is earlier in CAKUT than most of the non-CAKUT causes [36], and that the decline of eGFR is slower in CAKUT in the pre-dialysis period [2], the difference in the duration of exposure to CKD among CAKUT vs. non-CAKUT causes would be more marked among those with lower eGFR at dialysis initiation. This may affect time to mortality following dialysis initiation.

Several limitations of our study should be acknowledged. First, the present study may be subject to information bias because of potential coding errors in the primary cause of ESRD. The errors could be more prevalent in biopsy-proven glomerular diseases due to lack of available biopsy data in addition to physician error [37]. In fact, the prevalence of ambiguous GN (code: GN [histologically not examined] or GN) was 7% in our cohort. Although biopsy-proven glomerular diseases, i.e. GN and FSGS, accounted for high proportions of the non-CAKUT group, coding errors between main exposure variables, CAKUT and non-CAKUT, are less likely to occur. Because diagnoses in the primary causes of ESRD were more accurate after the CMS 2728 was revised in 1995 [37], we limited the patients to those who started dialysis after 1995 to minimize this potential information bias. In addition, information on comorbidities ascertained by the CMS 2728 form may be misclassified [38]. Second, analyses for specific causes of ESRD had a limited statistical power due to small sample size. However, mortality risk associated with most of specific causes with small sample size was consistent with overall analysis. In age-stratified analyses, consistent associations were observed in children as well. Third, stratified analyses by eGFR may have been subject to stratification bias. We performed stratified analysis because of a potential of effect modifiers based on results from interaction tests. However, eGFR at dialysis initiation may be an intermediate variable which lies on the causal pathway between primary cause of ESRD and mortality. Thus, the stratified analysis might increase bias due to a reduction in the total causal effect [39]. Although eGFR was missing in only 4% of patients, analysis according to eGFR may be subject to selection bias by including only those with available data. Another limitation would be lead-time bias. We were not able to take account of the length of pre-dialysis period. Finally, as this is an observational study, we could not make definitive statements about the causal associations of primary cause of ESRD with mortality. We were also not able to exclude the possibility of residual confounding and the presence of unmeasured confounders.

However, our study comes with a number of strengths, including its large sample size of US patients. We used data from the USRDS, which includes virtually all dialysis patients, including children, within the United States. Moreover, we had little selection bias, in that very few patients were excluded and were similar in underlying characteristics. However, compared to the 4,273 excluded patients, the included patients were older and were more likely to be black, Hispanic and to have information on initial dialysis modality; were more likely to have hypertension, heart disease as comorbidities, and lower eGFR at the time of dialysis initiation (Supplemental Table 5). CAKUT was more prevalent among excluded patients, whereas primary GN, FSGS, secondary GN and HTN were more prevalent among included patients (Supplemental Table 6).

In conclusion, CAKUT was associated with lower mortality among incident dialysis patients younger than 18 years old. On the other hand, CAKUT conferred a similar mortality risk to non-CAKUT in young adult patients (18 to 21 years old). Among the non-CAKUT group, mortality associated with primary GN and FSGS was comparable or slightly lower compared to CAKUT causes. CAKUT may be associated with higher mortality in those with eGFR <5 mL/min/1.73m^2, especially for young adult patients. Further studies are needed to investigate the mortality risk for specific primary causes of ESRD, particularly for rare

causes of ESRD in children. Exploring underlying mechanisms which contribute to these outcomes is also needed to improve the prognosis of non-CAKUT patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The data reported here have been supplied by the USRDS. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as official policy or interpretation of the US government.

Funding

The authors are supported by the research grants from the NIH/NIDDK including T32-DK104687 (M.L.), K23-DK102903 (C.M.R), R03-DK114642 (C.M.R), K24 DK091419 (K.K. Z), U01 DK102163 (K.K. Z), and philanthropist grants from H. Simmons, L. Chang and J. Lee. Y.T. is supported by the grant from Shengjing Hospital of China Medical University.

References

1. Ingelfinger JR, Kalantar-Zadeh K, Schaefer F; World Kidney Day Steering Committee (2016) Averting the legacy of kidney disease--focus on childhood. Kidney Int 89:512–518. doi:10.1016/j.kint.2015.10.014 [PubMed: 26880442]
2. Harambat J, van Stralen KJ, Kim JJ, Tizard EJ (2012) Epidemiology of chronic kidney disease in children. Pediatr Nephrol 27:363–373. doi:10.1007/s00467-011-1939-1 [PubMed: 21713524]
3. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013) KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl 3:1–150
4. Calderon-Margalit R, Golan E, Twig G, Leiba A, Tzur D, Afek A, Skorecki K, Vivante A (2018) History of Childhood Kidney Disease and Risk of Adult End-Stage Renal Disease. N Engl J Med 378:428–438. doi:10.1056/NEJMoa1700993 [PubMed: 29385364]
5. Chao SM, Saw AH, Yap HK, Tan SP, Murugasu B, Tay AH (1991) Comparison of progression of renal failure in children with hypoplastic-dysplastic kidneys and chronic glomerulonephritis. Singapore Med J 32:304–306 [PubMed: 1788570]
6. Soares CM, Diniz JS, Lima EM, Silva JM, Oliveira GR, Canhestro MR, Colosimo EA, Simoes e Silva AC, Oliveira EA (2008) Clinical outcome of children with chronic kidney disease in a pre-dialysis interdisciplinary program. Pediatr Nephrol 23:2039–2046. doi:10.1007/s00467-008-0868-0 [PubMed: 18560903]
7. Sanna-Cherchi S, Ravani P, Corbani V, Parodi S, Haupt R, Piaggio G, Innocenti ML, Somenzi D, Trivelli A, Caridi G, Izzi C, Scolari F, Mattioli G, Allegri L, Ghiggeri GM (2009) Renal outcome in patients with congenital anomalies of the kidney and urinary tract. Kidney Int 76:528–533. doi:10.1038/ki.2009.220 [PubMed: 19536081]
8. Matsell DG, Cojocaru D, Matsell EW, Eddy AA (2015) The impact of small kidneys. Pediatr Nephrol 30:1501–1509. doi:10.1007/s00467-015-3079-5 [PubMed: 25794549]
9. Wuhl E, van Stralen KJ, Verrina E, Bjerre A, Wanner C, Heaf JG, Zurriaga O, Hoitsma A, Niaudet P, Palsson R, Ravani P, Jager KJ, Schaefer F (2013) Timing and outcome of renal replacement therapy in patients with congenital malformations of the kidney and urinary tract. Clin J Am Soc Nephrol 8:67–74. doi:10.2215/CJN.03310412 [PubMed: 23085722]
10. Vidal E, van Stralen KJ, Chesnaye NC, Bonthuis M, Holmberg C, Zurowska A, Trivelli A, Da Silva JEE, Herthelius M, Adams B, Bjerre A, Jankauskiene A, Miteva P, Emirova K, Bayazit AK, Mache CJ, Sanchez-Moreno A, Harambat J, Groothoff JW, Jager KJ, Schaefer F, Verrina E; ESPN/ERA-EDTA Registry (2017) Infants Requiring Maintenance Dialysis: Outcomes of Hemodialysis and Peritoneal Dialysis. Am J Kidney Dis 69:617–625. doi:10.1053/j.ajkd.2016.09.024 [PubMed: 27955924]

11. Schwartz GJ, Feld LG, Langford DJ (1984) A simple estimate of glomerular filtration rate in full-term infants during the first year of life. J Pediatr 104:849–854 [PubMed: 6726515]
12. Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL (2009) New equations to estimate GFR in children with CKD. J Am Soc Nephrol 20:629–637. doi:10.1681/ASN.2008030287 [PubMed: 19158356]
13. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med 150:604–612 [PubMed: 19414839]
14. Austin PC (2009) Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 28:3083–3107. doi:10.1002/sim.3697 [PubMed: 19757444]
15. Austin PC (2011) Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat 10:150–161. doi:10.1002/pst.433 [PubMed: 20925139]
16. Fine JP, Gray RJ (1999) A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association 94:496–509. doi:10.1080/01621459.1999.10474144
17. Atkinson MA, Oberai PC, Neu AM, Fivush BA, Parekh RS (2010) Predictors and consequences of higher estimated glomerular filtration rate at dialysis initiation. Pediatr Nephrol 25:1153–1161. doi:10.1007/s00467-010-1459-4 [PubMed: 20191370]
18. Stel VS, Dekker FW, Ansell D, Augustijn H, Casino FG, Collart F, Finne P, Ioannidis GA, Salomone M, Traynor JP, Zurriaga O, Verrina E, Jager KJ (2009) Residual renal function at the start of dialysis and clinical outcomes. Nephrol Dial Transplant 24:3175–3182. doi:10.1093/ndt/gfp264 [PubMed: 19515803]
19. Kazmi WH, Gilbertson DT, Obrador GT, Guo H, Pereira BJ, Collins AJ, Kausz AT (2005) Effect of comorbidity on the increased mortality associated with early initiation of dialysis. Am J Kidney Dis 46:887–896. doi:10.1053/j.ajkd.2005.08.005 [PubMed: 16253729]
20. Okuda Y, Soohoo M, Tang Y, Obi Y, Laster M, Rhee CM, Streja E, Kalantar-Zadeh K (2019) Estimated GFR at Dialysis Initiation and Mortality in Children and Adolescents. Am J Kidney Dis 73:797–805. doi:10.1053/j.ajkd.2018.12.038 [PubMed: 30833086]
21. Alexander RT, Foster BJ, Tonelli MA, Soo A, Nettel-Aguirre A, Hemmelgarn BR, Samuel SM; of the Pediatric Renal Outcomes Group Canada (2012) Survival and transplantation outcomes of children less than 2 years of age with end-stage renal disease. Pediatr Nephrol 27:1975–1983. doi:10.1007/s00467-012-2195-8 [PubMed: 22673972]
22. Mitsnefes MM, Laskin BL, Dahhou M, Zhang X, Foster BJ (2013) Mortality risk among children initially treated with dialysis for end-stage kidney disease, 1990–2010. JAMA 309:1921–1929. doi:10.1001/jama.2013.4208 [PubMed: 23645144]
23. Warady BA, Chadha V (2007) Chronic kidney disease in children: the global perspective. Pediatr Nephrol 22:1999–2009. doi:10.1007/s00467-006-0410-1 [PubMed: 17310363]
24. Mitsnefes MM (2005) Cardiovascular morbidity and mortality in children with chronic kidney disease in North America: lessons from the USRDS and NAPRTCS databases. Perit Dial Int 25 Suppl 3:S120–122 [PubMed: 16048275]
25. Tsai TC, Chen YC, Lo CW, Wang WS, Lo SS, Tang GJ, Thien PF (2014) Incidence and renal survival of ESRD in the young Taiwanese population. Clin J Am Soc Nephrol 9:302–309. doi:10.2215/CJN.12761212 [PubMed: 24262507]
26. Orr NI, McDonald SP, McTaggart S, Henning P, Craig JC (2009) Frequency, etiology and treatment of childhood end-stage kidney disease in Australia and New Zealand. Pediatr Nephrol 24:1719–1726. doi:10.1007/s00467-009-1181-2 [PubMed: 19373494]
27. McDonald SP, Craig JC; Australian, New Zealand Paediatric Nephrology Association (2004) Long-term survival of children with end-stage renal disease. N Engl J Med 350:2654–2662. doi:10.1056/NEJMoa031643 [PubMed: 15215481]

28. Sule S, Fivush B, Neu A, Furth S (2012) Increased hospitalizations and death in patients with ESRD secondary to lupus. Lupus 21:1208–1213. doi:10.1177/0961203312451506 [PubMed: 22736748]
29. Holtta T, Bonthuis M, Van Stralen KJ, Bjerre A, Topaloglu R, Ozaltin F, Holmberg C, Harambat J, Jager KJ, Schaefer F, Groothoff JW (2016) Timing of renal replacement therapy does not influence survival and growth in children with congenital nephrotic syndrome caused by mutations in NPHS1: data from the ESPN/ERA-EDTA Registry. Pediatr Nephrol 31:2317–2325. doi:10.1007/s00467-016-3517-z [PubMed: 27761660]
30. Roy S, Dillon MJ, Trompeter RS, Barratt TM (1997) Autosomal recessive polycystic kidney disease: long-term outcome of neonatal survivors. Pediatr Nephrol 11:302–306 [PubMed: 9203177]
31. Pavkov ME, Bennett PH, Knowler WC, Krakoff J, Sievers ML, Nelson RG (2006) Effect of youth-onset type 2 diabetes mellitus on incidence of end-stage renal disease and mortality in young and middle-aged Pima Indians. JAMA 296:421–426. doi:10.1001/jama.296.4.421 [PubMed: 16868300]
32. Temme J, Kramer A, Jager KJ, Lange K, Peters F, Muller GA, Kramar R, Heaf JG, Finne P, Palsson R, Reisaeter AV, Hoitsma AJ, Metcalfe W, Postorino M, Zurriaga O, Santos JP, Ravani P, Jarraya F, Verrina E, Dekker FW, Gross O (2012) Outcomes of male patients with Alport syndrome undergoing renal replacement therapy. Clin J Am Soc Nephrol 7:1969–1976. doi:10.2215/CJN.02190312 [PubMed: 22997344]
33. Cattran DC, Rao P (1998) Long-term outcome in children and adults with classic focal segmental glomerulosclerosis. Am J Kidney Dis 32:72–79. doi:10.1053/ajkd.1998.v32.pm9669427 [PubMed: 9669427]
34. Ha IS, Yap HK, Munarriz RL, Zambrano PH, Flynn JT, Bilge I, Szczepanska M, Lai WM, Antonio ZL, Gulati A, Hooman N, van Hoeck K, Higuita LM, Verrina E, Klaus G, Fischbach M, Riyami MA, Sahpazova E, Sander A, Warady BA, Schaefer F; International Pediatric Peritoneal Dialysis Network Registry (2015) Risk factors for loss of residual renal function in children treated with chronic peritoneal dialysis. Kidney Int 88:605–613. doi:10.1038/ki.2015.108 [PubMed: 25874598]
35. Shafi T, Jaar BG, Plantinga LC, Fink NE, Sadler JH, Parekh RS, Powe NR, Coresh J (2010) Association of residual urine output with mortality, quality of life, and inflammation in incident hemodialysis patients: the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study. Am J Kidney Dis 56:348–358. doi:10.1053/j.ajkd.2010.03.020 [PubMed: 20605303]
36. Renkema KY, Winyard PJ, Skovorodkin IN, Levtchenko E, Hindryckx A, Jeanpierre C, Weber S, Salomon R, Antignac C, Vainio S, Schedl A, Schaefer F, Knoers NV, Bongers EM; EUCAKUT consortium (2011) Novel perspectives for investigating congenital anomalies of the kidney and urinary tract (CAKUT). Nephrol Dial Transplant 26:3843–3851. doi:10.1093/ndt/gfr655 [PubMed: 22121240]
37. Layton JB, Hogan SL, Jennette CE, Kenderes B, Krisher J, Jennette JC, McClellan WM (2010) Discrepancy between Medical Evidence Form 2728 and renal biopsy for glomerular diseases. Clin J Am Soc Nephrol 5:2046–2052. doi:10.2215/CJN.03550410 [PubMed: 20688886]
38. Mu Y, Chin AI, Kshirsagar AV, Bang H (2018) Data concordance between ESRD Medical Evidence Report and Medicare claims: is there any improvement? PeerJ 6:e5284. doi:10.7717/peerj.5284 [PubMed: 30065880]
39. Schisterman EF, Cole SR, Platt RW (2009) Overadjustment bias and unnecessary adjustment in epidemiologic studies. Epidemiology 20:488–495. doi:10.1097/EDE.0b013e3181a819a1 [PubMed: 19525685]

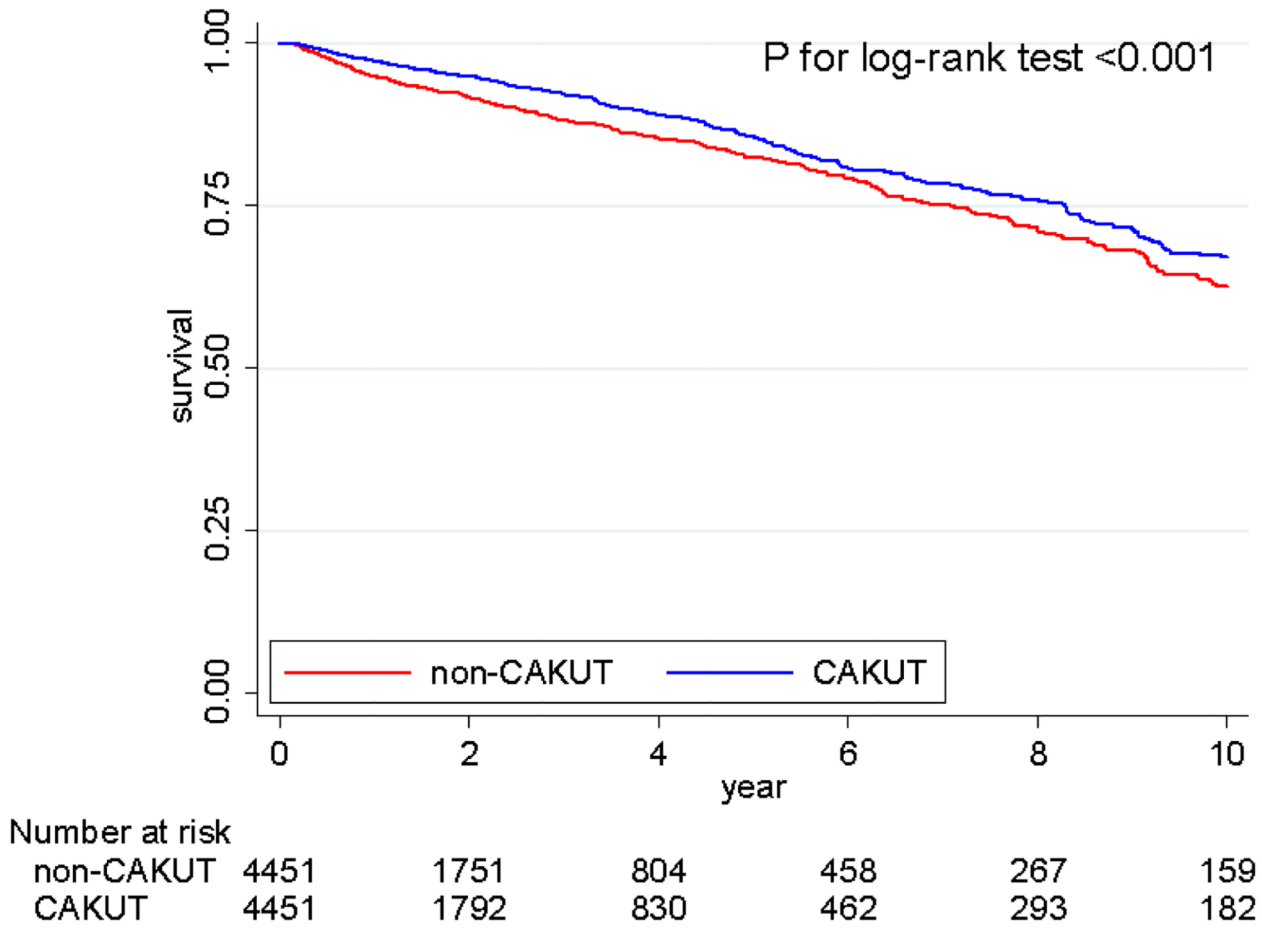

Fig. 1.

Kaplan-Meier survival curve for mortality in the propensity score-matched cohort.

Abbreviation: CAKUT, congenital anomalies of the kidney and urinary tract.

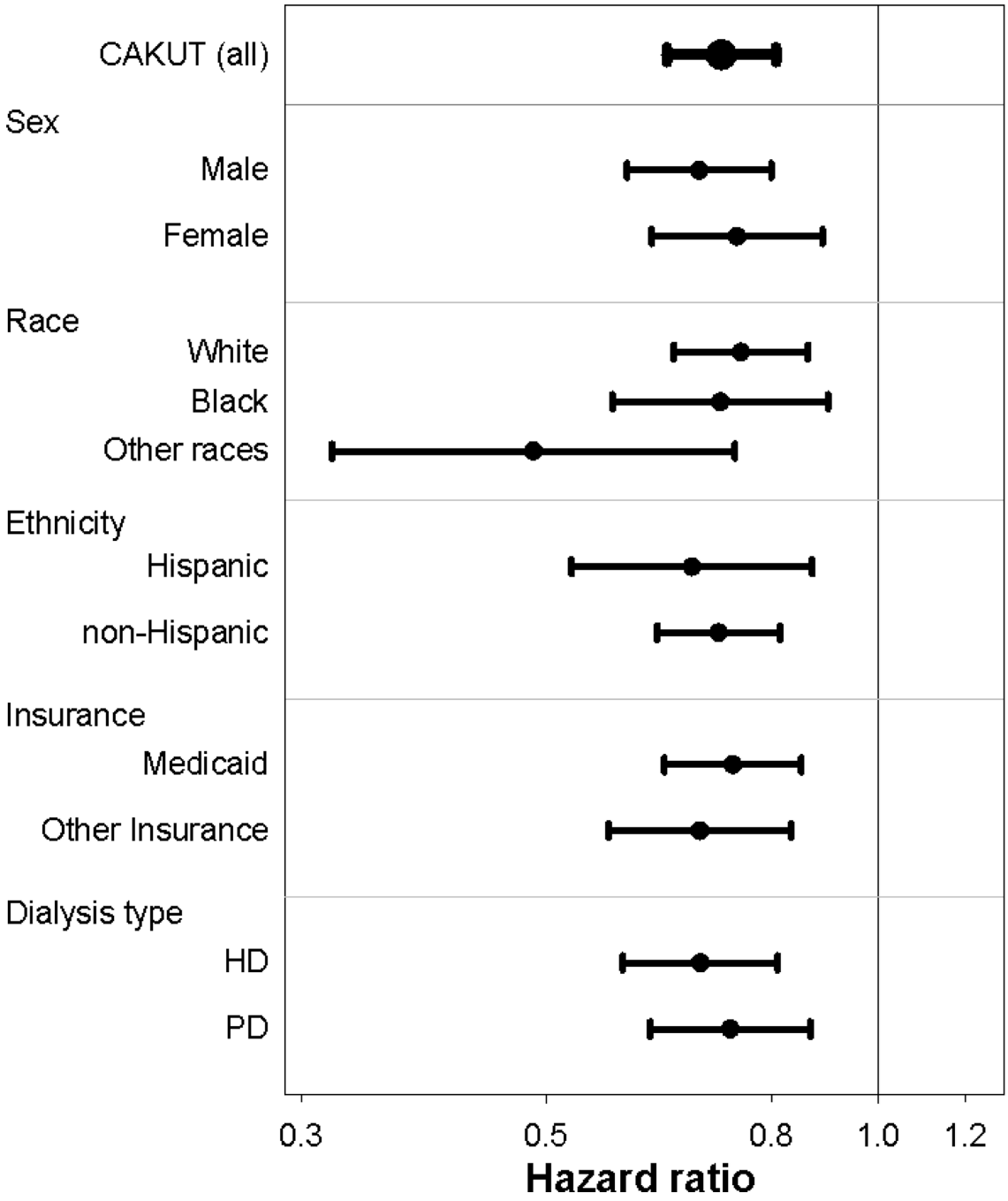

Fig. 2.

Case mix-adjusted hazard ratios for mortality in CAKUT in subgroup analyses by case mix variables (reference: non-CAKUT). Abbreviations: CAKUT, congenital anomalies of the kidney and urinary tract; HD, hemodialysis; PD, peritoneal dialysis.

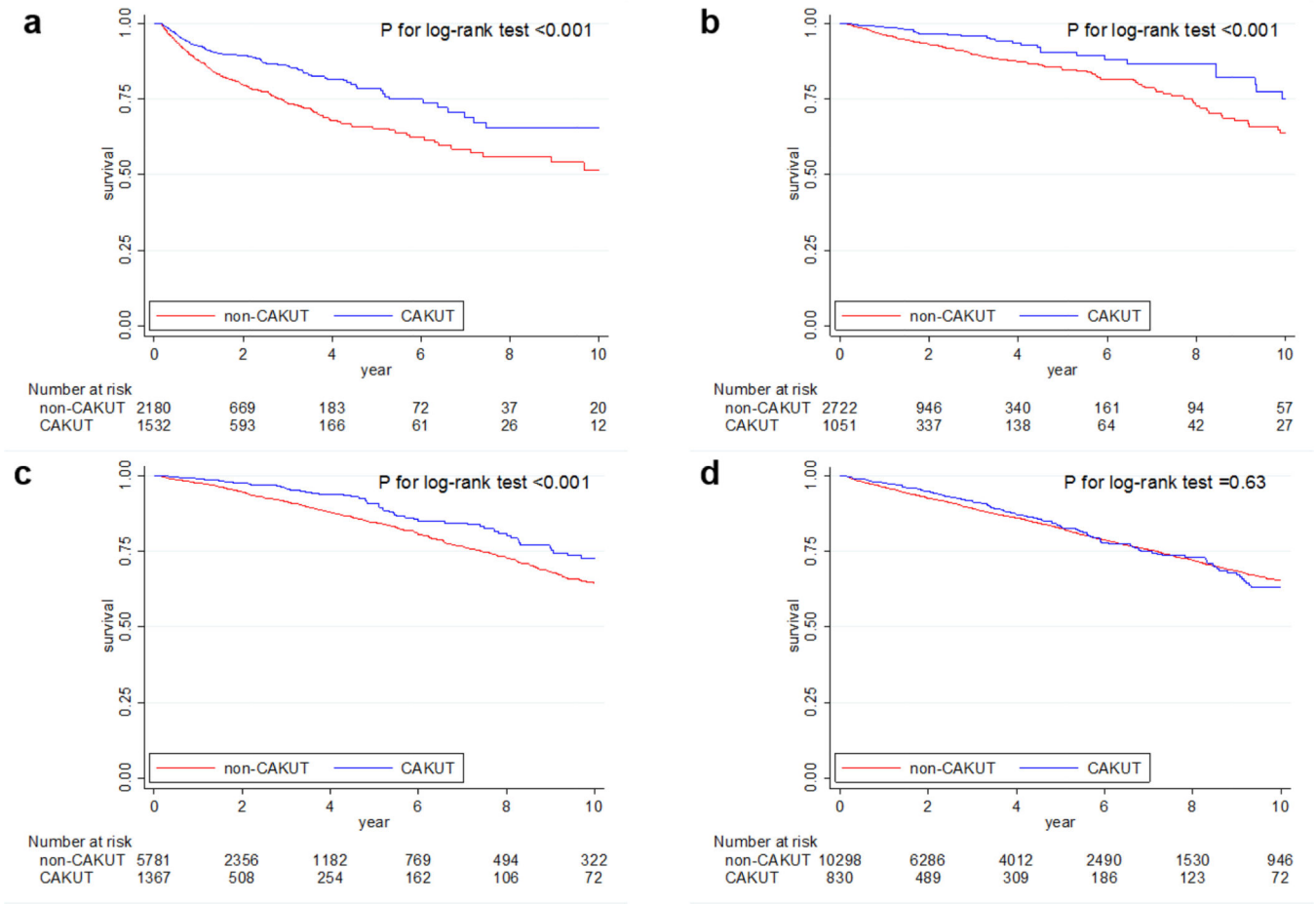

Fig. 3.

Kaplan-Meier survival curves for mortality in patients (a) <6 years old, (b) 6–<13 years old, (c) 13–<18 years old, and (d) ≥18 years old. Abbreviation: CAKUT, congenital anomalies of the kidney and urinary tract.

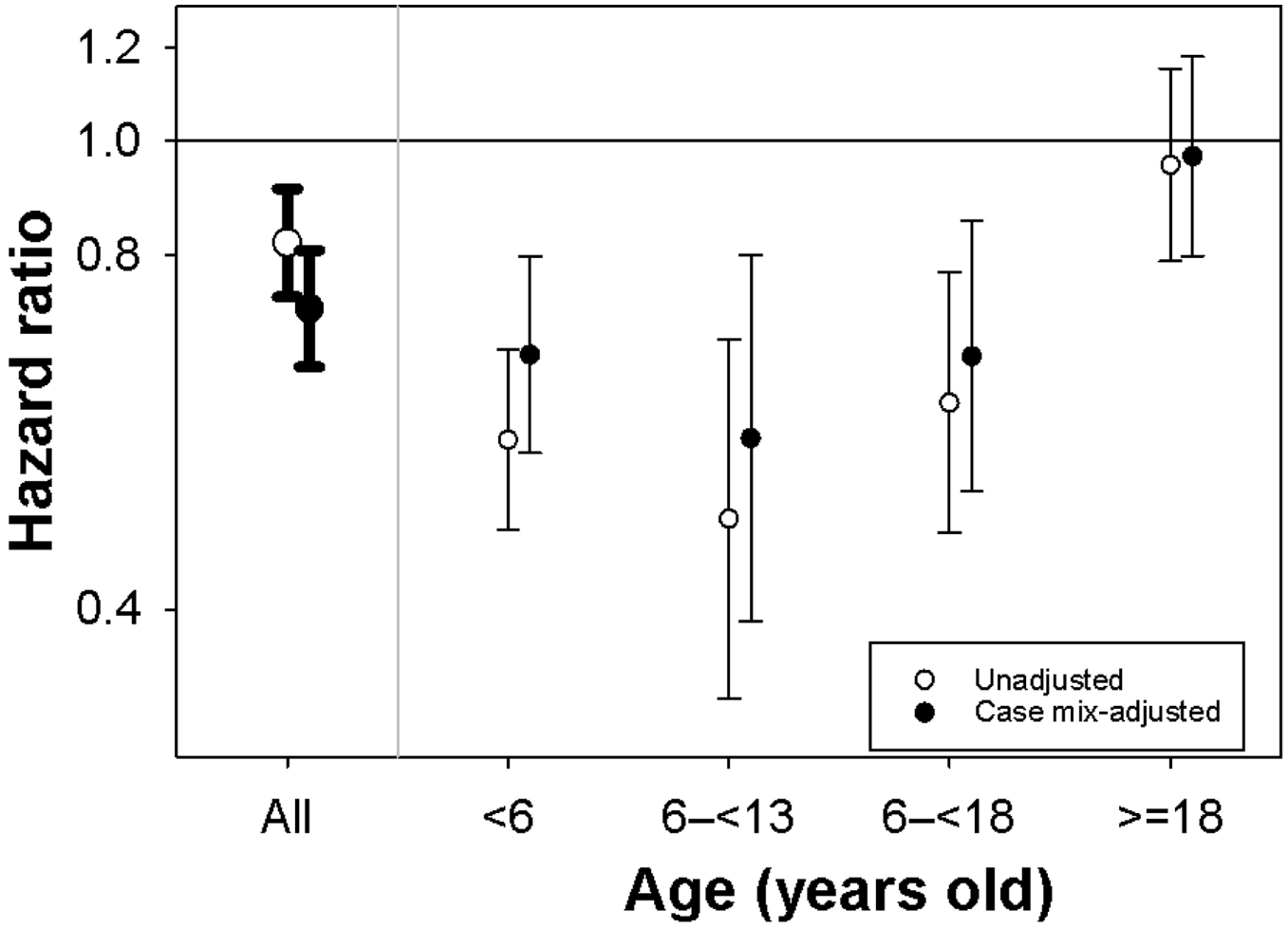

Fig. 4.
Hazard ratios for mortality in congenital anomalies of the kidney and urinary tract (CAKUT) group across age strata (reference: non-CAKUT group).

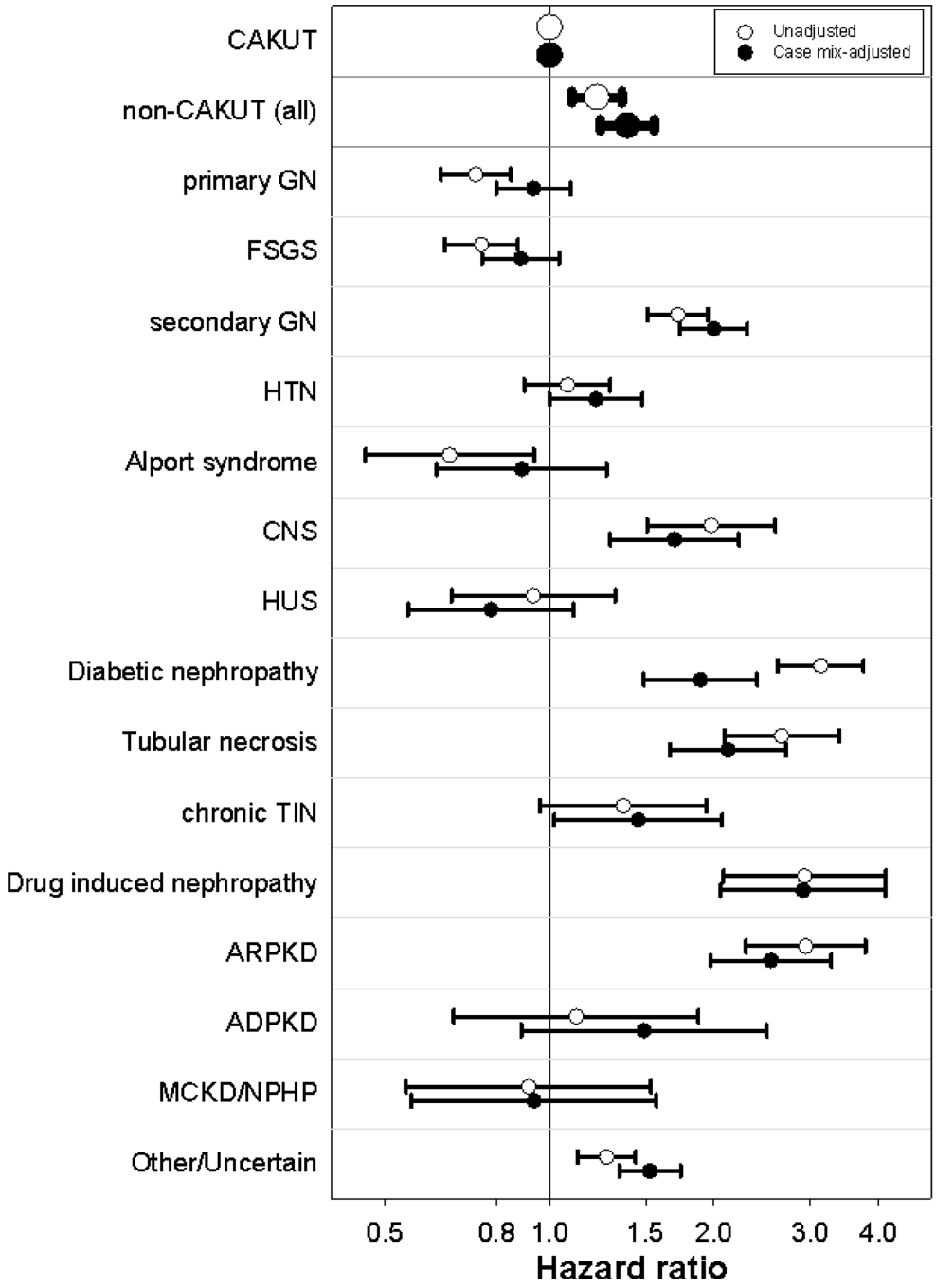

Fig. 5.

Hazard ratios for mortality in specific causes (reference: CAKUT group). Abbreviations: CAKUT, congenital anomalies of the kidney and urinary tract; GN, glomerulonephritis; FSGS, focal segmental glomerulosclerosis; HTN, hypertensive nephropathy; CNS, congenital nephrotic syndrome; HUS, hemolytic uremic syndrome; TIN, tubulointerstitial nephritis; ARPKD, autosomal recessive polycystic kidney disease; ADPKD, autosomal dominant polycystic kidney disease; MCKD, medullary cystic kidney disease; NPHP, nephronophthisis.

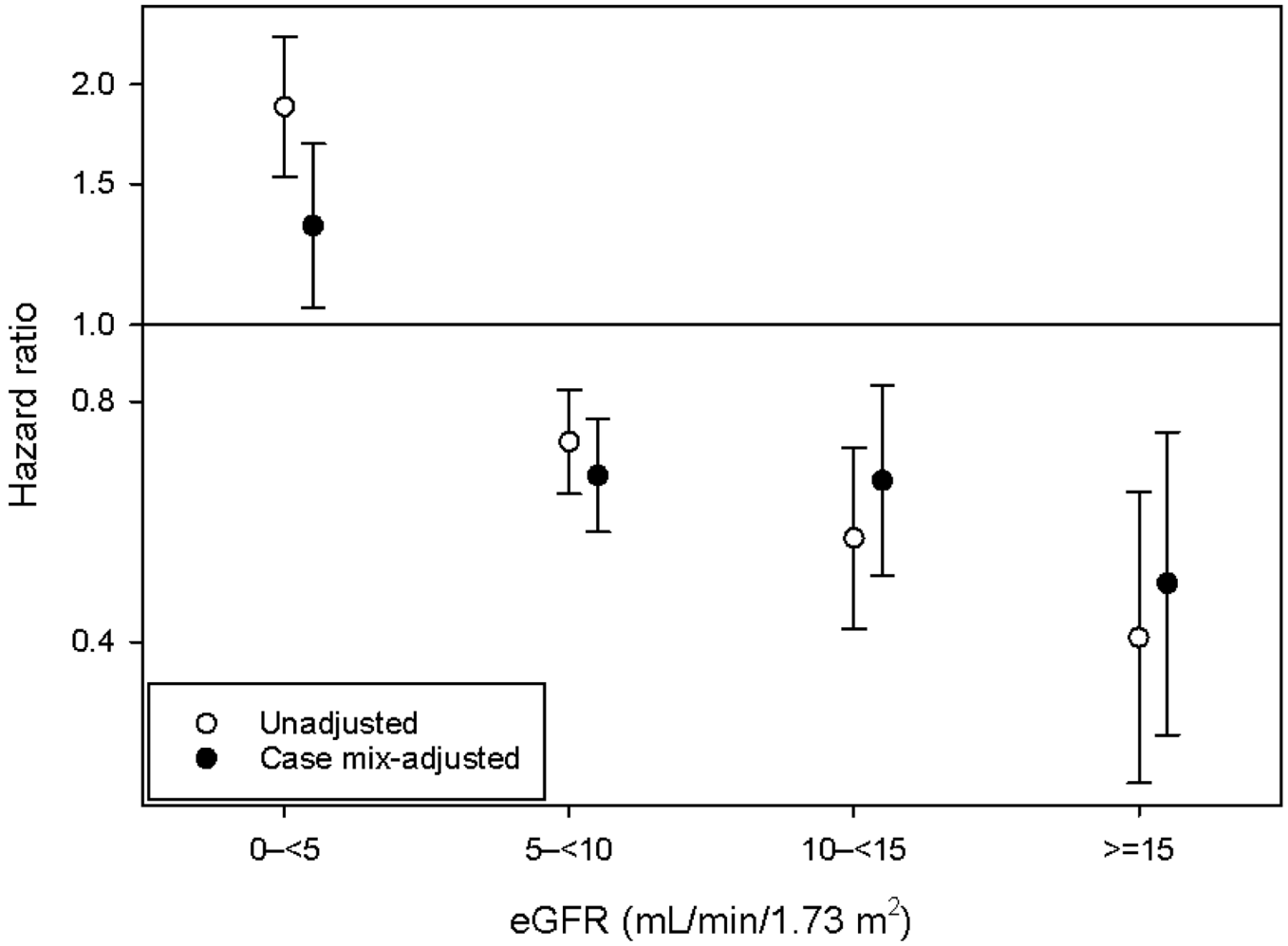

Fig. 6.

Hazard ratios for mortality in congenital anomalies of the kidney and urinary tract (CAKUT) group across eGFR strata (reference: non-CAKUT group). Abbreviation: eGFR, estimated glomerular filtration rate.

Table 1.

Characteristics at dialysis initiation

	CAKUT	non-CAKUT	Standardized Difference
N (%)	4,780 (19)	20,981 (81)	
Age (years)	12 (2–16)	17 (13–20)	−0. 83
<6 (%)	1,532 (32)	2,180 (10)	
≥6, <13 (%)	1,051 (22)	2,722 (13)	
≥13, <18 (%)	1,367 (29)	5,781 (28)	
≥18 (%)	830 (17)	10,298 (49)	
Male (%)	3,146 (66)	10,983 (52)	0.28
Race (%)			
White	3,481 (73)	12,698 (61)	0.26
Black	995 (21)	6,673 (32)	−0.25
Other	304 (6)	1,610 (8)	−0.05
Hispanic (%)	1,309 (27)	5,763 (27)	0.00
Medicaid (%)	2,669 (56)	9,388 (45)	0.22
Dialysis type (%)			
HD	2,149 (45)	13,867 (66)	−0. 44
PD	2,587 (54)	6,880 (33)	0.44
Uncertain	44 (1)	234 (1)	−0.02
Incidence year (%)			
1995–1999	1,032 (22)	4,686 (22)	−0.02
2000–2004	1,226 (26)	5,358 (26)	0.00
2005–2009	1,161 (24)	5,222 (25)	−0.01
2010–2016	1,361 (28)	5,715 (27)	0.03
Comorbidities (%)			
Hypertension	1,437 (30)	11,747 (56)	−0. 54
Heart disease	148 (3)	1,382 (7)	−0.16
Non-renal anomaly	286 (6)	391 (2)	0.21
Malignancy	17 (0)	287 (1)	−0.11
Diabetes	36 (1)	925 (4)	−0.23
eGFR (mL/min/1.73 m^2)	7.5 (5.4–10.0)	7.3 (5.0–10.4)	0.02
<5 (%)	958 (21)	4,970 (25)	
≥5, <10 (%)	2,475 (54)	9,555 (48)	
≥10, <15 (%)	889 (19)	3,767 (19)	
≥15 (%)	273 (6)	1,751 (9)	

Note: Values for categorical variables are given as number (percentage); values for age and eGFR, as median (interquartile range). Standardized differences of 0.2 (−0.2), 0.5 (−0.5), and 0.8 (−0.8) are considered small, medium, and large differences, respectively.

Abbreviations: CAKUT, congenital anomalies of the kidney and urinary tract; HD, hemodialysis; PD, peritoneal dialysis; eGFR, estimated glomerular filtration rate

Table 2.

Specific primary causes of ESRD and their prevalence across age strata.

		Age (years)			
	All	**< 6**	**≥6, <13**	**≥13, <18**	**≥18**
N (%)	25,761	3,712 (14)	3,773 (15)	7,148 (28)	11,128 (43)
CAKUT	4,780 (19)	1,532 (41)	1,051 (28)	1,367 (19)	830 (7)
Primary GN	4,096 (16)	104 (3)	437 (12)	1,156 (16)	2,399 (22)
FSGS	3,564 (14)	269 (7)	603 (16)	1,232 (17)	1,460 (13)
Secondary GN	3,087 (12)	36 (1)	306 (8)	884 (12)	1,861 (17)
HTN	995 (4)	31 (1)	27 (1)	162 (2)	775 (7)
Alport syndrome	638 (2)	9 (0)	66 (2)	265 (4)	298 (3)
CNS	505 (2)	344 (9)	60 (2)	61 (1)	40 (0)
HUS	457 (2)	191 (5)	93 (2)	76 (1)	97 (1)
Diabetic nephropathy	461 (2)	47 (1)	9 (0)	42 (1)	363 (3)
Tubular necrosis	401 (2)	180 (5)	52 (1)	63 (1)	106 (1)
Chronic TIN	285 (1)	21 (1)	50 (1)	93 (1)	121 (1)
Drug induced nephropathy	146 (1)	21 (1)	21 (1)	38 (1)	66 (1)
ARPKD	397 (2)	275 (7)	52 (1)	44 (1)	26 (0)
ADPKD	130 (1)	21 (1)	10 (0)	30 (0)	69 (1)
MCKD/NPHP	295 (1)	37 (1)	116 (3)	95 (1)	47 (0)
Other/Uncertain	5,524 (21)	594 (16)	820 (22)	1,540 (22)	2,570 (23)

Note: All values are given as number (percentage).

Abbreviations: ESRD, end-stage renal disease; CAKUT, congenital anomalies of the kidney and urinary tract; GN, glomerulonephritis; FSGS, focal segmental glomerulosclerosis; HTN, hypertensive nephropathy; CNS, congenital nephrotic syndrome; HUS, hemolytic uremic syndrome; TIN, tubulointerstitial nephritis; ARPKD, autosomal recessive polycystic kidney disease; ADPKD, autosomal dominant polycystic kidney disease; MCKD, medullary cystic kidney disease; NPHP, nephronophthisis