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The Impact of Primary Renal Diagnosis on Prognosis and the Varying Predictive Power of Albuminuria in the NURTuRE-CKD Study

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Keywords
Albuminuria · Chronic kidney disease · Precision medicine · Primary renal diagnosis · Risk stratification

Abstract

Introduction: The definition of CKD is broad, which neglects the heterogeneity of risk across primary renal diseases. ***Methods:*** The National Unified Renal Translational Research Enterprise (NURTuRE)-CKD is an ongoing UK, prospective multicenter cohort study of 2,996 adults with an eGFR of 15–59 mL/min/1.73 m^2 or eGFR ≥60 mL/min/1.73 m^2 with a urine albumin-to-creatinine ratio (uACR) >30 mg/mmol. Outcomes and predictive performance of eGFR and uACR were subcategorized by ERA-EDTA primary renal diagnosis (PRD) codes. ***Results:*** 2,638 participants were included, with baseline median eGFR of 33.5 mL/min/1.73 m^2 and uACR 29.8 mg/mmol. Over a median 49.2 months follow-up, 630 (23.9%) experienced kidney failure (KF), and 352 (13.3%) died before KF, the median eGFR slope was −1.97 mL/min/1.73 m^2/year. There were significant differences in risk across the PRD, persisting after adjustment for age, sex, baseline eGFR, and modifiable risk factors (blood pressure, HbA1c, and renin-angiotensin-aldosterone system inhibitors). Diabetic kidney disease (DKD), glomerulonephritis, and familial/hereditary nephropathy were associated with the greatest risk, while tubulointerstitial disease and vasculitis carried a low risk of KF. eGFR had good predictive accuracy across all PRD. However, the addition of uACR showed variable benefit, depending on the PRD. The largest benefit was seen in vasculitis, renal vascular, and DKD groups, but uACR added no predictive value to the familial/hereditary group. ***Conclusion:*** Significant differences in the risk of kidney-related outcomes occurred across the various primary renal diagnoses persisting after adjustment for age, sex, baseline eGFR, and modifiable risk factors. Albuminuria's

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discriminatory ability as a biomarker of progression varies by diagnosis. CKD care should, therefore, take a personalized approach that always considers the primary renal diagnosis.

Plain Language Summary

Chronic kidney disease (CKD) is a broad term that describes a reduction in kidney function. However, there are several underlying causes of CKD. Using the NURTuRE-CKD study, we explore how the individual causes of CKD affect the risk of disease progression and how some of the tests we do are more accurate in predicting kidney failure (KF) in some causes of CKD rather than others. We found that a person's type of kidney disease can significantly impact their risk of KF and death. For example, people with DKD or certain genetic conditions had a higher risk of KF, while those with other types, like tubulointerstitial disease, had a lower risk. Albuminuria, which measures the amount of a protein called albumin in the urine, is commonly used to predict kidney disease progression. However, we found that its effectiveness varies depending on the type of kidney disease. It was most helpful in predicting outcomes for people with vasculitis and DKD but added little value for those with genetic kidney diseases. In conclusion, recognizing the specific type of kidney disease is crucial for accurate risk assessment and effective treatment planning in CKD. This study highlights the importance of a tailored approach to managing kidney disease based on the primary diagnosis.

Introduction

Chronic kidney disease (CKD) is a global healthcare problem, with an estimated prevalence of over 13% in adults and higher rates in lower and middle-income countries [1, 2]. Unlike other noncommunicable diseases, CKD mortality is on the rise and is projected to be the 5th leading cause of death worldwide in 2040 [3].

Our awareness of the epidemiology and global significance of CKD has improved greatly since the turn of the century [4]. This is likely, in part, the result of a unified definition of CKD. Before the publication of KDOQI's definition in 2002 [5], further developed by KDIGO in 2012 [6], there was great variability in how clinicians defined what we now call CKD [7]. This unified definition has not only led to a better understanding of CKD epidemiology but was also a key stepping stone to the conduct of large clinical trials focused on common pathway mechanisms of CKD progression, a shortfall that was lamented in the early 2000s [8].

However, the definition of CKD is broad. It encompasses all with a persistent eGFR <60 mL/min/1.73 m^2 or a higher eGFR with the presence of albuminuria or other evidence of kidney damage [6]. Under this umbrella are numerous primary renal diseases, each with their own unique pathophysiology and rate of progression [9]. Heterogeneity of risk within CKD has been previously described; an Australian study identified nine different patterns of CKD progression, which varied significantly according to CKD stage, kidney disease etiology, and patient age [10]. Some older epidemiological studies have also shown how CKD progression varies by primary diagnosis, but more data are needed [9, 11]. To encourage clinicians to consider the primary renal diagnosis (PRD), the KDIGO classification system categorized CKD according to cause, GFR category, and albuminuria category ("CGA") [12]. However, the former is often neglected, and in many cases, the primary renal disease is unknown.

Only a small proportion of people with CKD progress to kidney replacement therapy (KRT), yet KRT accounts for over half of renal healthcare expenditure and carries a significant relative risk of death and worse quality of life [13]. Understanding the risk factors associated with progression in disease subcategories is crucial for enabling personalized treatment strategies. However, current endorsed risk prediction models do not incorporate PRD and instead adopt a "one size fits all" approach [14]. This is problematic, as expecting just four biomarkers to perform excellently across every PRD and represent the underlying biology of each is unrealistic.

We aimed to further investigate outcomes and heterogeneity of risk by PRD from a large prospective study of people cared for in UK nephrology clinics, NURTuRE-CKD [15]. We also examined how the traditional risk factors for progression to kidney failure (KF), eGFR, and albuminuria perform in individual primary renal diagnoses to understand if a more personalized approach to CKD care is warranted.

Methods

Study Design

The National Unified Renal Translational Research Enterprise (NURTuRE)-CKD is an ongoing UK, prospective multicentre cohort study of 2,996 adults with an

eGFR of 15–59 mL/min/1.73 m^2 or eGFR ≥60 mL/min/1.73 m^2 with a uACR >30 mg/mmol. Recruitment from 16 nephrology centers in England, Wales, and Scotland was completed in 2019. Data regarding outcomes (deaths, initiation of KRT) and all biochemistry results generated as part of clinical care, including serial eGFR measurements until December 31, 2022, were sourced from the UK Renal Registry. The study design and methods of NURTuRE-CKD have been reported [15]. Angiotensin-converting enzyme inhibitors or receptor blockers (ACEi/ARB) use was collected; however, due to the study enrolment period (July 2017–September 2019), sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide-1 receptor agonists, and nonsteroidal mineralocorticoid receptor antagonist use was not.

Laboratory Methods

Baseline visit serum creatinine and urine albumin-to-creatinine ratio (uACR) were measured centrally on stored samples at Geneva University Hospitals, Switzerland, and analyzed on routine Roche Cobas 8000/c702/c502 chemistry analyzers under ISO 15189 certification. Other routine biochemistry analyses and full blood counts were performed in local hospital laboratories. GFR was estimated using the 2009 Chronic Kidney Disease Epidemiology Collaboration equation without the ethnicity variable, as recommended by the National Institute for Health and Care Excellence in 2021 [16].

Outcomes

The primary outcome was a combined outcome of KF defined as the first event of (1) eGFR <15 mL/min/1.73 m^2 for a sustained period of at least 28 days or (2) initiation of hemodialysis or peritoneal dialysis (KRT) or (3) kidney transplantation. Secondary outcomes were the components of the primary outcome (KRT, transplant and eGFR <15 mL/min/1.73 m^2), eGFR slope (eGFR slope over time in mL/min/1.73 m^2/year), and all-cause mortality (including only those who died before the primary outcome of KF). The eGFR slope was calculated from all available values from the date of enrolment in participants with a minimum of three eGFR values over a minimum of 12 months using linear regression.

Statistical Methods

Baseline and outcome variables are presented for the whole cohort and subgroups according to "primary CKD diagnosis" obtained from clinical records using ERA-EDTA PRD codes [17]. The "glomerular disease" group was separated into a "glomerulonephritis" (GN) and "vasculitis "group" to highlight the differences between these two distinct pathological entities. Patients with idiopathic nephrotic syndrome (primary focal and segmental glomerulosclerosis or idiopathic minimal change disease) were excluded because they were enrolled in the NURTuRE Nephrotic Syndrome cohort study.

Categorical variables are expressed as numbers (percentage total). Continuous variables are expressed as median (interquartile range). Covariates were compared across PRD. Categorical variables were compared by the χ^2 test. Continuous variables were compared via the Kruskal-Wallis test. A p value of <0.05 was regarded as statistically significant.

Linear regression was used to calculate the post-enrolment eGFR slope. Spearman's correlation was used to assess the relationship between baseline eGFR and eGFR slope (estimated by linear regression). Spearman's correlation was chosen because both variables were not normally distributed, as determined by histograms, the Shapiro-Wilk test, and skewness analysis.

Multivariable Cox proportional hazards regression models were constructed to analyze the time to KF across different primary renal diagnoses. Miscellaneous renal disease, of which 742 (90.4%) was CKD of unknown cause, was used as the reference class, selected to highlight the role of specific CKD diagnoses in influencing the progression to KF. Unadjusted hazard ratios (HRs) for the 7 CKD diagnosis categories in relation to CKD miscellaneous are depicted. Model 1 adjusts for age and sex, model 2 additionally adjusts for baseline eGFR, and model 3 adjusts for modifiable risk factors renin-angiotensin-aldosterone system inhibitors (RAASi), blood pressure (BP) and HBA1c; each model is additive, including the variables in the previous models. The Fine and Gray sub-distribution hazard model was applied to address the competing risk of death prior to KF [18]. Adjustments were made for the same covariates as in the Cox proportional hazards models, ensuring consistency across analyses and allowing for a direct comparison of the impact of competing risks on our findings. Cumulative incidence function curves were used to analyze the event of KF, accounting for the competing risk of death before KF. Gray's test was applied to assess the differences between groups in the presence of competing risks. Time-to-event data were defined as the duration from study enrolment to the event of interest, with censoring occurring at either death (unless an event of interest) or the last follow-up (December 31, 22).

To understand the added discriminatory value that albuminuria provides, in addition to eGFR and other important covariates, for the outcome of KF in the total cohort and by individual PRD, the multivariate Cox

proportional hazards regression model (model 3). The predictive performance of the Cox model was evaluated using Harrell's C-index, comparing model 3 (which includes eGFR, age, sex, BP, HbA1c, and RAASi) with model 3 + uACR. The "systemic diseases" group was too small for meaningful analysis and was excluded from this analysis.

To assess the incremental predictive value of adding uACR to model 3, the gross difference in Harrell's C-index is presented. Additionally, the Net Reclassification Index (NRI) was used to quantify the improvement in prediction accuracy when uACR was added. The NRI was calculated based on the median follow-up time of 1,463 days and includes the overall NRI, as well as category-specific NRIs for events (NRI+) and nonevents (NRI−). All statistical analysis was performed using IMB SPSS statistics version 29 and R Studio version 2023.09.1.

Results

Table 1 describes baseline variables for the total cohort and by PRD. At the time of centralized assessment, 95 of the 2,996 participants had an eGFR <15 mL/min/1.73 m^2 and 263 did not have uACR results, hence, were excluded from the analysis, resulting in 2,638 participants for analysis. Median age was 67 years, 58.8% were male, and 86.6% were white, 30.5% of participants had a diagnosis of diabetes (type 1 or 2), and 85% had a diagnosis of hypertension. Median eGFR was 33.5 mL/min/1.73 m^2, uACR 29.8 mg/mmol. The renal vascular group had the highest median age at 71 years, followed by CKD miscellaneous at 70 years and diabetic kidney disease (DKD) at 67 years. The lowest median age was the familial/hereditary group at 54 years. At the baseline visit, the systemic disease group had the lowest median BP at 111/66 mm Hg. The DKD group had the highest recorded median BP at 145/75 mm Hg. ACEi/ARB use was highest in the GN group at 86.2% and lowest in the tubulointerstitial disease group at 45.5%. Median uACR was highest in the GN group at 103.1 mg/mmol followed by DKD at 80.2 mg/mmol. Median uACR was lowest in the familial/hereditary group at 12 mg/mmol. Median eGFR was lowest in the DKD group at 29.7 mL/min/1.73 m^2 and highest in the systemic diseases group at 40.5 mL/min/1.73 m^2.

Outcomes for the total cohort and by PRD can be seen in Table 2. Median follow-up was 49.2 months. Of the 2,638 participants, 630 (23.9%) experienced the combined outcome of KF. Of which, 45 (7.1%) initiated dialysis (either hemodialysis or peritoneal dialysis), 9 (2.5%) received a kidney transplant, and 576 (91.4%) experienced a sustained eGFR <15 mL/min/1.73 m^2. The median eGFR slope of the entire cohort was −1.97 mL/min/1.73 m^2. There were 352 (13.3%) deaths prior to KF.

All outcome events differed significantly between the primary renal diagnoses. The DKD group had the highest rates of KF (35.7%), closely followed by the familial/hereditary group (30.5%). The rates of death were highest in the DKD (22.2%) and systemic diseases group (25%). The familial/hereditary group evidenced the lowest mortality rate at 4.3%, although they were the youngest.

eGFR slope by PRD can be seen in Figure 1 and Table 2. The median number of eGFR values used to calculate the eGFR slope was 21, there were 174 (6.6%) without adequate data (≥3 values over a minimum of 12 months) for slope calculation. The familial/hereditary and DKD groups progressed most rapidly with median eGFR slopes of −3.5 (−5.3 to −2.1) and −3.2 (−5.3 to −1.0) mL/min/1.73 m^2/year, respectively. The tubulointerstitial and vasculitis groups progressed the slowest with eGFR slopes of −1.0 (−3.3 to +0.6) and −0.6 (−2.8 to +1) mL/min/1.73 m^2/year, respectively. Given the variation in baseline median eGFR across the primary renal diseases and acknowledging this may affect the post-enrolment eGFR slope estimation by linear regression, Spearman's correlation was conducted to assess the relationship between baseline eGFR and eGFR slope. The Spearman's correlation coefficient was 0.055 ($p = 0.006$), indicating a very weak but statistically significant positive association.

The cumulative incidence function curves were constructed to analyze the event of KF while accounting for the competing risk of death prior to KF (Fig. 2) (online suppl. Table 1; for all online suppl. material, see https://doi.org/10.1159/000541770). The highest cumulative incidence of KF at 1 year was observed in patients with DKD, with a cumulative incidence of 12.1%. The lowest incidence of KF at 1 year was found in patients with tubulointerstitial disease at 1.4%. By 5 years, patients with familial/hereditary nephropathies showed the highest cumulative incidence of KF at 37.0%, despite starting with a relatively low 1-year incidence of 5.6%, surpassing the 5-year incidence in DKD at 36.3%. Familial/hereditary nephropathies followed by tubulointerstitial diseases had the lowest 5-year mortality cumulative incidences. The relatively low competing risk of death in these two groups may account for the steeper rise in cumulative incidence of KF over the 5-year follow-up. Statistical analysis using Gray's test indicated significant differences

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Table 1. Baseline variables by primary renal diagnosis

	DKD	Familial/ hereditary	GN	Renal vascular	CKD miscellaneous	Systemic	Tubulointerstitial	Vasculitis	All patients	*p* value
Number	297	302	398	232	821	60	292	236	2,638	
Age, years	67 (59–73.5)	54 (45–66.5)	60 (47–71.5)	71 (64–79.5)	70 (61–75)	66.5 (60–75)	59 (50–71)	70 (59.5–76)	67 (56–74)	<0.001
Male	189 (63.6%)	140 (46.4%)	269 (67.6%)	161 (69.4%)	485 (59.1%)	37 (61.7%)	149 (51%)	121 (51.3%)	1,551 (58.8%)	<0.001
White	247 (83.2%)	258 (85.4%)	319 (80.2%)	197 (84.9%)	740 (90.1%)	55 (91.7%)	254 (87%)	214 (90.7%)	2,284 (86.6%)	<0.001
Diabetes (Type 1 or 2)	297 (100%)	26 (8.8%)	51 (13%)	70 (30.4%)	238 (29.4%)	19 (32.2%)	55 (19.5%)	33 (14.6%)	789 (30.5%)	<0.001
Prior ascular disease	84 (28.3%)	14 (4.7%)	36 (9.2%)	65 (28.3%)	162 (20%)	15 (25.4%)	22 (7.8%)	27 (11.9%)	425 (16.4%)	<0.001
BMI	31.6 (27.2–36.1)	27.0 (24.4–30.1)	29.4 (25.8–32.7)	29.9 (27.1–33.4)	31.8 (27.3–35.3)	28.8 (25.3–32.6)	29.2 (26.3–32.7)	29.6 (27.0–34.8)	30.2 (26.6–34.9)	<0.001
SBP, mm Hg	145 (134–159)	136 (126–143)	137 (120.5–149)	140 (123.5–151)	141 (126–153.5)	111 (102–125)	133 (117–143)	137 (126.5–157.5)	139 (125–153)	<0.001
DBP, mm Hg	75 (70–81)	82 (75–89)	81 (73–87.5)	74 (65–82)	77 (71–85)	66 (60–77)	78 (72–87)	80 (73–83)	77 (70–85)	<0.001
HTN	274 (92.3%)	265 (89.8%)	356 (91%)	214 (93%)	679 (83.9%)	40 (67.8%)	194 (68.8%)	179 (79.2%)	2201 (85%)	<0.001
ACEi/ARB	231 (77.8%)	243 (80.5%)	343 (86%)	163 (70.3%)	491 (59.8%)	44 (73.3%)	133 (45.5%)	140 (59.3%)	1,788 (67.8%)	<0.001
Statin	249 (84.1%)	109 (37.2%)	229 (58.1%)	146 (63.5%)	485 (60.2%)	33 (55%)	123 (43.5%)	134 (56.8%)	1,508 (58.1%)	<0.001
Ever smoked	151 (52.1%)	126 (42%)	194 (49%)	132 (57.1%)	425 (52.6%)	35 (58.3%)	123 (43.3%)	98 (42.1%)	1,284 (49.3%)	<0.001
Albumin, g/L	39.0 (35.0–41.0)	44.0 (39.5–46.0)	41.0 (36.0–44.5)	42.0 (39.0–45.0)	42.0 (38.0–45.0)	39.0 (33.0–44.0)	45.0 (42.0–46.0)	40.0 (37.5–44.0)	41.0 (37.0–44.0)	<0.001
Potassium, mmol/L	4.8 (4.5–5.2)	4.5 (4.2–4.8)	4.6 (4.3–4.9)	4.6 (4.3–5.0)	4.6 (4.2–5.0)	4.7 (4.5–4.9)	4.7 (4.4–5.1)	4.3 (4.2–4.7)	4.7 (4.3–5.0)	<0.001
Bicarbonate, mmol/L	24 (22–27)	24.7 (23–26.9)	24.3 (22.5–27)	24.5 (23–27)	25 (23–27)	26.5 (24–29)	23.8 (21.8–26)	26 (24–29)	24.7 (22.9–27)	0.004
HbA1c, mmol/mol	58.8 (49–69)	40 (35.5–46.2)	42.1 (38–50)	45 (39.5–52)	45 (38–60)	54.5 (41–70)	41 (36–48)	39 (36–55.6)	46.4 (39–60)	<0.001
Hb, g/L	117 (107–128)	135 (126–146.5)	129 (119.5–143)	125 (114–137.5)	125 (112–137)	122 (106–134)	131 (120–139)	125 (112.5–133)	125 (113–137)	<0.001

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Table 1 (continued)

	DKD	Familial/ hereditary	GN	Renal vascular	CKD miscellaneous	Systemic	Tubulointerstitial	Vasculitis	All patients	*p* value
Phosphate, mmol/L	1.15 (1.03–1.32)	1.1 (0.96–1.28)	1.06 (0.95–1.2)	1.06 (0.94–1.21)	1.11 (1.01–1.29)	1.19 (0.95–1.33)	1.04 (0.96–1.24)	1.04 (0.89–1.17)	1.1 (1.0–1.3)	<0.001
PTH, pmol/L	34.2 (13.9–85.5)	9.3 (5.2–15.3)	8.9 (4.3–35)	15.0 (8.3–38)	14.2 (7.1–41.5)	24.5 (8.4–58)	8.6 (5.6–16.7)	21.0 (7.3–53)	15.4 (6.8–49.2)	<0.001
uACR, mg/ mmol	80.2 (17.5–224.5)	12.0 (2.9–42.4)	103.1 (45.9–201.5)	10 (3.2–41.6)	18.7 (3.6–94.6)	3.5 (1.8–60.6)	12.0 (2.2–35.9)	25.0 (4.5–58.7)	29.8 (5.4–121.5)	<0.001
eGFR-EPI, mL/ min/1.73 m^2	29.7 (22.0–41.1)	40.7 (34.2–60.8)	39.2 (30.4–59.1)	29.6 (22.7–37.3)	31.5 (23.1–42.4)	40.5 (28.9–50.0)	35.8 (27.4–48.8)	38.5 (30–48.1)	33.5 (23.9–45.5)	<0.001

Categorical variables are expressed as numbers (%), and continuous variables are expressed as median (25th to 75th percentile). The medians of variables were compared across all groups simultaneously using the Kruskal-Wallis test, while the categorical variables were compared via the χ^2 test. The resulting *p* value reflects the presence of any significant differences between the groups. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, diagnosis of hypertension; ACEi/ARB, ACE inhibitor or angiotensin receptor blocker use; Hb, hemoglobin; PTH, parathyroid hormone; uACR, urinary albumin-to-creatinine ratio; eGFR-EPI, estimated glomerular filtration rate by CKD-EPI 2009 equation.

Table 2. Outcomes for the total cohort and by primary renal diagnosis

	DKD	Familial/ hereditary	GN	Renal vascular	CKD miscellaneous	Systemic	Tubulointerstitial	Vasculitis	All patients	*p* value
Follow-up, months	39.2 (16.0–50.3)	49.4 (40.7–55.4)	49.6 (37.2–55.7)	47.8 (33.4–55.8)	49.0 (33.9–55.5)	48.1 (20.4–58.4)	51.9 (44.1–56.4)	50.9 (43.1–56.3)	49.2 (35.3–55.7)	<0.001
KF	106 (35.7%)	92 (30.5%)	101 (25.4%)	55 (23.7%)	181 (22%)	11 (18.3%)	51 (17.5%)	33 (14%)	630 (23.9%)	<0.001
Dialysis	7 (6.6%)	3 (3.3%)	7 (6.9%)	6 (10.9%)	10 (5.5%)	3 (27.3%)	1 (2.0%)	8 (24.2%)	45 (7.1%)	
Transplant	1 (0.9%)	2 (2.2%)	2 (2.0%)	0	2 (1.1%)	0	1 (2.0%)	1 (3.0%)	9 (2.5%)	
eGFR<15	98 (92.5%)	87 (94.6%)	92 (91.1%)	49 (89.1%)	169 (93.4%)	8 (72.7%)	49 (96.1%)	24 (72.7%)	576 (91.4%)	
Death	66 (22.2%)	13 (4.3%)	35 (8.8%)	41 (17.7%)	130 (15.8%)	15 (25.0%)	23 (7.9%)	29 (12.3%)	352 (13.3%)	<0.001
GFR slope, mL/ min/1.73 m^2/ year	−3.2 (−5.5 to −1.0)	−3.5 (−5.3 to −2.1)	−2.4 (−4.9 to −0.4)	−1.7 (−3.5 to −0.1)	−1.6 (−3.3 to −0.2)	−1.3 (−4.0 to −0.2)	−1.0 (−3.3 to 0.6)	−0.6 (−2.6 to 1.0)	−1.97 (−4.1 to −0.3)	<0.001

Categorical variables are expressed as numbers (%). Continuous variables are expressed as median (25th to 75th percentile). The medians of variables were compared across all groups simultaneously using the Kruskal-Wallis test, while the categorical variables were compared via the χ^2 test. The resulting *p* value reflects the presence of any significant differences between the groups. The proportions of the three components defining KF – dialysis, transplant, and eGFR <15 – are detailed. The percentages reflect the proportion of each component among those who experienced KF within each diagnostic group.

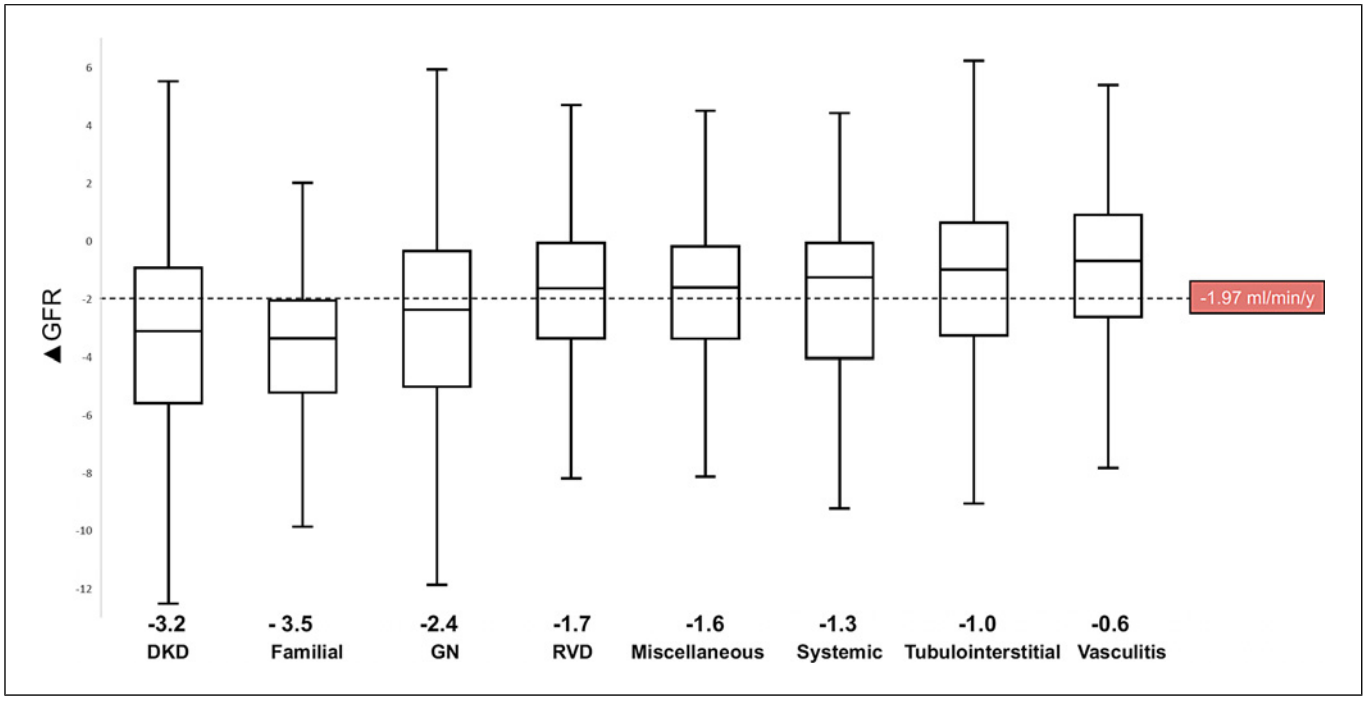

Fig. 1. Boxplot of post-enrolment delta eGFR slopes (mL/min/1.73 m^2/year) by primary renal diagnosis. The dotted horizontal line represents the median delta eGFR for the entire cohort. DKD, diabetic kidney disease; Familial, familial/hereditary nephropathies; GN, glomerulonephritis; RVD, renal vascular; Miscellaneous, CKD miscellaneous; Systemic, other systemic diseases affecting the kidneys).

across the groups for both KF and death prior to KF, with *p* values of less than 0.001 for both outcomes.

Table 3 shows multivariable Cox proportional hazards regression analyses predicting the time to KF by PRD compared to the CKD miscellaneous group. In unadjusted analysis, DKD and familial/hereditary nephropathies were positively associated with KF, while the vasculitis and tubulointerstitial diseases groups were negatively associated with the event, compared to CKD miscellaneous. Model 1 adjusts for age and sex; this did not change the directionality or significance of any associations. Model 2 adjusts for eGFR at baseline. In this model, DKD and familial/hereditary nephropathies remained positively associated with KF, and GN emerged as significant. Vasculitis and tubulointerstitial disease lost their negative association with KF after adjustment for baseline eGFR. Model 3 adjusted for modifiable risk factors but did not alter the trends. The Fine and Gray analysis was then used to model the competing risk of death; sub-distribution HRs (sHR) can also be seen in Table 3. Adjusting for the competing risk of death did not significantly alter the associations; however, the sHR was lower for each when modeling for the competing risk of death.

In the total cohort and each PRD, Harrell's C-index was used to assess the predictive accuracy of model 3 and model 3 plus uACR to understand the additive value uACR for KF across each specific PRD category (see Table 4). Overall, the C-index of model 3 was 0.857. When combined with uACR, the C-index increased to 0.873. The Net Reclassification Improvement (NRI) was 0.04, indicating that the addition of uACR to the model provided an overall modest improvement of 4% in classification accuracy for KF over eGFR plus age, sex, BP, HBA1c, and RAASi. Concerning individual primary renal diagnoses, the added predictive benefit of uACR was greatest in the vasculitis group with an NRI of 21.1% followed by renal vascular at 13.4% and DKD at 8.8%. It offered minimal to no value in the familial/hereditary group and the GN group with an NRI of 1.2% and 0%, respectively.

Discussion

The major finding of the study was the significant differences in the risk of kidney-related outcomes that occurred across the various primary renal diagnoses,

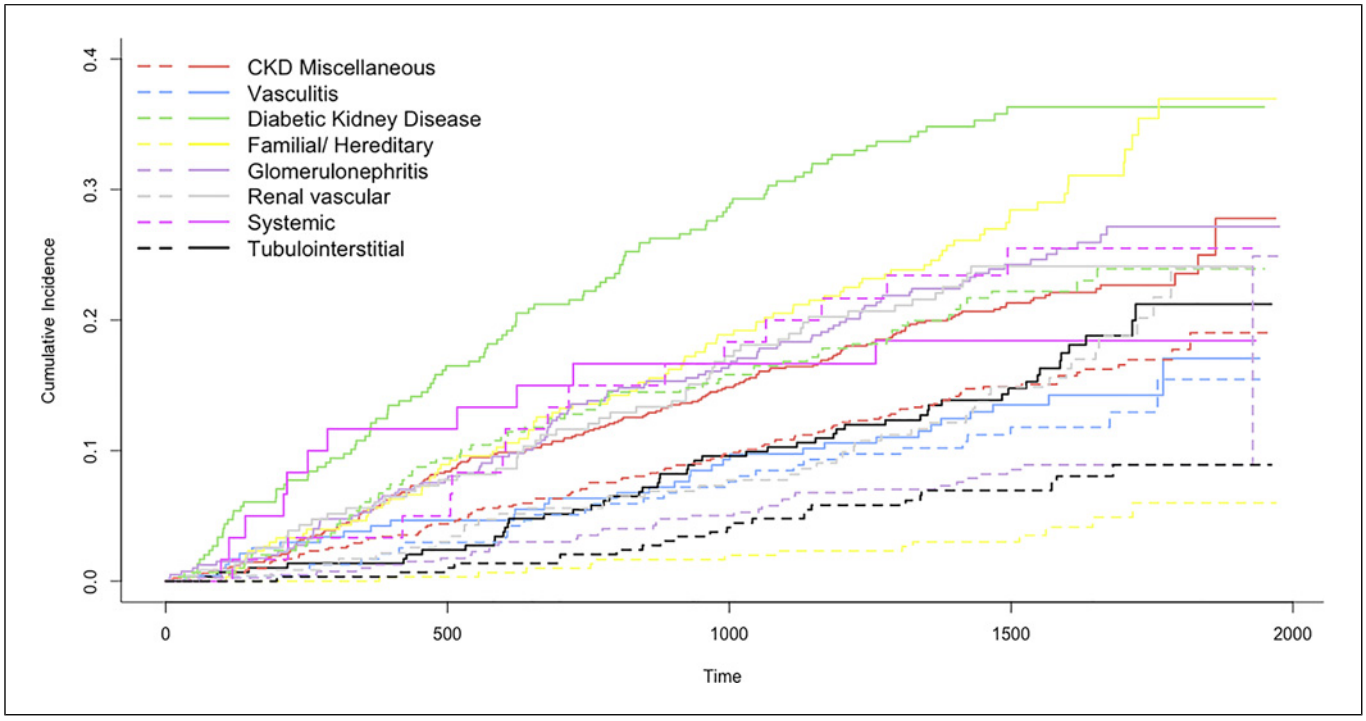

Fig. 2. Cumulative incidence curve for KF while accounting for the competing risk of death by primary renal diagnosis (the blocked line is the event of KF, and the dotted line is the event of death pre-KF).

Table 3. Hazard ratios and sub-distribution hazard ratios for KF by primary renal diagnosis: multivariable Cox and competing risk models

	Unadjusted		Model 1		Model 2		Model 3		Competing risk	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	sHR	95% CI
Vasculitis	**0.59**	**(0.40–0.85)**	**0.60**	**(0.41–0.87)**	1.05	(0.73–1.53)	1.12	(0.53–2.37)	1.10	(0.74–1.64)
DKD	**2.04**	**(1.60–2.59)**	**2.00**	**(1.57–2.54)**	**1.89**	**(1.49–2.40)**	**1.71**	**(1.18–2.49)**	**1.53**	**(1.17–2.01)**
Familial/hereditary nephropathies	**1.32**	**(1.03–1.70)**	**1.33**	**(1.03–1.73)**	**2.13**	**(1.65–2.76)**	**2.54**	**(1.36–4.73)**	**2.31**	**(1.78–3.00)**
GN	1.11	(0.87–1.42)	1.05	(0.81–1.34)	**1.62**	**(1.26–2.09)**	**1.91**	**(1.16–3.14)**	**1.66**	**(1.23–2.22)**
Renal vascular	1.07	(0.79–1.44)	1.03	(0.76–1.39)	1.01	(0.75–1.37)	1.50	(0.93–2.43)	1.03	(0.73–1.44)
Other systemic diseases	0.90	(0.49–1.65)	0.90	(0.49–1.65)	1.33	(0.72–2.44)	1.69	(0.52–5.46)	1.26	(0.67–2.39)
Tubulointerstitial disease	**0.70**	**(0.52–0.96)**	**0.71**	**(0.52–0.97)**	0.73	(0.54–1.00)	0.86	(0.45–1.62)	0.82	(0.59–1.13)

Multivariable Cox proportional hazards models predicting time to kidney failure (KF) across seven primary renal diagnoses (PRDs), with CKD miscellaneous as the reference category. Unadjusted hazard ratios (HRs) are shown for each PRD. Model 1 adjusts for age and sex, model 2 adds adjustments for baseline eGFR, and model 3 further adjusts for renin-angiotensin-aldosterone system inhibitors (RAASi), BP, and HbA1c. Each model builds on the covariates from the previous model. The competing risk of death is handled using the Fine and Gray sub-distribution hazard model (sHR), incorporating the same covariates as in the Cox proportional hazards model. The values in bold represent the statistically significant hazard ratios.

Table 4. Improvement in predictive accuracy of KF by albuminuria across primary renal diagnoses: Harrell's C-index and NRI

	C-index, model 3	C-index, model 3 + ACR	Difference	NRI	NRI+	NRI-
Total cohort	0.857	0.873	0.016	0.040	0.043	−0.003
DKD	0.843	0.867	0.024	0.088	0.090	−0.002
Familial/hereditary nephropathies	0.916	0.917	0.001	0.012	0.012	0.000
GN	0.844	0.847	0.003	0.000	0.000	0.000
Renal vascular	0.841	0.872	0.031	0.134	0.134	0.000
CKD miscellaneous	0.858	0.885	0.027	0.054	0.066	−0.012
Tubulointerstitial	0.860	0.866	0.006	0.044	0.048	−0.004
Vasculitis	0.867	0.884	0.017	0.211	0.216	−0.005

Comparison of Harrell's C-index for model 3 (adjusted for age, sex, baseline eGFR, renin-angiotensin-aldosterone system inhibitors [RAASi], BP, and HbA1c) and model 3 + uACR for predicting kidney failure (KF) over a median follow-up of 1,463 days. The difference in C-index indicates the incremental predictive benefit of adding uACR to the model. The Net Reclassification Index (NRI) quantifies the improvement in the classification of individuals into risk categories with the addition of uACR, reported as overall NRI, NRI for improved classification of events (NRI+), and NRI for improved classification of nonevents (NRI–).

persisting after adjustment for age, sex, and baseline eGFR. Diabetic kidney disease (DKD) and familial/hereditary nephropathy were associated with the greatest risk, while tubulointerstitial disease and vasculitis carried a low risk of KF. The predictive performance of albuminuria for the outcome of KF varied by PRD, performing best in the vasculitis group and offering no benefit in the familial/hereditary group. Our observations demonstrate the importance of considering cause as well as eGFR and albuminuria categories in the risk-based classification system for CKD proposed by KDIGO. Recognizing the heterogeneity of risk within CKD is not only key to providing personalized care but also key to understanding disease-specific mechanisms of progression.

The description of CKD as a clinical entity is supported by a large body of research identifying common pathways and mechanisms of disease progression, tracking disease epidemiology, and defining entry criteria for clinical trials. However, for the practice of personalized medicine, it is essential to recognize the diverse nature of CKD. In line with NURTuRE-CKD, prior studies have shown differing rates of CKD progression by PRD. Rapid progression in those with autosomal dominant polycystic kidney disease (ADPKD), the predominant diagnosis in the familial/hereditary group, was previously observed in the Modification of Diet in Renal Disease (MDRD) study [9, 11]. Additionally, those with DKD and glomerular disorders have also been shown to progress quickly [9, 11]. In contrast, those with vasculitis and tubulointerstitial disease in NURTuRE progressed at rates similar to the average yearly age-related eGFR loss [19]. Acknowledging the heterogeneity within CKD has significant clinical implications. We have demonstrated that after controlling for age, sex, and eGFR, the risk of KF was significantly higher in those with DKD and ADPKD compared to those where the diagnosis was not known. Yet in this scenario, guidelines recommend a uniform approach to dialysis planning [20]. This analysis underscores not only the importance of considering the PRD when assessing risk but also the vital need for pursuing a specific diagnosis.

An additional important aspect to consider when evaluating dialysis planning is the competing risk of death before KF. Acknowledging this clinically is essential, as overlooking it may lead to conflated risk, a limitation observed in current risk prediction models [21, 22]. Despite the relatively high mortality rates seen in the DKD group, when the competing risk of death was modeled in NURTuRE, DKD remained significantly associated with the outcome of KF, though the strength of the association was lower.

Several risk prediction tools have been proposed to help discern who will need to initiate dialysis [23], with the 4 variable kidney failure risk equation (KFRE) being the most well-validated [14]. Its use has been suggested for both referral to nephrology and for guiding the timing of vascular access [24]. The 4 components of the KFRE are age, sex, uACR, and eGFR. In this, albuminuria is the only "damage marker" and is predominately a marker of glomerular damage [25, 26]. Mechanistically, one would expect it to perform best in those diseases with primarily

glomerular pathologies. A scientific workshop conducted an evaluation of evidence regarding the use of albuminuria as an endpoint for clinical trials and recommended avoiding its use in diseases not characterized by albuminuria, such as polycystic kidney disease or tubulointerstitial diseases. Instead, it proposed that total kidney volume or markers of tubular injury, respectively, might serve as more effective biomarkers in these conditions [27].

Measured by C-index, eGFR, age, sex, BP, HAB1c, and RAASi use was a good predictor of KF in all individual primary renal diseases in NURTuRE. However, the addition of uACR showed variable benefits, depending on the PRD. The largest improvement was seen in vasculitis, renal vascular, and DKD. However, when added to the familial/hereditary group, it added minimal discriminatory value, reflecting the conclusion of the scientific workshop referred to above. This observation has implications from both a mechanistic and personalized risk prediction perspective. Mechanistically, it makes sense. The primary insult in DKD, vasculitis, and ischemic nephropathy is glomerular. In DKD, albuminuria has strong evidence as both a predictive and prognostic biomarker [27, 28]. In contrast, ADPKD is primarily a tubular disorder, with the development and growth of cysts originating primarily from tubular epithelial cells [29]. The "Biomarkers, EndpointS, and other Tools" (BEST) resource states a biomarker should have "biological plausibility," hence applying uACR in ADPKD lacks the direct pathophysiological correlation seen in DKD, suggesting the need for more disease-specific biomarkers [30]. uACR also added no additional discriminatory value for KF among the GN cohort. This initially would seem surprising as GN is primarily a glomerular disorder. However, even with the exclusion of idiopathic nephrotic syndrome, there was still noticeable heterogeneity within this group, including patients who were on immunosuppression. Compared to other disease groups such as DKD, albuminuria might not represent a mechanism of CKD progression in our GN group but rather a potential signal of relapse/remission. Additionally, since uACR was highest in this group at baseline, the widespread presence of albuminuria may dilute its effectiveness as a marker for distinguishing progression risks. Interestingly, uACR performed well in the miscellaneous CKD group, where the diagnosis was unknown for 90.4% of the cases. This may provide insight into underlying diagnoses, such as hypertensive disease. It also underscores the value of measuring uACR in undiagnosed cases, particularly in primary care, where this is often the case.

When considering the validity of KFRE in primary renal disease, one study showed that KFRE underappreciated risk in ADPKD [31]. This could be attributed to the weight of uACR as a predictive variable in the KFRE equation, which is not an effective prognostic biomarker in ADPKD. Nevertheless, KFRE has been examined in several other cohorts of diverse primary renal diseases and tends to perform well. Indeed, the combined C-index of KFRE + modifiable risk factors in NURTuRE for the familial/hereditary cohort was the highest of all primary renal diseases. However, adding uACR to the model did not significantly enhance the predictive accuracy. This reveals that the strong performance of the combined model is driven solely by eGFR and also highlights that merely assessing the discriminatory metric of the combined models is not sufficient, and the additive value of individual biomarkers must be demonstrated [32].

Strengths and Limitations

NURTuRE-CKD is a large, well-phenotyped cohort of secondary care non-dialysis CKD participants with very few exclusion criteria. There was a broad spectrum of included primary renal diagnoses and a large number of events over the follow-up period which allowed comparison of events between groups.

One limitation of this study was the residual heterogeneity within each subgroup, despite dividing the cohort into eight distinct primary renal diagnoses following the ERA coding system. This is particularly evident in the renovascular group, as well as the GN group. Although the ERA "glomerular diseases" category was subdivided into GN and vasculitis, the authors balanced the need for further segmentation into individual GN types against maintaining sufficient statistical power to discern differences between groups. This suggests the potential for more detailed analysis to explore variations between subcategories. Furthermore, this was a predominately white cohort from UK secondary care. Hence, its findings may not be generalizable to primary care settings or populations with differing demographics.

Conclusion

Within NURTuRE-CKD, there were significant differences in the risk of kidney-related outcomes that occurred across the various primary renal diagnoses, persisting after adjustment for age, sex, and baseline eGFR. Defining CKD by GFR and albuminuria category alone risks neglect of important cause-specific impact on prognosis and treatment [33]. The discriminatory ability

of albuminuria as a biomarker of progression varies by diagnosis, which reflects differences in the mechanisms of disease progression. Our data support the notion that in this era of precision medicine, CKD care should be personalized and always consider the PRD.

Statement of Ethics

All participants provided written informed consent. The study was approved by the South Central-Berkshire Research Ethics Committee REC reference: 16/SC/0623, abides by the principles of the Declaration of Helsinki, and is registered at ClinicalTrials.gov (NCT04084145).

Conflict of Interest Statement

T.M. has no conflict of interest. P.A.K. reports grant funding from Vifor and Astellas, consulting fees from Astra Zeneca, Vifor, Unicyte and UCB, honoraria from Vifor, Astra Zeneca and Pfizer, support for attending meetings from Pharmacosmos and Vifor. N.V. reports leadership positions at the swiss clinical chemistry association and swiss laboratory medicine (FAMH) associations and a patent with Roche. P.C. reports a leadership position in the UK Kidney Association; S.D.S.F. reports grant funding from Kidney Research UK; D.C.W. reports grant funding from Kidney Research UK, consultancy fees from Astellas, AstraZenca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Gilead, Janssen, ProKidney, and Tricida, honoraria from Amgen, Mundipharma, Merck Sharp and Dohme and Zydus; support for attending meetings from Astellas and Astra Zeneca; participation in the data safety monitoring board for the following studies: ProKidney; Galderma; Eledon and a leadership role in the International Society of Nephrology; R.E.B. reports grant funding and a patent with Randox Laboratories. M.W.T. reports consulting fees from Boehringer Ingelheim, honoraria from Bayer and support to attend conferences from Bayer and a leadership role in the International Society of Nephrology.

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Author Contributions

Manuscript was drafted by T.M. P.A.K. N.V, and M.W.T. Data analysis was performed by T.M and interpreted by T.M. P.A.K. N.V, and M.W.T. P.A.K. N.V P.C. S.D.S.F. D.C.W. R.E.B., and M.W.T. contributed to conception and design of the NURTuRE-CKD study. Manuscript was reviewed and revised by all co-authors.

Data Availability Statement

The data that support the findings of this study are not publicly available due to the requirements of the UK Data Protection Act and conditions of the Research Ethics Committee approval. Access to anonymized participant-level data will be made available to external investigators upon successful application to the independent data access committee which can be made via the NURTuRE website: https://nurturebiobank.org/information-for-researchers/applying-for-data-and-samples/.

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