PILOT CLINICAL AND VALIDATION STUDY OF THE PROPKD SCORE IN CLINICAL PRACTICE AMONGST PATIENTS WITH Autosomal Dominant Polycystic Kidney Disease

SAMUEL CHAN,¹,² CHIRAG PATEL³ and ANDREW J MALLETT¹,²,³

1.Kidney Health Service, Royal Brisbane and Women’s Hospital, Metro North Health Services, 2Faculty of Medicine, The University of Queensland, and 3Genetic Health Queensland, Royal Brisbane and Women’s Hospital, Metro North and Hospital Health Service, Brisbane, Queensland, Australia

Worldwide, Autosomal Dominant Polycystic Kidney Disease (ADPKD) affects approximately 4–7 million individuals and accounts for 10% of patients receiving renal replacement therapy.¹,² Recently, the PROPKD score was developed from the GENKYST cohort to stratify risk of progression to end-stage kidney disease (ESKD) in patients with ADPKD, based on gender, hypertension <35 years, urological event <35 years and causative PKD1 or PKD2 genotype.³ The PROPKD score showed significant differences in kidney survival between ADPKD patients who were low risk (0–3 points), intermediate risk (4–6 points) and high risk (>6 points) in terms of progression to ESKD.³ Here, we evaluate the PROPKD score amongst 39 unrelated individuals with genetically confirmed ADPKD encountered by the Queensland Conjoint Renal Genetics Clinic Service between 2013 and 2018. Clinical and genetic factors were examined using the PROPKD score to assess its relationship with kidney function decline prediction over 3 years period.

The change in estimated glomerular filtration rate (eGFR) over the most recent 3 years period for each patient was identified by calculating the median value of a minimum of three available eGFR values over 3 years period. The diagnostic sequencing methods used in this study were from accredited diagnostic laboratories, specifically Addenbrooke’s Hospital, Cambridge, United Kingdom, which uses targeted next-generation sequencing and Genome.One, Sydney, Australia which uses whole-genome sequencing. Full methods are available in Appendix S1.

Of the 39 individuals in this pilot study, 15 patients were low risk, 17 were intermediate risk and 7 were high risk (Table 1 and Table S1). All 39 patients harboured a heterozygous pathogenic or likely pathogenic variant in PKD1 or PKD2 accompanying an ADPKD clinical phenotype. There were an additional eight patients who had a PKD1/PKD2 variant of uncertain significance and there were 20 patients who had no mutation detected, and thus these additional 28 patients were not included in the study cohort. The median age for the low-risk group commencing renal replacement therapy (RRT) was 60 years (n = 1/15), 54.5 (n = 6/17) years for the intermediate-risk group, and 55.3 (n = 1/7) years for the high-risk group. The median change in eGFR (Chronic Kidney Disease Epidemiology Collaboration) over the most recent 3 years period for each patient was identified by calculating the median value of a minimum of three available eGFR values over 3 years period. The diagnostic sequencing methods used in this study were from accredited diagnostic laboratories, specifically Addenbrooke’s Hospital, Cambridge, United Kingdom, which uses targeted next-generation sequencing and Genome.One, Sydney, Australia which uses whole-genome sequencing. Full methods are available in Appendix S1.

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To the best of our knowledge, this pilot study is the first reported validation of a prediction tool for kidney dysfunction.

Table 1 Demographic characteristics of the study cohort

| Characteristics                                      | Low risk, n = 15 | Intermediate risk, n = 17 | High risk, n = 7 | P value |
|------------------------------------------------------|-----------------|--------------------------|-----------------|---------|
| Demographics                                         |                 |                          |                 |         |
| Age (interquartile range) (years)                     | 43.5 (36–58)    | 44 (32–54)               | 40 (35–53)      | 0.12    |
| Male gender                                          | 6 (40%)         | 4 (24%)                  | 5 (71%)         | 0.09    |
| Hypertension before 35 years                         | 0 (0%)          | 5 (29%)                  | 7 (100%)        | <.0001  |
| Urological event before 35 years                      | 1 (7%)          | 1 (6%)                   | 4 (57%)         | <.0001  |
| Genetic profile                                       |                 |                          |                 |         |
| PKD2 mutation                                        | 9 (60%)         | 0 (0%)                   | 0 (0%)          | <.0001  |
| Non-truncating PKD1 mutation                         | 6 (40%)         | 0 (0%)                   | 0 (0%)          | <.0001  |
| Truncating PKD1 mutation                              | 0 (0%)          | 17 (100%)                | 7 (100%)        | <.0001  |

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progression in an Australian adult cohort of ADPKD patients in clinical practice. Furthermore, this adds to the previous validation of the PROPKD score in clinical trial cohorts.\textsuperscript{3} This pilot study illustrates two findings. First, the PROPKD score predicts renal dysfunction progression and prognosis in a clinical setting of ADPKD patients. Second, this study shows that patients with a causative PKD2 variant are unlikely to progress to ESKD compared with those who have a PKD1 truncating variant.

To date, published studies examining the progression of ADPKD patients have been based on registry data\textsuperscript{4} or retrospective analysis of clinical trial cohorts.\textsuperscript{5} These studies have not been performed in an unselected clinical setting where patients present with a clinical conundrum. Despite this, there are a few stipulations associated here including the small sample size, although at present, this pilot study represents the largest current single centre sample size of genetically confirmed cases of ADPKD in Australia and is reflective of clinical practice. The analysis performed regarding eGFR decline is clinically significant although the three validation sub-cohorts are limited by size, suggesting that the PROPKD has validity in prognosticating kidney function decline trajectory. Moreover, the proportions of PKD1 truncating variants versus PKD1 hypomorphic variants versus PKD2 variants (19\%, 69\% and 23\%) are different to previous cohorts which may be a result of the limited cohort size. A component of selection bias needs to be considered as patients who were referred to this clinic presented with a clinical indication, rather than participating in a registry study or clinical trial. Finally, although the patients in this cohort do not represent the entire population of those affected by ADPKD in the general community, the median ages of the three risk groups in this cohort correspond to the original cohort\textsuperscript{1} and the TEMPO3:4 study.\textsuperscript{2}

In summary, this pilot study showed that PROPKD score accurately predicts kidney function decline in Queensland ADPKD patients. This prediction tool may enable future personalised clinical prognostication and therapeutic management of ADPKD, as well as for potential participants to be identified for clinical trials.

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**DISCLOSURE**

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**SUPPORTING INFORMATION**

Additional supporting information may be found in the online version of this article at the publisher’s website:

Appendix S1 Details of study population and data collection

Table S1 Identified mutations and corresponding PROPKD score in all patients in this pilot validation study