Urine Albumin:Creatinine Ratio (ACR), Protein:Creatinine Ratio (PCR) and non-albumin proteinuria to predict Kidney Failure in rare kidney diseases, using data from the National Registry of Rare Kidney Diseases (RaDaR)

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Background

- Proteinuria has been shown to be associated with increased risk of Kidney Failure (KF) and cardiovascular events in large, population-based CKD cohort studies
- Urine Albumin:Creatinine Ratio (ACR) has been the preferred urinary protein measurement in clinical guidelines, risk prediction models and clinical trials in CKD, due in part to increased sensitivity in identifying early diabetic nephropathy, a significant contributor to CKD globally.
- However, how ACR, urine Protein:Creatinine Ratio (PCR) and non-albumin proteinuria predict KF in patients with rare kidney diseases, where distinct aetiologies may lead to different glomerular/tubular proteinuria profiles to general CKD, is unknown. Additionally, there is little information regarding how equations converting PCR to ACR, developed in large unselected CKD cohorts, perform in rare kidney diseases. Finally, whether ACR estimated from PCR (estACR) predicts KF with the same accuracy as measured ACR in this cohort is unclear.
- We aimed to address these questions using same-day paired ACR and PCR data for 4478 patients from the UK National Registry of Rare Kidney Diseases.

Methods

- RaDaR receives laboratory data for fully consented patients from 108 renal sites via the UK Renal Data collaboration, and validated data on KRT initiation and death via the UK Renal Registry. Patients with same-day ACR and PCR measurements were eligible. Data after KRT initiation, and within 6 months of diagnosis were excluded. For patients with multiple paired measurements, one was chosen at random. Analyses were undertaken for the whole cohort, and by disease subtype (Glomerular, Cystic, Tubular, Other)
- Calibration plots were used to assess the performance of conversion of PCR to ACR using approximate factor of ACR = PCR*0.7 and the *Weaver et al* model[1]
- To assess whether ACR or PCR has a stronger association with outcomes, Cox regression models adjusting for age, sex, eGFR and rare disease group were run with four different methods of quantifying proteinuria; ACR, PCR, ACR and non-albumin proteinuria (NAP), and ACR estimated from PCR using *Weaver's* model (estACR). Model fit was assessed using AIC (Akaike information criterion) and SBC (Schwarz Bayesian information Criterion) values, Receiver Operator Curves and estimated time-dependent AUC at 5-years, and Uno's C-statistic was used to compare concordance of each quantification method.
- 5-year KFRE (Kidney Failure Risk Equation) scores were estimated using observed ACR and estACR and Brier scores calculated for each method.

Results

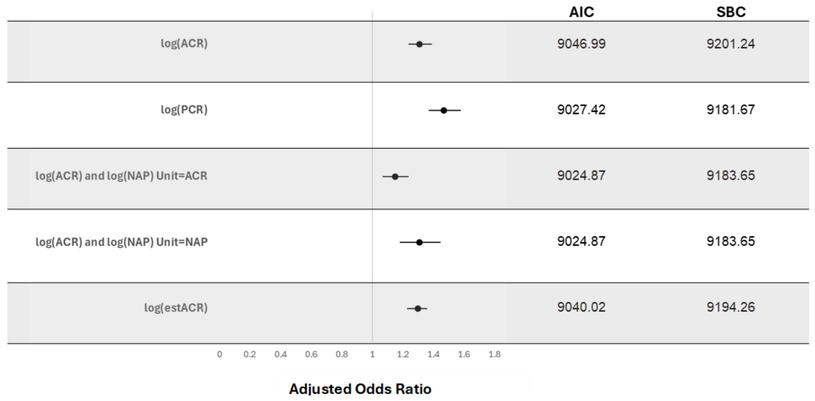
4478 patients
2015 (45%) female
Median age 54 years (IQR 40-67)

710 experienced a KF or death event

983 (22%) cystic 3180 (71%) glomerular, 75 (2%) tubular, 240 (5%) other kidney disease

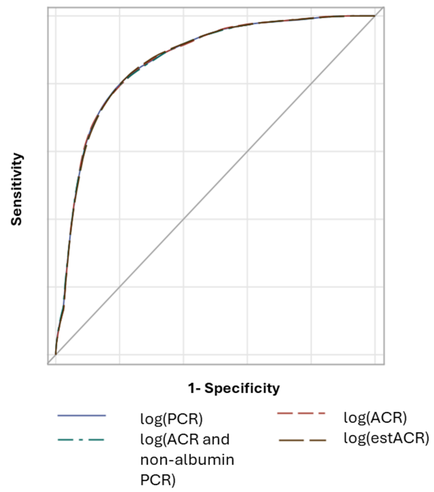
ACR, PCR and non-albumin proteinuria to predict KF

Figure 1: Multivariable cox models of time to kidney failure or death and associated model fit statistics, using each proteinuria measurement



*adjusted for eGFR, age, sex, rare disease group
ACR=urine Albumin Creatinine Ratio; **PCR**= urine Protein Creatinine Ratio; **NAP**= non-albumin proteinuria **AIC**= Akaike information criterion **SBC**= Schwarz Bayesian Information Criterion, where lower AIC and SBC indicate better model fit

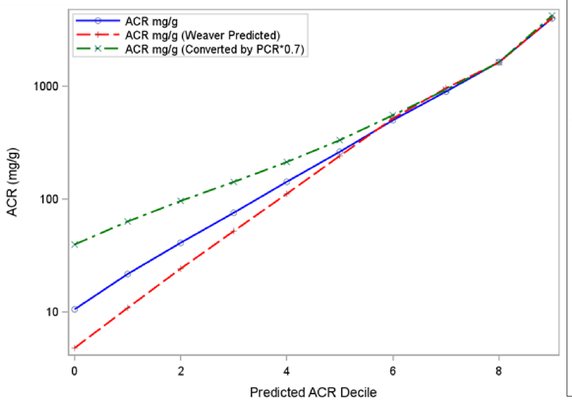
Figure 2: ROC curves at 5-years for Cox models of time from concurrent uACR-uPCR values to Kidney Failure or Death



- **Very similar AIC and SBC statistics (model fit) for all proteinuria measurements, including estimated ACR (estACR).**
- **For glomerular diseases SBC and AIC lowest (indicating best fit) for Cox model using log(PCR), for cystic diseases log(ACR)**
- **ROC curves at 5-years >0.85 for all models**
- **No statistically significant differences in model concordance (using Uno's C-statistic) between any two models (Chi² p>0.2 for all comparisons)**

Conversion of ACR to PCR

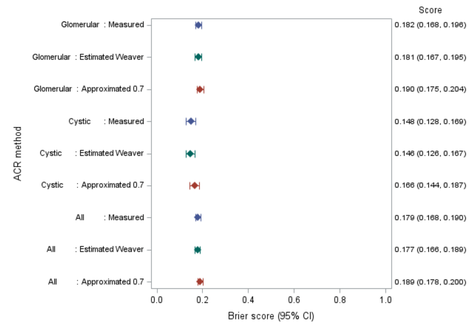
Figure 3:Calibration plot of measured ACR, estACR and approximated ACR= PCR*0.7



- **Non linear association between ACR and PCR, as seen in previous general CKD studies**
- **At lower predicted ACR deciles, conversion of PCR to ACR by the Weaver equation underestimates true ACR, and using the 0.7 conversion ratio overestimates true ACR**

Estimated ACR

Figure 4: Brier scores for accuracy of KFRE using measured ACR, estACR and approximated ACR, by disease sub-type



- **It is known that the KFRE underestimates KF risk at higher risk levels in our rare disease cohort.**
- **That considered, we observed no difference in the performance of the KFRE using measured ACR and estACR: Brier score 0.177 for measured ACR, and 0.176 estACR**

Conclusions

- There was no consistent evidence of superiority of ACR over PCR, non-albumin proteinuria and estACR for prediction of KF or death in our rare kidney disease cohort
- Our results also indicate that estACR had very similar discriminative and predictive ability to measured ACR and PCR, suggesting that estimated ACR can be used interchangeably with measured ACR for patients with rare kidney diseases clinically when using the KFRE for risk prediction, and also in Cox regression models of time to KF for observational studies or clinical trials.

- References: (1) Weaver RG, James MT, Ravani P, Weaver CGW, Lamb EJ, Tonelli M, Manns BJ, Quinn RR, Jun M, Hemmelgarn BR. Estimating Urine Albumin-to-Creatinine Ratio from Protein-to-Creatinine Ratio: Development of Equations using Same-Day Measurements. J Am Soc Nephrol. 2020 Mar;31(3):591-601. doi: 10.1681/ASN.2019060605.

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Celebrating 15 Years RaDaR Registry of Rare Kidney Diseases