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Original Article

ORIGINAL ARTICLE

Comparative analysis of tools to predict rapid progression in autosomal dominant polycystic kidney disease

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ABSTRACT

Background. Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic kidney disease and shows a wide phenotype. Only patients with rapid progression (RP) are included in clinical trials or are approved to receive disease-modifying drugs. This study aims at comparing different available predictive tools in ADPKD with the Mayo classification (MC) identification of rapid progressors based on high total kidney volume (TKV) according to age.
Methods. A total of 164 ADPKD patients were recruited retrospectively from a single centre. The performance of diverse tools to identify RP defined as being in MC categories 1C–1E was assessed.
Results. A total of 118 patients were MC 1C–1E. The algorithm developed by the European Renal Association–European Dialysis and Transplant Association Working Group on Inherited Kidney Disorders/European Renal Best Practice had a low sensitivity in identifying MC 1C–1E. The sensitivity and specificity of TKV to predict RP depend on the cut-off used. A kidney length of >16.5 cm before age 45 years has high specificity but low sensitivity. Assessing the MC by ultrasonography had high levels of agreement with magnetic resonance imaging (MRI) data, especially for 1A, 1D and 1E. The estimated glomerular filtration rate (eGFR) decline was very sensitive but had low specificity. In contrast, the Predicting Renal Outcome in Polycystic Kidney Disease (PROPKD) score was very specific but had poor sensitivity. Having hypertension before 35 years of age is a good clinical predictor of MC 1C–1E. Family history can be of help in suggesting RP, but by itself it lacks sufficient sensitivity and specificity.

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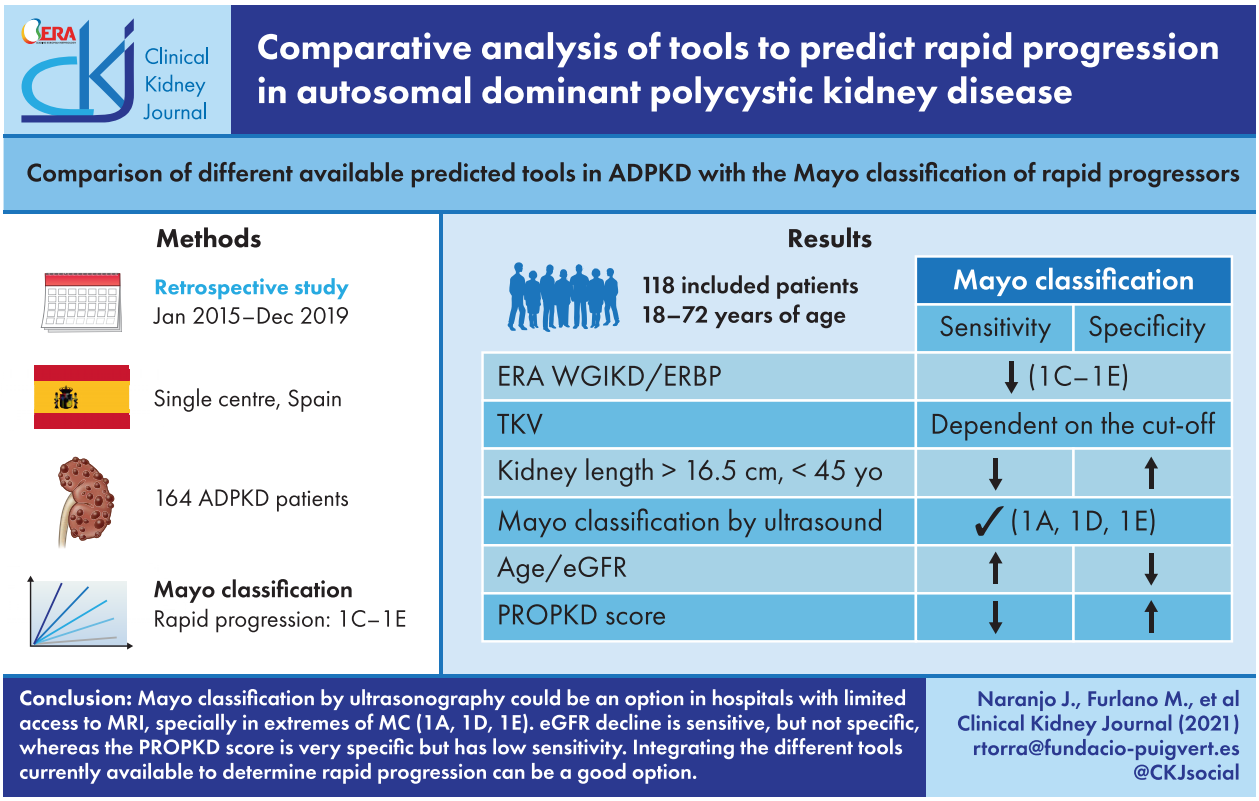
Conclusions. The MC by ultrasonography could be an option in hospitals with limited access to MRI as it performs well generally, and especially at the extremes of the MC, i.e. classes 1A, 1D and 1E. The eGFR decline is sensitive but not very specific when compared with the MC, whereas the PROPKD score is very specific but has low sensitivity. Integrating the different tools currently available to determine RP should facilitate the identification of rapid progressors among patients with ADPKD.

GRAPHICAL ABSTRACT



Keywords: ADPKD, Mayo classification, prediction, PROPKD, rapid progression, total kidney volume

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disorder. It is characterized by fluid-filled cyst development from birth and causes progressive and irreversible deterioration of kidney function, leading to kidney failure [1–3]. ADPKD is genetically heterogeneous and is caused by pathogenic variants in PKD1 (78%), PKD2 (15%), GANAB (0.3%) and DNAJB11 (0.1%) [4–6]. The natural course of ADPKD varies significantly, both within and between families [7]. Identifying patients at high risk for rapid progression (RP) to needing kidney replacement therapy (KRT) has become increasingly important given the emergence of potential new treatments [8, 9]. For example, tolvaptan has been approved only for patients with ADPKD and RP [10]. Currently, multiple potential tools are available to predict disease progression in ADPKD [11]. Unfortunately, there is no consensus on the optimal prediction model for the identification of RP [12]. In 2016, the European Renal Association–European Dialysis and Transplant Association Working Group on Inherited Kidney Disorders/European Renal Best Practice (ERA WGIKD/ERBP) developed an algorithm to identify patients with RP and an indication for treatment [13]. Since this publication, more evidence has been provided on the efficacy of tolvaptan in other subpopulations and also concerning prediction tools for RP assessment in ADPKD [14–17], so this algorithm is now outdated (https://www.era-online.org/en/erbp/blog/category/guidance/). To date, the single most accepted prediction tool is the Mayo classification (MC) [18]. In this study, MC categories 1C–1E were used as the gold standard to define RP for purposes of comparison. We aimed at evaluating the performance of different tools to predict RP (MC categories 1C–1E) in patients with ADPKD.

MATERIALS AND METHODS

A total of 178 patients aged 18–72 years with a diagnosis of ADPKD (according to the criteria proposed by Pei *et al.* [19]), followed at an outpatient clinic for inherited kidney diseases, were studied for RP. All of them underwent magnetic resonance imaging (MRI) between January 2015 and December 2019. Fourteen presented atypical imaging on the MRI and were excluded [20]. The study was conducted in accordance with the declaration of Helsinki and the International Council for Harmonization

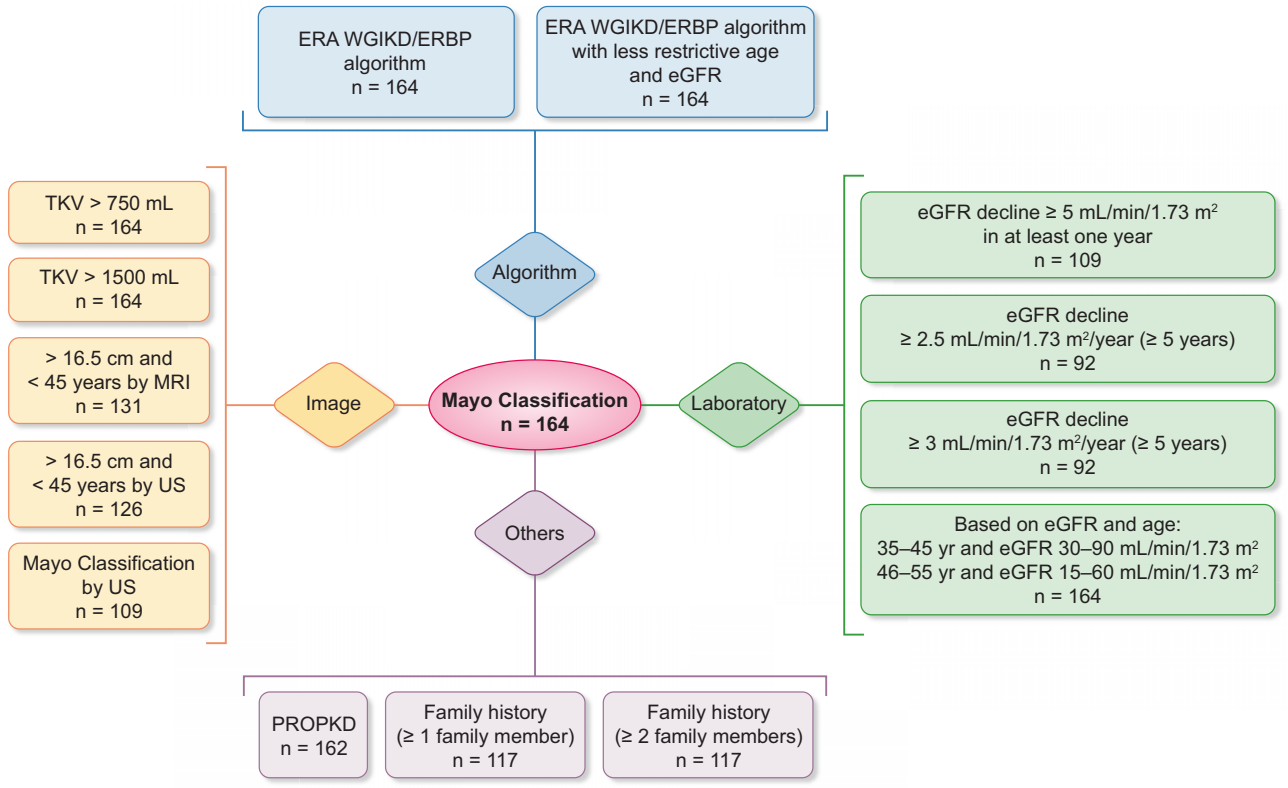


FIGURE 1: Different prediction tools used for the assessment of rapid kidney disease progression in ADPKD. European Renal Association Working Group on Inherited Kidney Disorders/European Renal Best Practice.

guidelines and was approved by the Fundació Puigvert institutional review board. All patients gave signed informed consent.

Data at the time of MRI study were collected by reviewing medical records and included age, height, sex, historical estimated glomerular filtration rate (eGFR using the Chronic Kidney Disease Epidemiology Collaboration formula [21]), family history, left and right kidney lengths as measured by ultrasound (US) and by MRI, total kidney volume (TKV) as measured by MRI and by US, genotype, age at the onset of hypertension and urological events. Radiologists with extensive experience in kidney imaging performed US and assessed MRI. TKV, together with age and height, was introduced into the Mayo ADPKD calculator and patients were classified accordingly [22]. Patients with MC 1C, 1D or 1E were considered to have RP [20]. The following prediction models for determining RP in ADPKD were also assessed (Figure 1) and compared with the MC.

ERA WGIKD/ERBP algorithm

The ERA WGIKD/ERBP algorithm [13] was assessed in all patients and was considered as one of the prediction models for RP. A modification of the algorithm incorporating less restrictive age and an eGFR criteria based on more recent findings [9] was also analysed. It included patients 18–35 years old with an eGFR of ≥30 mL/min/1.73 m^2, those aged 35–45 years with an eGFR of ≥30 to <90 mL/min/1.73 m^2 and those aged 45–55 years with an eGFR of ≥15 to <60 mL/min/1.73 m^2.

Total kidney volume

The ellipsoid formula was used to calculate TKV. TKV >750 mL and TKV >1500 mL were considered as different thresholds to determine RP [8, 23].

Kidney length >16.5 cm at age <45 years

Kidney length was measured by US and MRI from longitudinal images obtained in a sagittal plane. Patients with a kidney length of >16.5 cm and aged >45 years were excluded because the age at which their kidneys had reached this diameter was unknown. Patients with a kidney length of <16.5 cm and aged >45 years were considered as not having RP. Patients with a kidney length of <16.5 cm and aged <45 years were considered as not having RP at the time of the study while recognizing that they might meet the criterion in the future. Patients with a kidney length of >16.5 cm and aged <45 years were considered to have RP [24].

Mayo classification by ultrasound

The MC was assessed by MRI and, as an exploratory experiment, was also calculated using height-adjusted total kidney volume (htTKV) as measured by US.

Kidney function decline

Historical eGFR decline was calculated retrospectively based on clinical records from 2011 to 2019. Patients with two or fewer blood tests were excluded from eGFR decline prediction models. Patients with chronic kidney disease (CKD) group 1 were also excluded due to the unreliability of eGFR changes at this stage [13]. An eGFR decline of ≥5 mL/min/1.73 m^2 in 1 year, as suggested by the KDIGO Guideline [13, 25], and an eGFR decline of ≥2.5 mL/min/1.73 m^2/year over 5 years [20] were considered as thresholds for RP. An eGFR decline of ≥3 mL/min/1.73 m^2/year over 5 years was also analysed to see whether it was more accurate in identifying patients with RP.

Table 1. Baseline characteristics of patients with ADPKD

Characteristics	All patients, $n = 164$	MC 1A–1B, $n = 46$	MC 1C–1E, $n = 118$	P-value*
Female, *n* (%)	84 (51.2)	31 (67.4)	53 (44.9)	0.01
Age (years)	40.5 ± 11.4	38.7 ± 12.7	41.2 ± 10.8	0.16
eGFR (mL/min/1.73 m^2)	88.6 ± 27.8	92.2 ± 24.4	87.2 ± 29.0	0.39
CKD, *n* (%)				0.04
G1 (eGFR >90 mL/min/1.73 m^2)	48 (29.3)	20 (43.5)	28 (23.7)	
G2 (eGFR 60–90 mL/min/1.73 m^2)	54 (32.8)	19 (41.3)	35 (29.7)	
G3a (eGFR 45–60 mL/min/1.73 m^2)	26 (15.9)	1 (2.2)	25 (21.2)	
G3b (eGFR 30–45 mL/min/1.73 m^2)	10 (6.1)	1 (2.2)	9 (7.6)	
G4 (eGFR 15–30 mL/min/1.73 m^2)	21 (12.8)	5 (10.9)	16 (13.6)	
G5 (eGFR <15 mL/min/1.73 m^2)	5 (3.0)	0 (0.0)	5 (4.2)	
TKV measured by MRI (mL)	1139 (687–1965)	519 (410–671)	1488 (1051–2414)	<0.0001
htTKV measured by MRI (mL)	678 (398–1109)	302 (248–396)	843 (637–1413)	<0.0001
Kidney length (cm)				
MRI	16.7 ± 4.0	12.8 ± 1.4	18.7 ± 3.6	<0.0001
US	15.8 ± 3.0	12.8 ± 1.6	17.1 ± 2.4	
Genotype, *n* (%)				0.08
PKD1 truncating	31 (45.6)	4 (20.0)	27 (56.3)	
PKD1 nontruncating	23 (33.8)	9 (45.0)	14 (29.2)	
PKD2	10 (14.7)	6 (30.0)	4 (8.3)	
No mutation identified	4 (5.9)	1 (5)	3 (6.3)	
Hypertension <35 years, *n* (%)	57 (34.8)	8 (17.4)	49 (41.5)	0.005
Urological events <35 years, *n* (%)	22 (13.4)	4 (8.7)	18 (15.3)	0.32

All patients, slow progressors (MC 1A–1B) and rapid progressors (MC 1C–1E) are shown.
*P-value for comparisons between MC groups.

Rapid disease progression based only on age and eGFR

As an exploratory experiment, an eGFR under a certain threshold at a certain age was evaluated as a criterion for RP. Patients aged 35–45 years with CKD groups 2 and 3, and patients aged 46–55 years with CKD groups 3 and 4 were considered to have RP.

Predicting Renal Outcome in Polycystic Kidney Disease (PROPKD) score

The PROPKD score was calculated in all patients [26]. A genetic test was carried out in patients with a PROPKD score of at least 3 before genetic data were added to the score (potentially RP patients). The reason for this was to minimize the number of genetic tests for the present purpose. Two of these patients were unavailable for genetic testing. Patients with a PROPKD score of >6 were considered to have RP [26].

Family history

The number of affected family members and age at which these family members needed KRT were collected. Patients with no affected parents were considered *de novo* cases. Patients without family members reaching KRT or without data on their family history were excluded. Patients with at least two family members who reached KRT before 58 years of age were considered to have RP [7]. In addition, we assessed, and considered as having RP, those patients with at least one family member who reached KRT before the age of 58 years, as long as this was the only family member who had reached KRT.

Statistical analysis

For descriptive statistics, continuous variables are presented as mean ± standard deviation or median (interquartile range, i.e. 25th–75th percentiles), according to their adherence to the Gaussian distribution and categorical data, are presented as frequencies and percentages. Fisher's exact test was used to compare categorical variables, whereas the *t*-test or the Mann–Whitney test was used for continuous variables, as appropriate.

Kidney function decline was assessed using a slope analysis by means of mixed models for repeated measurements taking into account the intrasubject correlation. The Bland–Altman approach was used to compare US and MRI assessments [27, 28]. Lin's coefficient was also employed to assess the concordance [29]. For sensitivity and specificity, the 95% confidence intervals (CIs) are based on the Clopper–Pearson exact method [30]. Logistic regression models were used to calculate the area under the receiver operating characteristic curve (AUROC) as a measure of the overall performance of the diagnostic predictors [31].

The analysis was performed using the SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA), and the level of significance was established at the 0.05 level (two-sided).

Genetic testing

Genetic testing was performed in index cases by next-generation sequencing using a kidney disease gene panel as previously described [32, 33].

Limitations

There is no gold standard prediction model for the definition of RP in ADPKD, and in choosing the MC as the gold standard to compare the different prediction models, we accepted its limitations. Not all patients in our cohort were available for assessment by all the prediction tools used. Our population may have been biased towards patients with more severe diseases.

RESULTS

A total of 164 ADPKD patients were included in the study. Out of 164 patients, 46 were classified as MC 1A ($n = 11$) or 1B ($n = 35$) and 118 as MC 1C ($n = 47$), 1D ($n = 51$) or 1E ($n = 20$). Patients' baseline characteristics are described in Table 1.

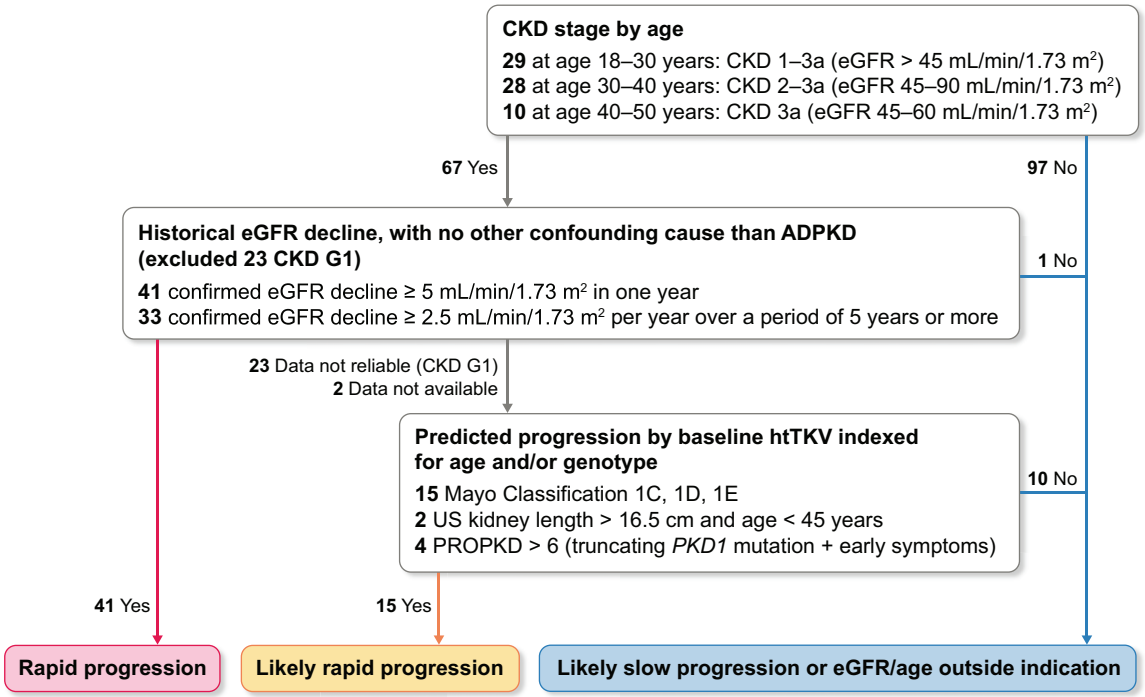


FIGURE 2: The ERA WGIKD/ERBP algorithm used in our cohort to identify patients with rapid disease progression (adapted from [13]). Numbers in bold indicate the number of patients who met each criterion.

ERA WGIKD/ERBP algorithm

A total of 67 patients (40.9%) met the age and eGFR criteria of the ERA WGIKD/ERBP algorithm for evaluation for RP. Of them, 56 patients (34.1% of the entire cohort) were considered to have RP using the algorithm (Figure 2). An additional 42 patients, or 109 in total, met the less restrictive age and eGFR criteria applied to the algorithm (see the Materials and methods section). Ninety-three of these patients (56.7% of the entire cohort) were considered to have RP using these less restrictive criteria, increasing by 66% (93 versus 56) the number of patients identified by the algorithm as having RP (Figure 3).

Total kidney volume

Bland–Altman plots demonstrated high levels of agreement in TKV between MRI and the US, the level of agreement declining as TKV increased (Figure 4). The US underestimated TKV mainly at TKV >1500 mL. Lin's coefficient was 0.71 (0.52–0.83) at TKV <750 mL and 0.49 (0.20–0.7) at TKV >1500 mL. One hundred and twenty patients had a TKV of >750 mL on MRI and were considered to have RP. Of these, 93.3% were 1C, 1D or 1E on MC. Fifty-nine patients had a TKV of >1500 mL on MRI and were considered to have RP; 98.3% of these patients were 1C–1E on MC, the single exception being a 68-year-old who was 1B on MC.

Kidney length >16.5 CM at age <45 years

Bland–Altman plots also demonstrated high levels of agreement between MRI and US with respect to kidney length, the level of agreement declining as kidney length increased (Figure 5). The US again tended to give underestimations of larger kidney lengths. Lin's coefficient was 0.73 (0.62–0.81) for kidney length of <16.5 cm and 0.20 (0.04–0.35) for kidney length of >20 cm. A total of 37 patients <45 years old had a kidney length of >16.5 cm on either MRI (28.2%) or US (29.4%) and were considered to have RP. All of them were 1C–1E on MC.

Mayo classification by ultrasound

TKV measured by US was available for 69.9% (119/157) of patients who underwent US. US and MRI were performed less than a year apart in 90% of cases. Median TKV measured by MRI and US was 1042 mL (924–1160) and 900 mL (810–989), respectively. MCs using US and MRI were compared and presented high levels of agreement, with a Kendall's coefficient of 0.83 (0.77–0.88) (Table 2). Of those patients identified as having RP using MC by US, 94.6% were also identified as having RP using MC by MRI. Only three patients were considered to have RP using MC by the US but not using MC by the MRI.

Kidney function decline

The mean retrospective follow-up (time from first blood test to baseline) was 6.8 ± 2.7 years with a mean of 6.3 ± 2.6 blood tests. The eGFR annual decline increased at each stage of MC, as expected (Supplementary data, Figures S1 and S2). Forty-eight patients with CKD G1 and seven patients with two or fewer blood tests were excluded from this analysis. Of the 109 included patients, 102 (93.6%) had an eGFR decline of 5 mL/min/1.73 m^2 in 1 year and were considered to have RP. The proportion of patients with such an eGFR decline was similar for MC 1A–1B (92%) and MC 1C–1E (94.1%).

A total of 92 patients had at least two or more blood tests within a period of 5 years. Seventy-two of these (78.3%) had a mean eGFR decline of 2.5 mL/min/1.73 m^2/year and were considered to have RP. Of them 60 patients (83.3%) were 1C–1E on MC.

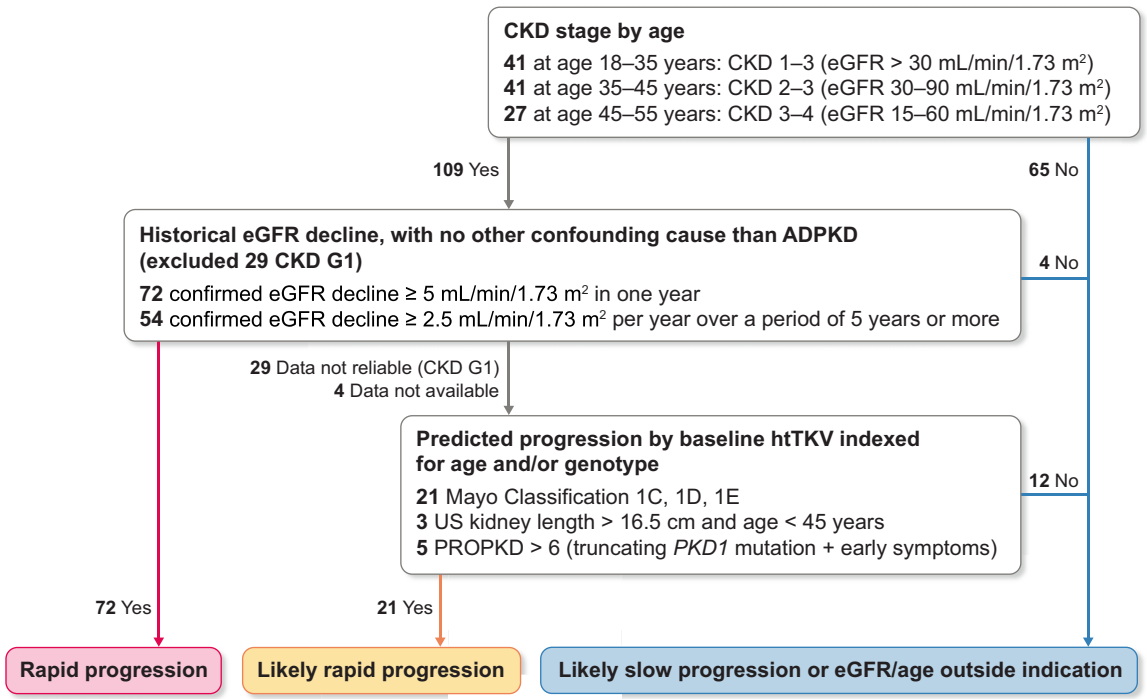


FIGURE 3: The ERA WGIKD/ERBP algorithm with less restrictive age and eGFR criteria (adapted from [13]). Numbers in bold indicate the number of patients who met each criterion.

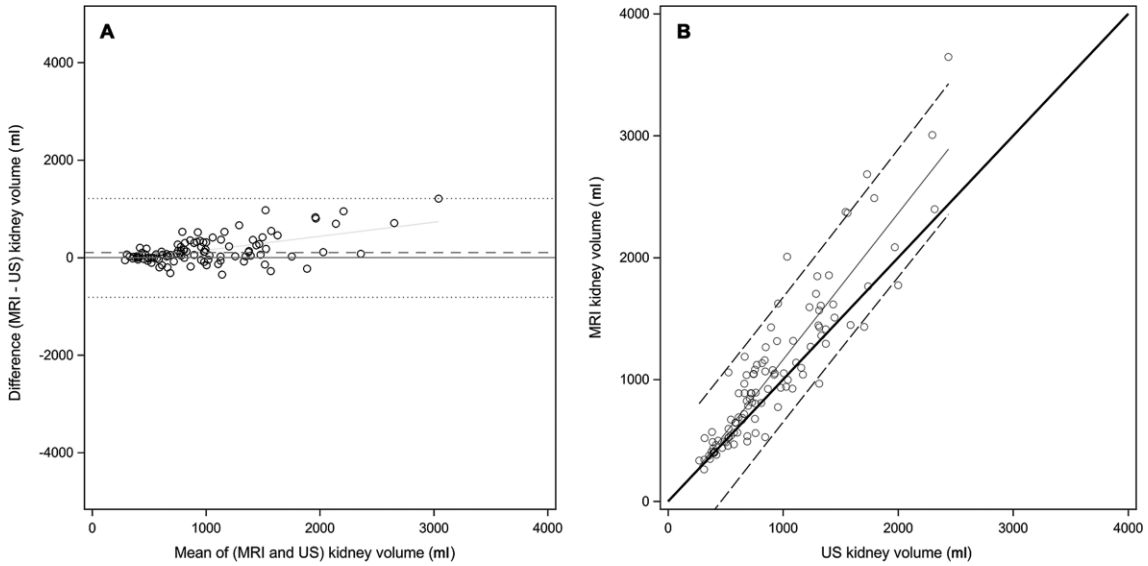


FIGURE 4: Total kidney volume (TKV) assessed by US and MRI. (A) Bland–Altman plots showing the disagreement between the TKV measured by MRI and by US. The dashed line represents the mean difference (bias) and dotted lines 95% limits of agreement. (B) Concordance between TKV measured by MRI and by US. The bold line at 45 degrees represents the perfect concordance; the grey line indicates the observed regression line and dashed lines the 95% prediction intervals.

Sixty-five patients (70.6%) were identified as having RP based on a mean eGFR decline of 3 mL/min/1.73 m^2/year. Of them 54 (83.1%) were 1C–1E on MC.

RAPID DISEASE PROGRESSION BASED ONLY ON AGE AND eGFR

Forty-one patients were aged between 35 and 45 years old and had an eGFR of 30–90 mL/min/1.73 m^2. Twenty-eight patients were aged between 46 and 55 years old and had an eGFR of 15–60 mL/min/1.73 m^2. In total, therefore, 69 patients met the age and eGFR criteria and were considered to have RP. Of them 60 patients (87%) were MC 1C–1E.

Propkd score

A total of 57 patients had hypertension before the age of 35 years, of whom 49 patients (86%) were classified as having RP by MC

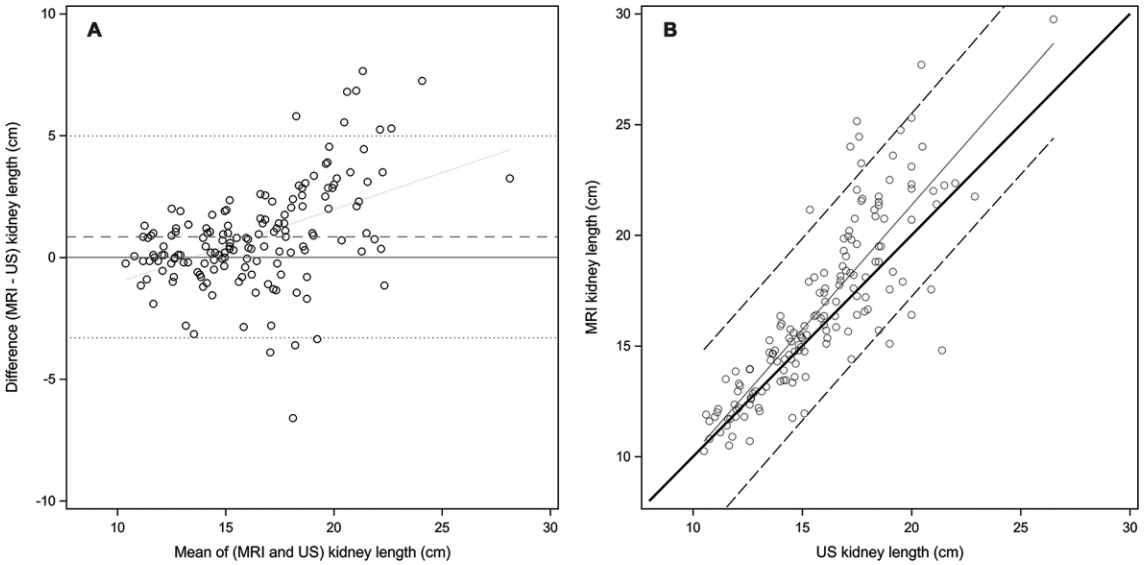


FIGURE 5: Kidney length assessed by US and MRI. **(A)** Bland–Altman plots showing the disagreement between the kidney lengths measured by MRI and by US. The dashed line represents the mean difference (bias) and dotted lines 95% limits of agreement. **(B)** Concordance between the kidney lengths measured by MRI and by US. The bold line at 45 degrees represents the perfect concordance; the grey line indicates the observed regression line and dashed lines the 95% prediction intervals.

Table 2. Comparison of the MC as assessed by US and MRI

US	1A	1B	1C	1D	1E
MRI					
1A	11	0	0	0	0
1B	2	28	3	0	0
1C	0	12	19	1	0
1D	0	0	12	13	1
1E	0	0	0	3	4

($P = 0.005$). Twenty-seven patients (16.7%) met the criterion of a PROPKD score of >6 and were considered to have RP. Of these patients, 25 (92.6%) were MC 1C–1E.

Family history

A total of 24 patients who did not have family members reaching KRT and 11 without available data on family history were excluded. Twelve patients were identified as *de novo* cases. Of the remaining 117 patients, 44 (37.6%) had at least two family members reaching KRT before 58 years of age and were considered to have RP. Thirty-five (79.5%) of these patients were MC 1C–1E. Eighty-one (69.2%) had at least one family member who reached KRT before the age of 58 years. Sixty (74.1%) of these patients were MC 1C–1E.

Sensitivity and specificity of the different tools to predict RP

The sensitivity and specificity of the different predictive models compared with the MC-based definition of RP as categories 1C–1E are shown in Figure 6.

DISCUSSION

Although certain factors are well known to influence the progression of ADPKD [11], the reasons for the huge interfamilial and even intrafamilial variability remain to be totally elucidated. There is a need to define RP in ADPKD for the purposes of selection of disease-modifying therapies and recruitment to clinical trials [8, 10]. ADPKD with RP may be defined as onset of kidney failure at a relatively young age, though the threshold has yet to be clearly determined. Currently, the only two objective means of determining RP are retrospective analysis of an eGFR decline and retrospective TKV data. Although there is evidence that they are correlated [20], this is not always the case. As is known from clinical practice, some patients have large kidneys with preserved kidney function, while others have impaired kidney function with not very large kidneys. As retrospective decline in eGFR is not useful in patients with normal kidney function and retrospective TKV data are often unavailable, there is a need for prediction tools. Although several prediction tools have been proposed for the assessment of the progression of ADPKD, we chose MC as the gold standard for the definition of RP, accepting its limitations. The reason for this decision is that only imaging tools are able to discriminate RP at early stages of the disease, and MC has been shown to perform very accurately for this purpose [15, 20].

A recent study comparing the various decision algorithms showed a high variability in treatment selection among different countries [12]. We previously demonstrated how the ERA WGIKD/ERBP algorithm, with eGFR stratified by age cut-off, is too stringent in the clinical setting, preventing RP from being considered in a significant percentage of young patients [16]. In the present cohort, application of less restrictive eGFR and age criteria resulted in a significant increase in the percentage of patients identified as having RP, confirming that the original algorithm misses a substantial number of cases of RP.

When considering eGFR decline, we observed that an eGFR decline of ≥5 mL/min/1.73 m^2 within 1 year does not seem to be a good criterion for RP. In our cohort, 93.6% of patients had an eGFR decline ≥5 mL/min/1.73 m^2 within 1 year at some point during the follow-up regardless of MC, indicating this eGFR decline to be a very unspecific criterion. An average annual eGFR decline over a certain period seems more reliable to avoid fluctu-

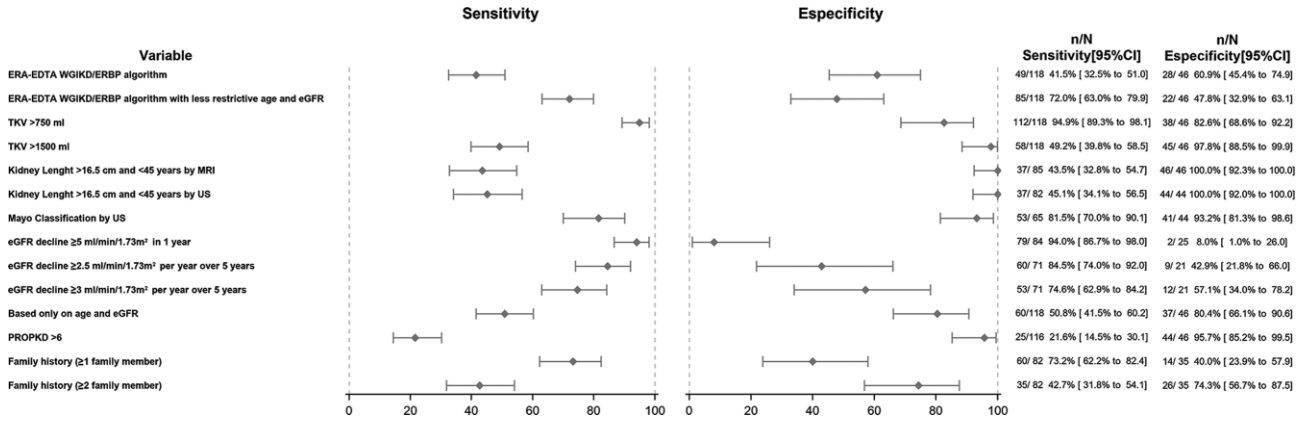


FIGURE 6: Forest plot of sensitivity and specificity estimates. The proportion estimates (percentage) and [AUROC] were pooled according to (1) the ERA WGIKD/ERBP algorithm [0.512], (2) the ERA WGIKD/ERBP algorithm with less restrictive age and eGFR [0.599], (3) TKV >750 mL [0.888], (4) TKV >1500 mL [0.735], (5) kidney length >16.5 cm on MRI and age <45 years [0.718], (6) kidney length >16.5 cm on US and age <45 years [0.726], (7) MC by US [0.874], (8) eGFR decline ≥5 mL/min/1.73 m^2 in 1 year [0.510], (9) eGFR decline ≥2.5 mL/min/1.73 m^2/year over 5 years [0.637], (10) eGFR decline ≥3 mL/min/1.73 m^2/year over 5 years [0.659], (11) based only on age and eGFR [0.656], (12) PROPKD >6 [0.586], (13) family history (≥2 family members reaching KRT before the age of 58 years) [0.566] and (14) family history (≥1 family member reaching KRT before the age of 58 years) [0.585].

ations in creatinine. In line with the findings of Irazabal *et al.* [20], a more pronounced eGFR decline was observed with increasing MC. In our opinion, an eGFR decline of 2.5 mL/min/1.73 m^2/year is below the threshold for RP (–2.63 for MC 1C according to Irazabal *et al.* [20] and –3.57 in the present study). This is why we tested our cohort using a 3 mL/min/1.73 m^2/year eGFR decline. The AUROC improved when the yearly eGFR decline increased from 2.5 to 3 mL/min/1.73 m^2/year. The moderate performance of the retrospective eGFR decline may be attributed both to the variability of the creatinine measurement and to the possibility that TKV does not always correlate with eGFR. Larger studies are needed to define the eGFR decline threshold that performs best in predicting RP as eventually what will lead the patient to KRT is eGFR and not TKV.

Indexing eGFR by age could represent an easy prognostic tool. In the present study, stratification of patients based on age and eGFR proved to be very specific. It has the advantage that it is always available, but also the limitation of not being useful in young patients with preserved kidney function.

As expected, all imaging prediction tools were in closer agreement with MC than the other prediction models. Many of our patients who underwent MRI were patients with enlarged kidneys on US. In the present cohort, having a TKV of >750 mL on MRI (the selection criterion used in the TEMPO trial [8]) identified 94.9% of patients classified as having RP by MC. Six patients classified as having RP by MC and with a TKV <750 mL were young and their kidneys had still not reached this volume. Also, a TKV >1500 mL on MRI was analysed as a criterion for RP; it was found to be very specific but had low sensitivity. Consequently, one may conclude that MC performs much better than TKV alone.

Although MRI is known to be a more accurate technique than US for measuring kidney size, it is still expensive and difficult to access in many hospitals. For this reason, we explored, for the first time to our knowledge, the use of TKV measurement by US in order to calculate MC. The AUROC of MC on US showed an excellent performance, particularly in extreme MC, i.e. classes 1A, 1D and 1E. In the present cohort, all patients classified as MC 1A by US corresponded to non-RP according to MC by MRI. On the other hand, all patients with MC 1D or 1E on US corresponded to RP according to MC by MRI. However, classification as MC 1B and 1C by US did not perform well enough to discriminate between RP and non-RP. In hospitals where access to MRI is complicated, MC by US could be used to guide the decision to order an MRI to assess disease progression. In line with the use of US, and as shown in previous studies [24], we obtained a high level of agreement with MRI when the kidney length was <16.5 cm. Based on the results of Bhutani *et al.* [24], the ERA WGIKD/ERBP algorithm proposed that patients <45 years old with a kidney length of >16.5 cm on US should be classified as having RP. In our cohort, 92% of patients who met this criterion were classified as having RP by MC. This could be considered a very specific criterion for the determination of RP, but its sensitivity is not so good because it does not detect young patients who still have normal-sized kidneys. Interestingly in our cohort, 94.4% of patients with a kidney length of <13 cm and aged >30 years corresponded to non-RP patients according to MC, while 97.1% of patients with a kidney length of >15 cm and aged <50 years were classified as having RP by MC.

The PROPKD score has been proved to be an excellent predictor of RP [26, 34]. In patients with early presentation of hypertension or urological events, it seems wise to perform a genetic test in order to use the PROPKD score. In our cohort, 95% of patients who had a PROPKD score of >6 were considered to have RP according to MC, this being the most specific but least sensitive non-imaging prediction tool. Interestingly, presenting hypertension before the age of 35 years showed a good correlation, by itself, with MC 1C–1E. This single item of clinical data could draw attention to a high possibility of RP.

It is well known that intrafamilial variability is less pronounced than interfamilial variability, and it is therefore expected that age at the onset of KRT in relatives would be highly predictive of RP. However, there is evidence of marked intrafamilial variability, highlighting the complexity of the factors determining RP [35, 36]. Although family history can be of help in suggesting RP, by itself it lacks sufficient sensitivity and specificity.

In summary, imaging prediction tools have more agreement with MC than the other prediction tools. MC by US performs very well for MC 1A, 1D and 1E, and could replace MC by MRI in poorly

resourced hospitals. The eGFR decline is sensitive but not very specific when compared with the MC, whereas the PROPKD score is very specific but has low sensitivity. Probably, the task of prediction cannot be absolutely entrusted to a single tool, but the common sense of the nephrologist in conjunction with the use of several of the above-mentioned prediction tools, as well as new ones based mostly on biomarkers, will help to identify the subpopulation of ADPKD patients who will experience RP.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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CONFLICT OF INTEREST STATEMENT

R.T. is member of the CKJ editorial board. The results presented in this paper have not been published previously in whole or part, except in abstract form in the XLIX Congreso de la S.E.N. 2019 in A Coruña, Spain (Spanish Congress of Nephrology 2019).

REFERENCES

1. Suwabe T, Shukoor S, Chamberlain AM *et al*. Epidemiology of autosomal dominant polycystic kidney disease in Olmsted county. *Clin J Am Soc Nephrol* 2020; 15: 69–79
2. Willey CJ, Blais JD, Hall AK *et al*. Prevalence of autosomal dominant polycystic kidney disease in the European Union. *Nephrol Dial Transplant* 2017; 32: 1356–1363
3. Cornec-Le Gall E, Alam A, Perrone RD. Autosomal dominant polycystic kidney disease. *Lancet* 2019; 393: 919–935
4. Porath B, Gainullin VG, Cornec-Le Gall E *et al*. Mutations in GANAB, encoding the glucosidase IIα subunit, cause autosomal-dominant polycystic kidney and liver disease. *Am J Hum Genet* 2016; 98: 1193–1207
5. Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. *Lancet* 2007; 369: 1287–1301
6. Cornec-Le Gall E, Olson RJ, Besse W *et al*. Monoallelic mutations to DNAJB11 cause atypical autosomal-dominant polycystic kidney disease. *Am J Hum Genet* 2018; 102: 832–844
7. Barua M, Cil O, Paterson AD *et al*. Family history of renal disease severity predicts the mutated gene in ADPKD. *J Am Soc Nephrol* 2009; 20: 1833–1838
8. Torres VE, Chapman AB, Devuyst O *et al*. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2012; 367: 2407–2418
9. Torres VE, Chapman AB, Devuyst O *et al*. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. *N Engl J Med* 2017; 377: 1930–1942
10. European Medicines Agency. Summary of medicinal product characteristics Jinarc. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002788/WC500187921.pdf (10 April 2021, date last accessed)
11. Schrier RW, Brosnahan G, Cadnapaphornchai MA *et al*. Predictors of autosomal dominant polycystic kidney disease progression. *J Am Soc Nephrol* 2014; 25: 2399–2418
12. Wulfmeyer VC, Auber B, Haller H *et al*. Comparison of different selection strategies for tolvaptan eligibility among autosomal dominant polycystic kidney disease patients. *Am J Nephrol* 2019; 50: 281–290
13. Gansevoort RT, Arici M, Benzing T *et al*. Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease: a position statement on behalf of the ERA–EDTA Working Groups on Inherited Kidney Disorders and European Renal Best Practice. *Nephrol Dial Transplant* 2016; 31: 337–348
14. Lavu S, Vaughan LE, Senum SR *et al*. The value of genotypic and imaging information to predict functional and structural outcomes in ADPKD. *JCI Insight* 2020; 5: e138724
15. Messchendorp AL, Meijer E, Visser FW *et al*. Rapid progression of autosomal dominant polycystic kidney disease: urinary biomarkers as predictors. *Am J Nephrol* 2019; 50: 375–385
16. Furlano M, Loscos I, Martí T *et al*. Autosomal dominant polycystic kidney disease: clinical assessment of rapid progression. *Am J Nephrol* 2018; 48: 308–317
17. Perrone RD, Mouksassi MS, Romero K *et al*. Total kidney volume is a prognostic biomarker of renal function decline and progression to end-stage renal disease in patients with autosomal dominant polycystic kidney disease. *Kidney Int Rep* 2017; 2: 442–450
18. Chebib FT, Torres VE. Assessing risk of rapid progression in autosomal dominant polycystic kidney disease and special considerations for disease-modifying therapy. *Am J Kidney Dis* 2021; 78: 282–292
19. Pei Y, Obaji J, Dupuis A *et al*. Unified criteria for ultrasonographic diagnosis of ADPKD. *J Am Soc Nephrol* 2009; 20: 205–212
20. Irazabal MV, Rangel LJ, Bergstralh EJ *et al*. Imaging classification of autosomal dominant polycystic kidney disease: a simple model for selecting patients for clinical trials. *J Am Soc Nephrol* 2015; 26: 160–172
21. Orskov B, Borresen ML, Feldt-Rasmussen B *et al*. Estimating glomerular filtration rate using the new CKD-EPI equation and other equations in patients with autosomal dominant polycystic kidney disease. *Am J Nephrol* 2010; 31: 53–57
22. Mayo ADPKD Class Calculator. https://www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754 (10 April 2021, date last accessed)
23. Grantham JJ, Torres VE, Chapman AB *et al*. Volume progression in polycystic kidney disease. *N Engl J Med* 2006; 354: 2122–2130
24. Bhutani H, Smith V, Rahbari-Oskoui F *et al*. A comparison of ultrasound and magnetic resonance imaging shows that

kidney length predicts chronic kidney disease in autosomal dominant polycystic kidney disease. *Kidney Int* 2015; 88: 146–151
25. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013; 3: 1–150
26. Cornec-Le Gall E, Audrézet MP, Rousseau A *et al*. The PROPKD score: a new algorithm to predict renal survival in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 2016; 27: 942–951
27. Bland JM, Altman DG. Measuring agreement in method comparison studies. *Stat Methods Med Res* 1999; 8: 135–160
28. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; 62: 307–310
29. Lin L-K. A concordance correlation coefficient to evaluate reproducibility. *Biometrics* 1989; 45: 255
30. Clopper C, Pearson E. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika* 1934; 26: 404–413
31. Altman DG, Bland JM. Diagnostic tests 3: receiver operating characteristic plots. *BMJ* 1994; 309: 188
32. Bullich G, Domingo-Gallego A, Vargas I *et al*. A kidney-disease gene panel allows a comprehensive genetic diagnosis of cystic and glomerular inherited kidney diseases. *Kidney Int* 2018; 94: 363–371
33. Domingo-Gallego A, Pybus M, Bullich G *et al*. Clinical utility of genetic testing in early-onset kidney disease: seven genes are the main players. *Nephrol Dial Transplant* 2021; gfab019, https://doi.org/10.1093/ndt/gfab019
34. Cornec-Le Gall E, Blais JD, Irazabal MV *et al*. Can we further enrich autosomal dominant polycystic kidney disease clinical trials for rapidly progressive patients? Application of the PROPKD score in the TEMPO trial. *Nephrol Dial Transplant* 2018; 33: 645–652
35. Lanktree MB, Guiard E, Li W *et al*. Intrafamilial variability of ADPKD. *Kidney Int Rep* 2019; 4: 995–1003
36. Torra R, Darnell A, Estivill X *et al*. Interfamilial and intrafamilial variability of clinical expression in ADPKD. *Contrib Nephrol* 1995; 115: 97–101