



Retrospective Study

# Longitudinal assessment of measured and estimated glomerular filtration-rate in autosomal dominant polycystic kidney disease: Real practice experience

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**Specialty type:** Urology and nephrology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's classification**

**Scientific Quality:** Grade B

**Novelty:** Grade B

**Creativity or Innovation:** Grade A

**Scientific Significance:** Grade B

**P-Reviewer:** Herrero-Maceda MDR

**Received:** July 11, 2024

**Revised:** December 7, 2024

**Accepted:** December 27, 2024

**Published online:** March 25, 2025

**Processing time:** 192 Days and 9 Hours



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## Abstract

### BACKGROUND

Equations for estimation glomerular filtration rate (eGFR) have been associated with poor clinical performance and their clinical accuracy and reliability have been called into question.

### AIM

To assess the longitudinal changes in measured glomerular filtration rate (mGFR) in patients with autosomal dominant polycystic kidney disease (ADPKD).

## METHODS

Analysis of an ambispective data base conducted on consecutive patients diagnosed with ADPKD. The mGFR was assessed by iothexol clearance; while eGFR was calculated by three different formulas: (1) The chronic kidney disease epidemiology collaboration (CKD-EPI); (2) Modification of diet in renal disease (MDRD); and (3) The 24-hour urine creatinine clearance (CrCl). The primary end-points were the mean change in mGFR between the baseline and final visit, as well as the comparison of the mean change in mGFR with the change estimated by the different formulas.

## RESULTS

Thirty-seven patients were included in the study. As compared to baseline, month-6 mGFR was significantly decrease by  $-4.4 \text{ mL/minute} \pm 10.3 \text{ mL/minute}$  ( $P = 0.0132$ ). However, the CKD-EPI, MDRD, and CrCl formulas underestimated this change by 48.3%, 89.0%, and 45.8% respectively, though none of these differences reached statistical significance ( $P = 0.3647$ ;  $P = 0.0505$ ; and  $P = 0.736$ , respectively). The discrepancies between measured and estimated glomerular filtration rate values, as evaluated by CKD-EPI ( $r = 0.29$ ,  $P = 0.086$ ); MDRD ( $r = 0.19$ ,  $P = 0.272$ ); and CrCl ( $r = 0.09$ ,  $P = 0.683$ ), were not correlated with baseline mGFR values.

## CONCLUSION

This study indicated that eGFR inaccurately reflects the decline in mGFR and cannot reliably track changes over time. This poses significant challenges for clinical decision-making, particularly in treatment strategies.

**Key Words:** Autosomal dominant polycystic kidney disease; Glomerular filtration rate; End-stage kidney disease; Iothexol; Chronic kidney disease epidemiology collaboration; Modification of diet in renal disease

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**Core Tip:** This analysis of an ambispective data base aimed to evaluate the longitudinal changes in measured glomerular filtration rate (mGFR) and the estimation glomerular filtration rate (eGFR). Glomerular filtration rate (GFR) in patients with autosomal dominant polycystic kidney disease (ADPKD) and their relationship between baseline eGFR and final mGFR. The three formulas for estimating GFR were notably imprecise and unreliable, especially for tracking changes in GFR in individuals with ADPKD. The change in mGFR was underestimated by 48.3%, 89.0%, and 45.8% by the chronic kidney disease epidemiology collaboration, modification of diet in renal disease, and the 24-hour urine creatinine clearance formulas, respectively, although none of these underestimations were statistically significant. These results could significantly influence clinical decision-making, particularly regarding treatment selection.

**Citation:** Fernandez JM, Rodriguez-Pérez JC, Lorenzo-Medina MM, Rodriguez-Esparragon F, Quevedo-Reina JC, Hernandez-Socorro CR. Longitudinal assessment of measured and estimated glomerular filtration-rate in autosomal dominant polycystic kidney disease: Real practice experience. *World J Nephrol* 2025; 14(1): 99044

**URL:** <https://www.wjgnet.com/2220-6124/full/v14/i1/99044.htm>

**DOI:** <https://dx.doi.org/10.5527/wjn.v14.i1.99044>

## INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a prevalent monogenic disorder affecting individuals worldwide[1,2]. The hallmark of the disease is the development of multiple cysts gradually compressing renal parenchyma, ultimately leading to end-stage kidney disease (ESKD) during adulthood[1-3]. Mutations in *polycystic kidney disease (PKD) 1* or *PKD2* genes cause the disease, with *PKD1* mutations being more common. Patients with *PKD2*-related ADPKD usually have milder symptoms and later onset of kidney failure compared to those with *PKD1* mutations[4,5]. This genetic variability can lead to underdiagnosis, especially in younger patients with less severe symptoms[5].

ADPKD involves complex renal cyst formation processes, including cell proliferation, apoptosis, altered cell phenotype, extracellular matrix changes, and inflammation[4-6]. Although its prognosis varies greatly, it is usually severe, because patients may develop ESKD or die to extra-renal complications. Additionally, progression rates differ, with some patients experiencing rapid decline of renal function and others a slower course. Renal cyst volume changes serve as a key indicator of disease progression, correlating with renal function loss[4-6].

Following the onset of ESKD, ADPKD progression tends to be constant and can be monitored by glomerular filtration rate (GFR)[7]. However, during the early stages of the disease, due to glomerular hyperfiltration, kidney function remains intact[8,9]. Renal volume, indeed, increases years before GFR starts to decrease, which means that GFR is not an accurate early predictor of ADPKD progression[9,10].

In clinical practice, renal function might be estimated by rutinary and standard techniques creatinine-based formulas[11]. Many different equations that focused on estimating renal function have been described. However, their clinical

performance has been questioned[12,13].

In general terms, the mean difference between the estimation GFR (eGFR) and the measured GRF (mGFR) is about 30%, although this difference may be even greater[11,14]. The current evidence evaluating the clinical performance in patients with ADPKD is limited[15-17]. In a previous study published by our group, estimating GFR by formulas did not provide reliable results[14].

The disparities observed between mGFR and eGFR measurements may exert detrimental effects on patient prognosis, potentially leading to treatment delays. Moreover, the consequences of variations in mGFR over time on clinical disease progression remain poorly understood. Consequently, there exists a need to investigate the longitudinal clinical performance of eGFR and its correlation with mGFR throughout follow-up periods, which could yield valuable insights into disease management and patient outcomes.

The intention of this study was to evaluate the changes of mGFR over time in patients with ADPKD. In addition, this study assessed the changes in eGFR (measured by different formulas) over time and the relationship between baseline eGFR and final mGFR.

## MATERIALS AND METHODS

### Study design

This was a retrospective analysis of a prospective data base conducted on consecutive patients diagnosed with ADPKD (all of them *PKD1*) attended in the third-level University Hospital of Gran Canaria Doctor Negrín (HUGCDN) (Las Palmas de Gran Canaria; Spain).

The study protocol received approval from the Ethics Committee of the HUGCDN (Protocol VO 05-2017; Review Board approval, No. 170071; May 2017). This study adhered to the principles outlined in the Good Clinical Practice/ International Council for Harmonization Guidelines, the Declaration of Helsinki, and all relevant country-specific regulations governing clinical research, prioritizing the highest level of individual protection.

Prior to participation, written informed consent was obtained from all patients. To ensure anonymity, any potentially identifying information was either encrypted or omitted from the data.

### Study participants

This study included patients, aged > 18 years; diagnosed with ADPKD, clinically stable[18]; and with a measured CKD-EPI > 60 mL/minutes (*i.e.*, absence of acute kidney injury, active infectious diseases, or cardiovascular events within the three months prior to the study enrollment).

Patients with allergy to iodine, active malignant tumor, uremia or impending dialysis, severe psychiatric disorders, or those who were pregnant or nursing were excluded.

### Study procedures

**mGFR:** On the study visit day (baseline), a 5 mL intravenous injection of iohexol solution (Omnipaque 300, GE Healthcare) was administered over 2 minutes. Iohexol levels were assessed using dried blood spot samples, which were subsequently forwarded to the University of La Laguna (Tenerife, Spain) for analysis[19]. Plasma clearance of iohexol was determined following the method described by Krutzén *et al*[20].

**EGFR:** Simultaneously to the clearance of iohexol, serum creatinine (enzymatic method) and cystatin-C (immunoturbidimetric method) were determined to calculate eGFR by different formulas. The chronic kidney disease epidemiology collaboration (CKD-EPI)[21], the modification of diet in renal disease (MDRD)[22], and 24-hour urine creatinine clearance (CrCl) equations were used to calculate eGFR.

### Outcomes

The primary end-points were the mean change in mGFR between the baseline and final visit, as well as the comparison of the mean change in mGFR with the change estimated by the different formulas.

The secondary end-points were the comparison of mGFR and eGFR at baseline and at the end of the study and the changes in blood and urine analysis data from baseline to month-6.

### Study groups

To assess the clinical performance of eGFR formulas, in addition to considering the overall study population, we stratified the study sample according to their baseline mGFR (median split). Patients were, therefore, divided in those with a baseline mGFR ≤ 80 mL/minutes and those with a baseline mGFR > 80 mL/minutes.

### Statistical analysis

Statistical analysis was performed using MedCalc® Statistical Software version 22.023 (MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org>; 2024).

The Shapiro-Wilks test was used for assessing quantitative variables normality.

In normally distribute variables repeated measures analysis of variance was used to analyzed the changes in mGFR and eGFR; while if such variables were no normally distribute, the Friedman test was use.

The Bland-Altman method with 95% limits of agreement was used to assess the differences between mGFR (determined as reference method) and the eGFR (estimated by CKD-EPI, MDRD, and CrCl formulas) at baseline and at the last follow-up visit. In addition, this method was also used to determine the differences between the mean changes (basal *vs* final) among the different techniques.

Linear regression analysis (considering Pearson correlation coefficient) was performed to assess the relationship month-6 changes between measured and estimated GFR values, as well as the relationship between month-6 changes in eGFR and baseline mGFR.

Additionally, the concordance correlation coefficient (CCC)[23] was performed to assess agreement between the mGFR (used as reference method) and the eGFR (by CKD-EPI, MDRD, and CrCl formulas). The CCC contains a measurement of precision *P* (which measures how far each observation deviates from the best-fit line) and accuracy *C<sub>b</sub>* (that measures how far the best-fit line deviates from the 45° line through the origin)[23]. CCC ranges from 0 to 1 and it should be interpreted as poor (< 0.9); moderate ( $\geq 0.90$  to  $\leq 0.95$ ); substantial ( $> 0.95$  to  $\leq 0.99$ ); and almost perfect ( $> 0.99$ )[24].

## RESULTS

### Baseline demographic, clinical, and analytical characteristics

A total of 37 subjects, 19 (51.4%) females and 18 (48.6%) males, were included in the study. The mean  $\pm$  SD age was 40.2 years  $\pm$  15.3 years. Twenty-two (59.5%) patients had systemic hypertension (21 of them well controlled with medication). Thirty-one (83.8%) patients had a family history of ADPKD.

The **Table 1** shows the main demographic and clinical characteristics of the study sample.

An overview of the blood and urine analysis data of the study sample is shown in **Supplementary Table 1**.

### Baseline GFR

The mean (SD) the mGFR at baseline was 85.6 mL/minute  $\pm$  24.6 mL/minute (median: 81.0 mL/minute; interquartile range: 69.4-101.0 mL/minute); with 17 (45.9%) and 20 (54.1%) patients with a baseline mGFR  $\leq$  80 mL/minute and  $>$  80 mL/minute, respectively.

Additionally, the mean (SD) estimated GFR at baseline was 81.3 mL/minute  $\pm$  23.7 mL/minute; 71.7 mL/minute  $\pm$  18.9 mL/minute; and 97.4 mL/minute  $\pm$  34.3 mL/minute according to the CKD-EPI, MDRD, and CrCl formulas, respectively.

The **Figure 1** shows the baseline mGFR and eGFR. The CCC showed poor agreement between mGFR and eGFR regardless the formula used or the baseline mGFR (**Table 2**).

Additionally, the Bland-Altman plots (**Figure 2A**) show that as compared to mGFR, systematic mean difference (95%CI) were 4.31 mL/minute (95%CI: -3.01 to 11.64); 14.64 mL/minute (95%CI: 7.71-21.57); and -13.07 mL/minute (95%CI: -21.80 to -4.36) for the CKD-EPI; MDRD; and CrCl formulas, respectively.

There was a borderline, but not significant, correlation between serum creatinine levels and mGFR at baseline (slope: -29.6; 95%CI: -60.1 to 1.0;  $r = 0.32$ ;  $P = 0.0569$ ) (**Supplementary Figure 1A**). On the other hand, cystatin-C and mGFR were significantly correlated at baseline (slope: -69.3; 95%CI: -98.6 to -40.1;  $r = 0.72$ ;  $P = 0.0001$ ) (**Supplementary Figure 1B**).

### Baseline vs final GFR

The **Table 3** shows an overview of the mGFR and eGFR changes *vs* baseline in the overall study sample and according to their baseline mGFR (mGFR  $\leq$  80 mL/minute and  $>$  80 mL/minute).

In the overall study sample, at month 6, mGFR significantly decreased by  $-4.4 \pm 10.3$  *vs* baseline ( $P = 0.0132$ ). The mGFR change was underestimated by 48.3%, 89.0%, and 45.8% by the CKD-EPI, MDRD, and CrCl formulas, although none of them was statistically significant ( $P = 0.3647$ ,  $P = 0.0505$ , and  $P = 0.736$ , respectively).

The Bland-Altman plots (**Figure 2B**) show that as compared to mGFR change from baseline to month-6, systematic mean difference (95%CI) were -2.12 mL/minute (95%CI: -6.83 to 2.57); -4.11 mL/minute (95%CI: -8.23 to 0.01); and -1.96 mL/minute (-12.85 to 8.93) for the CKD-EPI, MDRD, and CrCl formulas, respectively.

The absolute differences between measured and estimated GFR values assessed by CKD-EPI ( $r = 0.29$ ,  $P = 0.086$ ); MDRD ( $r = 0.19$ ,  $P = 0.272$ ); and CrCl ( $r = 0.09$ ,  $P = 0.683$ ) were not related to baseline mGFR values (**Figure 3**).

In the overall study sample, no significant correlation was found between mGFR changes and changes estimated either by the CKD-EPI formula (slope: 0.32; 95%CI: -0.9 to 0.73;  $r = 0.26$ ;  $P = 0.0126$ ); the MDRD formula (slope: 0.21; 95%CI: -0.10 to 0.51;  $r = 0.23$ ;  $P = 0.1738$ ); or the CrCl formula (slope: 0.27; 95%CI: -0.67 to 1.16;  $r = 0.13$ ;  $P = 0.5447$ ). The analysis evaluating the relationship of the mean changes from baseline to month-6 between mGFR and eGFR, considering separately subjects with mGFR  $\leq$  80 mL/minute at baseline, showed that none of the formulas were able to predict changes in kidney function (**Supplementary Figure 2**).

Regarding blood and urine analysis data, except for thrombocytes and cystatin-C (which were significantly increased at month-6,  $P = 0.0054$  and  $P = 0.0067$ , respectively), none of the variables showed significant changes over the study follow-up (**Supplementary Table 2**).

## DISCUSSION

The current study assessed the clinical performance of three formulas to estimate GFR, namely CKD-EPI, MDRD, and CrCl, as compared to measured GFR assessed by the suggested gold standard procedure (*i.e.*, the iothexol plasma

**Table 1 Main baseline demographic and clinical characteristics of the study sample, *n* (%)**

| Variable                                                       | <i>n</i> = 37       |
|----------------------------------------------------------------|---------------------|
| Age (years)                                                    |                     |
| mean ± SD                                                      | 40.2 ± 15.3         |
| Median (IqR)                                                   | 37.0 (31.0-50.0)    |
| Body mass index (kg/m <sup>2</sup> )                           |                     |
| mean ± SD                                                      | 25.4 ± 5.8          |
| Median (IqR)                                                   | 24.5 (21.8-27.4)    |
| Gender                                                         |                     |
| Female                                                         | 19 (51.4)           |
| Male                                                           | 18 (48.6)           |
| Diabetes mellitus                                              |                     |
| Yes                                                            | 0 (0.0)             |
| No                                                             | 37 (100.0)          |
| Dyslipidemia                                                   |                     |
| Yes                                                            | 4 (11.1)            |
| No                                                             | 32 (88.9)           |
| HBP                                                            |                     |
| Yes                                                            | 22 (59.5)           |
| No                                                             | 15 (40.5)           |
| HBP controlled                                                 |                     |
| Yes                                                            | 21 (95.5)           |
| No                                                             | 1 (4.5)             |
| Systolic blood pressure (mmHg)                                 |                     |
| mean ± SD                                                      | 130.9 ± 15.5        |
| Median (IqR)                                                   | 131.0 (118.8-140.0) |
| Diastolic blood pressure (mmHg)                                |                     |
| mean ± SD                                                      | 79.4 ± 9.0          |
| Median (IqR)                                                   | 80.0 (72.8-84.3)    |
| Cardiovascular events                                          |                     |
| Yes                                                            | 0 (0.0)             |
| No                                                             | 37 (100.0)          |
| Smoker status                                                  |                     |
| Never                                                          | 32 (86.5)           |
| Former                                                         | 2 (5.4)             |
| Current                                                        | 3 (8.1)             |
| Family history of autosomal dominant polycystic kidney disease |                     |
| Yes                                                            | 31 (86.1)           |
| No                                                             | 5 (13.9)            |

HBP: High blood pressure; IqR: Interquartile range.

**Table 2** Concordance correlation coefficient between the measured glomerular filtration rate (used as reference method) and the estimated glomerular filtration rate (by chronic kidney disease epidemiology collaboration, modification of diet in renal disease and creatinine clearance formulas) in the overall study sample and according to the median split baseline measured glomerular filtration rate groups

|                            | mGFR (reference), overall study sample ( <i>n</i> = 37) |           |          |
|----------------------------|---------------------------------------------------------|-----------|----------|
|                            | CCC (95%CI)                                             | Precision | Accuracy |
| CKD-EPI                    | 0.576 (0.318-0.754)                                     | 0.585     | 0.983    |
| MDRD                       | 0.457 (0.223-0.641)                                     | 0.582     | 0.786    |
| CrCl                       | 0.598 (0.376-0.755)                                     | 0.697     | 0.858    |
| mGFR ≤ 80 ( <i>n</i> = 17) |                                                         |           |          |
|                            | CCC (95%CI)                                             | Precision | Accuracy |
| CKD-EPI                    | 0.315 (-0.038 to 0.599)                                 | 0.425     | 0.741    |
| MDRD                       | 0.356 (-0.069 to 0.672)                                 | 0.414     | 0.862    |
| CrCl                       | 0.418 (0.064-0.679)                                     | 0.599     | 0.698    |
| mGFR > 80 ( <i>n</i> = 20) |                                                         |           |          |
|                            | CCC (95%CI)                                             | Precision | Accuracy |
| CKD-EPI                    | 0.429 (0.069-0.690)                                     | 0.515     | 0.833    |
| MDRD                       | 0.277 (0.033-0.490)                                     | 0.529     | 0.524    |
| CrCl                       | 0.315 (-0.037 to 0.597)                                 | 0.423     | 0.745    |

CCC: Concordance correlation coefficient; CKD-EPI: Chronic kidney disease epidemiology collaboration; CrCl: Creatinine clearance; MDRD: Modification of diet in renal disease; mGFR: Measured glomerular filtration rate.

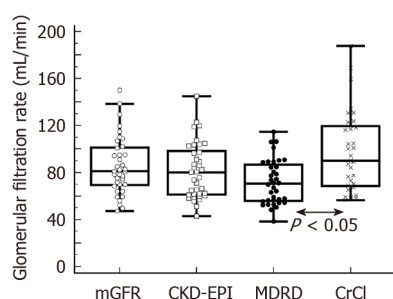


**Figure 1** Box and whisker plot (with dots) comparing the baseline measured glomerular filtration rate and estimated by the chronic kidney disease epidemiology collaboration, the modification of diet in renal disease, and creatinine clearance formulas. Measured glomerular filtration rate by modification of diet in renal disease was significantly different than that estimated by creatinine clearance ( $P < 0.05$ ). No significant differences were observed among the other methods. CKD-EPI: Chronic kidney disease epidemiology collaboration; CrCl: Creatinine clearance; MDRD: Modification of diet in renal disease; mGFR: Measured glomerular filtration rate.

clearance technique)[19,20,25] in a cohort of ADPKD patients with 1-2 chronic kidney disease (CKD) stages.

The results of this study indicated that the three formulas for estimating GFR were significantly inaccurate and unreliable, particularly for tracking GFR changes in individuals with ADPKD. Additionally, this inaccuracy was consistent regardless of the level of kidney function, affecting even those with mild-to-moderate renal insufficiency. Indeed, month-6 changes estimated by the three formulas failed to correlate to any appreciable extent with measured changes. Moreover, data were biased by a systematic underestimation of estimated GFR changes that ranged from 45.8% by CrCl formula to 89.0% by MDRD formula. On the other hand, estimated month-6 GFR changes were not associated with baseline mGFR, which indicated a wide and unpredictable deviation of estimated data.

The results of this study confirmed the current evidence indicating that prediction formulas do not accurately estimate GFR[14-17].

The key finding of the study was that eGFR formulas failed to accurately capture mGFR changes over time in individuals with ADPKD, a group highly susceptible to CKD progression.

The inaccurate estimation of actual GFR values and the unreliable prediction of GFR changes over time by the CKD-EPI, MDRD, and CrCl formulas might be associated with two important clinical issues. The first one is that this lack of

**Table 3 Measured and estimated month-6 glomerular filtration rates changes versus baseline in the overall study autosomal-dominant polycystic kidney disease patients (*n* = 37) and ranked according to measured glomerular filtration rate ≤ 80 (*n* = 17) and > 80 (*n* = 20) mL/minute**

|                                                   |                      | Glomerular filtration rate (mL/minute) |                            |                            |
|---------------------------------------------------|----------------------|----------------------------------------|----------------------------|----------------------------|
|                                                   |                      | Overall ( <i>n</i> = 37)               | mGFR ≤ 80 ( <i>n</i> = 17) | mGFR > 80 ( <i>n</i> = 20) |
| Iohexol                                           | Baseline (mean ± SD) | 85.6 ± 24.6                            | 65.6 ± 10.2                | 102.7 ± 19.8               |
|                                                   | Month-6 (mean ± SD)  | 81.2 ± 26.2                            | 63.2 ± 16.1                | 96.6 ± 16.3                |
|                                                   | Difference           |                                        |                            |                            |
|                                                   | mean ± SD            | -4.4 ± 10.3                            | -2.4 ± 9.5                 | -6.1 ± 10.8                |
|                                                   | 95%CI                | -7.8 to -1.0                           | -7.2 to 2.5                | -11.2 to -1.1              |
|                                                   | <i>P</i> value       | 0.0132 <sup>a</sup>                    | 0.2842 <sup>b</sup>        | 0.0136 <sup>b</sup>        |
| Chronic kidney disease epidemiology collaboration | Baseline (mean ± SD) | 81.3 ± 23.7                            | 71.2 ± 20.8                | 89.9 ± 23.0                |
|                                                   | Month-6 (mean ± SD)  | 79.0 ± 23.9                            | 69.1 ± 24.2                | 87.5 ± 20.6                |
|                                                   | Difference           |                                        |                            |                            |
|                                                   | mean ± SD            | -2.3 ± 12.7                            | -2.2 ± 15.2                | -2.4 ± 10.4                |
|                                                   | 95%CI                | -6.5 to 2.0                            | -10.0 to 5.7               | -7.3 to 2.5                |
|                                                   | <i>P</i> value       | 0.2824 <sup>a</sup>                    | 0.4691 <sup>b</sup>        | 0.4939 <sup>b</sup>        |
| Modification of diet in renal disease             | Baseline (mean ± SD) | 71.7 ± 18.9                            | 63.6 ± 17.6                | 78.2 ± 17.7                |
|                                                   | Month-6 (mean ± SD)  | 71.2 ± 19.2                            | 63.5 ± 18.6                | 77.4 ± 17.7                |
|                                                   | Difference           |                                        |                            |                            |
|                                                   | mean ± SD            | -0.5 ± 9.3                             | -0.1 ± 11.9                | -0.8 ± 6.9                 |
|                                                   | 95%CI                | -3.6 to 2.7                            | -6.4 to 6.2                | -4.0 to 2.3                |
|                                                   | <i>P</i> value       | 0.7560 <sup>a</sup>                    | 0.7119 <sup>b</sup>        | 0.5196 <sup>b</sup>        |
| Creatinine clearance <sup>c</sup>                 | Baseline (mean ± SD) | 100.6 ± 34.1                           | 74.0 ± 15.4                | 127.3 ± 27.4               |
|                                                   | Month-6 (mean ± SD)  | 98.2 ± 34.0                            | 77.6 ± 19.2                | 118.9 ± 33.5               |
|                                                   | Difference           |                                        |                            |                            |
|                                                   | mean ± SD            | -2.4 ± 24.5                            | 3.6 ± 10.3                 | -8.4 ± 32.7                |
|                                                   | 95%CI                | -12.7 to 8.0                           | -2.9 to 10.1               | -29.2 to 12.4              |
|                                                   | <i>P</i> value       | 0.7642 <sup>b</sup>                    | 0.3668 <sup>b</sup>        | 0.4697 <sup>b</sup>        |

<sup>a</sup>Paired samples *t* student test.<sup>b</sup>Wilcoxon test.<sup>c</sup>Month-6 measurements available in 24 patients in the overall study sample, 12 in the measured glomerular filtration rate (mGFR) ≤ 80 and in the mGFR > 80 groups, respectively.

mGFR: Measured glomerular filtration rate.

precision and reliability prevents these formulas from being used for assessing the impact of experimental treatments on the progressive loss of renal function in patients with ADPKD. The second implication is that these formulas failed to diagnose rapid progressors towards advanced CKD accurately. This failure can negatively affect clinical management by preventing the establishment of appropriate therapeutic strategies[26,27].

Recognizing ADPKD patients who are at elevated risk for rapid progression to requiring kidney replacement therapy has become increasingly important due to the advent of potential novel treatments[26,28]. It is, therefore, essential to establish criteria for rapid progression in patients with ADPKD to facilitate the selection of disease-modifying therapies and the recruitment of participants for clinical trials[28,29].

From a clinical perspective, failing to identify patients with rapid progression will postpone the starting of treatment in patients who could benefit from it[30,31]. Conversely, misdiagnosing patients with slow renal function decline or stable condition as rapid progressors may unnecessarily expose them to adverse effects, such as liver injury, severe polyuria, and hypernatremia, while also increasing the societal costs associated with the disease[30,31].

The findings of the current study corroborate the conclusions reported by Miquel-Rodríguez *et al*[31], who employed a methodology congruent with our approach. Their study revealed that formulas to estimate GFR, whether based on creatinine and/or cystatin-C, were inadequate in detecting the temporal changes and progression of renal function in

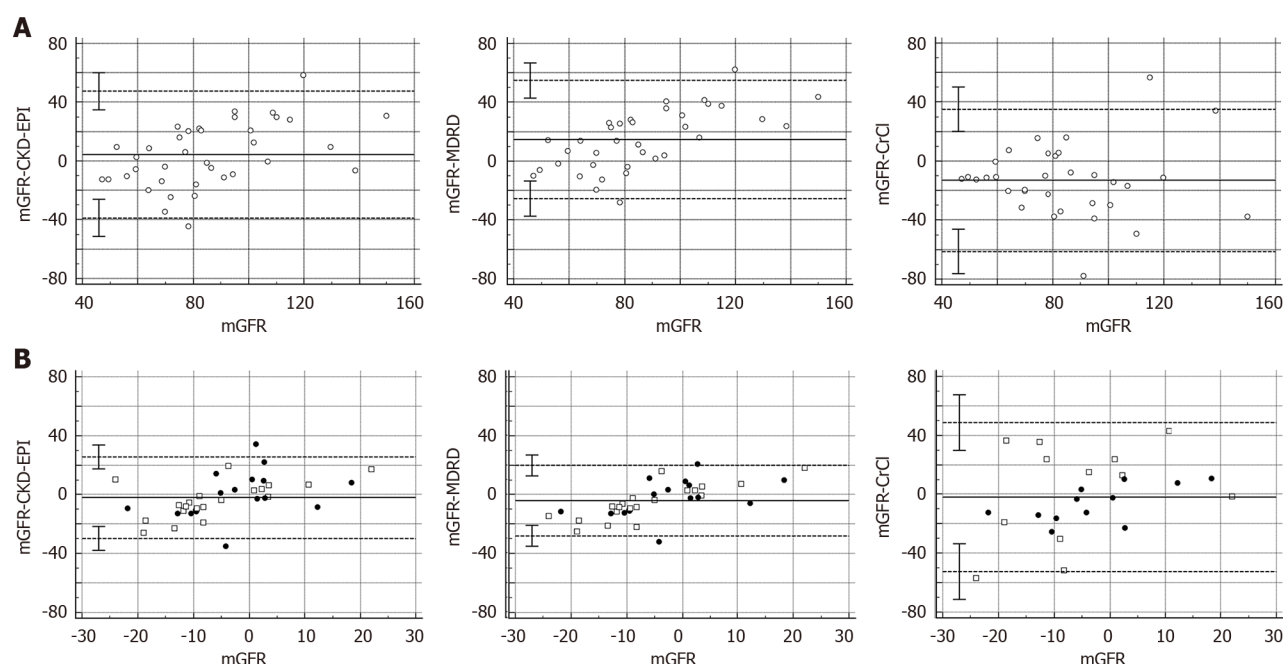


**Figure 2 Bland-Altman plot of study sample.** A: Bland-Altman plot of study sample comparing the measured glomerular filtration rate (mGFR) and the estimated glomerular filtration rate (eGFR) assessed by different formulas; B: Bland-Altman plot of study sample comparing the changes between baseline and month-6 mGFR and the eGFR assessed by different formulas. The mean score is plotted on the x-axis, and the difference between observers (mean of the differences) is plotted on the y-axis (mean difference  $\pm 1.96$  SD). Dark circles represent the patients with a baseline mGFR  $\leq 80$  mL/minute. The empty squares represent the patients with a baseline mGFR  $> 80$  mL/minute. mGFR: Measured glomerular filtration rate.

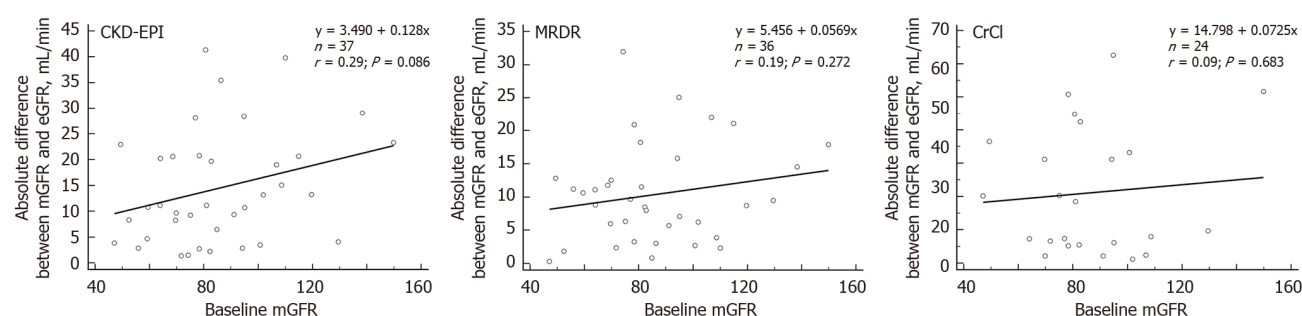


**Figure 3 Absolute differences between measured and estimated month-6 glomerular filtration rates changes vs baseline measured glomerular filtration rates.** There was no any relationship between the estimated glomerular filtration rates regardless the formula and the baseline measured glomerular filtration rates. mGFR: Measured glomerular filtration rate.

patients with ADPKD. They highlighted two principal implications of this discrepancy, namely the failure to correctly identify individuals with rapid disease progression, and the misclassification of patients with stable GFR or moderate disease progression as rapid progressors[31].

Porrini *et al*[12] reported that a single measurement of serum creatinine or cystatin-C could be associated with a value of mGFR ranging from 30 mL/minute to 90 mL/minute, indicating a variability of 200%. In our study, we found a significant correlation between cystatin-C levels and mGFR, while the correlation between serum creatinine and mGFR was borderline, but not significant. Despite this correlation, we noted comparable variability to that reported by Porrini *et al*[12] or Rodríguez *et al*[14].

For instance, serum creatinine values ranging between 0.87-0.88 were linked with mGFR ranging from 68.6 mL/minute to 149.9 mL/minute. Similarly, levels of cystatin-C ranging between 0.84 and 0.85 were associated with mGFR ranging from 78.3 mL/minute to 110.7 mL/minute.

It should be mentioned that, as compared to baseline, cystatin-C levels were significantly increased at month-6 in our sample. Therefore, it might be conjectured that individuals with ADPKD may experience heightened inflammatory activity, leading to elevated cystatin-C levels regardless of GFR, thereby potentially underestimating actual renal function.

The present study has several limitations that warrant consideration when interpreting its findings. The most important one was the relatively small sample size within subgroups, potentially limiting the ability to draw robust comparisons. Nevertheless, the study included a pertinent number of patients, adequate for meaningful stratification. The

6-month follow-up period in our study may be insufficient to fully capture disease-associated complications. Furthermore, inherited or external factors could contribute to acute, subacute, or chronic renal impairment, which may not have been fully assessed within the duration of our study. Lastly, incomplete data collection across all patients may restrict the statistical power of the analyses.

The main strength of the study is that it has been carried out under conditions of real clinical practice, which offers a more accurate representation of how these tools work outside of controlled research environments. Another strength was the use of a standardized method for measuring GFR, as it is the iothexol plasma clearance technique.

## CONCLUSION

In summary, the findings of this study clearly indicate that eGFR inadequately and imprecisely reflected the decline in mGFR. Furthermore, eGFR equations exhibited unreliable estimation of actual GFR values and were unable to detect changes in GFR over time. These results might critically impact on clinical decision-making, particularly on treatment strategies and highlighted the need for a more effective and efficient method to assess kidney function and its evolution over time. Finally, it will be necessary to develop future research, ideally prospective and multicenter, to evaluate the clinical performance of these new tools in daily practice.

## ACKNOWLEDGEMENTS

The authors would like to thank Dr. Porrini E and Dr. Lima SL for their collaboration during the research.

## FOOTNOTES

**Author contributions:** Fernandez JM and Rodriguez-Pérez JC participated in the conception and design of the study and were involved in the acquisition, analysis and interpretation of data and process of writing; Lorenzo-Medina MM, Quevedo-Reina JC, and Hernandez-Socorro CR accessed and verified the study data; Rodriguez-Esparragon F analysis and writing; all authors contributed to the preparation and critical review of the manuscript, and approved the final manuscript.

**Institutional review board statement:** The study protocol received approval from the Ethics Committee of the HUGCDN (Protocol VO 05-2017; Review Board approval, No. 170071; May 2017).

**Informed consent statement:** The need for patient consent was waived due to the retrospective nature of the study. Nevertheless, prior to participation and inclusion in the prospective database, written informed consent was obtained from all patients.

**Conflict-of-interest statement:** None of the authors have any conflict of interest to declare. Neither honoraria nor payments were made for authorship of this article. All authors declare no proprietary interest.

**Data sharing statement:** The data underlying this article will be shared on reasonable request to the corresponding author.

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**S-Editor:** Luo ML

**L-Editor:** A

**P-Editor:** Li X

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