Clinical Kidney Journal

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LEADING EUROPEAN NEPHROLOGY

Clinical Kidney Journal, 2021, vol. 14, no. 3, 909–916

doi: 10.1093/ckj/sfaa034
Advance Access Publication Date: 13 April 2020
Original Article

ORIGINAL ARTICLE

20-year longitudinal follow-up of measured and estimated glomerular filtration rate in kidney transplant patients

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ABSTRACT

Background. The slopes of estimated glomerular filtration rate (eGFR) equations are used in the longitudinal follow-up of transplant patients. A 30% reduction in eGFR over 2 years is often used to predict the subsequent risk of mortality or end-stage renal disease. Whether, at the individual level, such changes in eGFR correspond to changes in measured GFR (mGFR) is actually unknown.

Methods. The performance of serum creatinine–based eGFR equations was compared with mGFR during the longitudinal follow-up of 20 years in a monocentric study of 417 transplanted patients.

Results. The accuracy within 30% for the eGFR equations varied between 70 and 75%. All eGFR equations showed a similar pattern, very like the mGFR time profiles. Individual changes (slopes) of mGFR or eGFR were predictive of graft loss in the next months or years, following the decline in GFR, with no evidence for a difference. However, although the tendency is the same as for mGFR, the percentage of transplant patients with a >30% GFR decrease in the last period before graft loss is significantly lower for eGFR than for mGFR, with discordant results from mGFR in ~25% of the cases.

Conclusions. All eGFR equations showed similar trends as mGFR, but eGFR predictions may not be very useful at the individual patient level.

Keywords: kidney transplant patients, longitudinal follow-up, measured, and estimated GFR

INTRODUCTION

Measured and estimated glomerular filtration rate (mGFR, eGFR) are particularly important for the longitudinal follow-up of patients after kidney transplantation. There are few literature data on the long-term decline of mGFR in kidney transplant patients because serum creatinine (SCr) or SCr-based eGFR has long been and is still used for the follow-up of transplant

Received: 11.12.2019. Editorial decision: 10.2.2020

patients [1, 2]. Commonly used SCr-based eGFR equations [i.e. Modified Diet in Renal Disease (MDRD) [3, 4], Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [5] and full age spectrum (FAS) [6] equation] have been derived from non-transplant patients and may lack accuracy in the context of kidney transplantation [1, 2, 7–11]. As for longitudinal GFR change, it has been shown that GFR estimating equations are far from perfect to adequately assess the slope of mGFR [12–20]. In transplanted patients, few data are available. Gera *et al.* [21] described the trend of eGFR to underestimate the true decline of renal graft function. Fauvel *et al.* [22] showed that all equations failed to detect variations of mGFR <20%. Both studies occurred in a relatively short period after transplantation, as the mean follow-up was 3.4 ± 1.6 years in Gera *et al.* [21] and within a maximum of 6 years in the Fauvel *et al.* cohort [22]. Besides GFR slopes, relative variations of GFR are also of interest, as a 30% reduction in eGFR over 2 years has been shown to predict the subsequent risk of mortality or end-stage renal disease [23]. Such an association has also been described in transplanted patients [24]. Whether, at the individual level, such variations of eGFR correspond to variations in mGFR, both for short- and long-term follow-up, is actually unknown.

In this study we sought to evaluate the performance of SCr-based eGFR equations, MDRD, CKD-EPI and FAS compared with mGFR for the longitudinal follow-up in a monocentric study of transplanted patients with mGFR and eGFR every 5 years during a maximal follow-up of 20 years.

MATERIALS AND METHODS

Study population

We analysed all single kidney transplantations performed in the transplant centre of Saint-Etienne (France) between January 1989 and December 2000 ($n = 621$). We selected patients with a functioning graft at 5 years post-transplant and for whom inulin mGFR was available at 1 and 5 years post-transplant with concomitant SCr dosage ($n = 417$). Patients were followed to death or to 31 December 2016. Because few patients' data were available after 20 years, the follow-up was ended at this time. In total, there were 64 patients with a functioning graft at 20 years post-transplantation and with all data (mGFR, SCr, age and sex) available. The study protocol was approved by the institutional review board and was conducted in accordance with good international clinical practice guidelines.

Methods

Transplant patients had a direct measurement of GFR by urinary clearance of inulin, as previously described [25]. Briefly, every 5 years urinary clearance of inulin was conducted according to the continuous infusion method. After a loading dose of 300 mg/kg (half-dose if SCr concentration was >160 μmol/L) of INUTEST 25% (Fresenius, Linz, Austria), a continuous infusion of 400 mg/kg of inulin diluted in a 10% mannitol solution was started. After an equilibration period of 45 min, two or three clearance periods of 30 min each were analysed. Urine samples were collected by spontaneous voiding of the bladder. Blood samples, drawn from the arm opposite to the infusion site, were obtained at the midpoint of each clearance period. Inulin concentrations were quantified according to a standard colorimetric assay (resorcinol method) on a UV1205 spectrophotometer (Shimadzu, Kyoto, Japan) [26]. GFR was measured as the mean of at least two urinary clearances of inulin with the formula UV/P, where U and P are inulin concentrations in urine and plasma, respectively, and V is the urine flow rate (mL/min). GFR was corrected per 1.73 m^2 of body surface area. In our centre, the mean intra-individual coefficient of variation for this inulin clearance procedure has been previously determined to be 8.4% [25].

SCr was collected on the same day as the inulin clearance measurement and measured using an enzymatic test (Crea Vitros, Ortho-Clinical Diagnostics, Issy-les-Moulineaux, France), equivalent to the isotope dilution mass spectrometry (IDMS) gold standard method. eGFR was calculated using the MDRD [3, 4], CKD-EPI [5] and FAS equations [6]:

- $\text{eGFR-MDRD} = 175 \times \text{SCr}^{-1.159} \times \text{Age}^{-0.203}$ [× 0.742 if females]
- $\text{eGFR-CKD-EPI} = 141 \times \min(\text{SCr}/\kappa)^{\alpha} \times \max(\text{SCr}/\kappa)^{-1.209} \times 0.993^{\text{age}}$ [× 1.018 if female]
- $\kappa = 0.7$ for females and 0.9 for males; $\alpha = -0.329$ for females and −0.411 for males; min indicates the minimum of SCr/κ or 1 and max indicates the maximum of SCr/κ or 1.
- $\text{eGFR-FAS} = 107.3/[\text{SCr}/Q]$ [$\times\ 0.988^{(\text{Age}-40)}$ when age >40 years], with $Q = 0.70$ for females and 0.90 for males.

For the three formulas, SCr is serum creatinine in milligrams per decilitre.

Statistical analysis

Descriptive statistics are presented per subgroup using mean ± standard deviation (SD) or median [interquartile range (IQR)] depending on the normality of the data. The performances of the eGFR equations were evaluated in terms of bias, precision and accuracy within 30% (P30). We calculated slopes of mGFR and eGFR in two different ways:

a. Slope = [GFR(j) − GFR(i)]/[Time(j) − Time(i)], where j indicates the time point immediately following the time point i (two consecutive times). This method is very sensitive to accidental errors or variations in the mGFR or eGFR, as it depends only on two points
b. The slope is calculated by using regression analysis using all available data for two, three, four and five consecutive visits. This method takes into account the variability in mGFR and eGFR, as soon as the number of data points is greater than two.

Median slopes between mGFR and eGFR were compared by the Wilcoxon signed-rank test.

Variation of GFR was also studied relative to the preceding GFR value: [GFR(j) − GFR(i)]/GFR. Variation of 10 and 30% were considered, both for eGFR and mGFR at different consecutive time points (5, 10, 15 and 20 years of follow-up). About 10% variation was considered comparable to the intra-individual variation in mGFR measured by inulin clearance and 30% variation was considered because such a variation has been shown to be associated with outcome [24]. Discrepancies between patients reaching 30% variation with mGFR but not eGFR, or vice versa, were presented. Comparison between dependent proportions was performed with McNemar's exact test. All statistics were determined with SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Of 621 kidney transplantations performed between 1989 and 2000, 488 recipients had a functioning graft 1 year post-

transplant and had undergone an inulin clearance evaluation. Among them, 417 had a functioning graft 5 years post-transplant along with a usable value of inulin clearance. At 10 years, 312 patients remained, at 15 years, 191 patients still had a functioning graft and at 20 years, there were 64 patients left with a functioning graft. We defined subgroups of patients with the same number of follow-up visits and the same time points, that is, 63 patients had only one follow-up visit (at 1 year after transplantation) and lost their graft before the next planned follow-up visit at which GFR was directly measured (at 5 years). A total of 112 patients had two consecutive follow-up visits (1 and 5 years), 114 patients had three consecutive follow-up visits (1, 5 and 10 years), 120 patients had four consecutive follow-up visits (1, 5, 10 and 15 years) and 59 patients had five consecutive follow-up visits (1, 5, 10, 15 and 20 years). In Table 1 we present the patient characteristics at the time of transplantation of those patients having a functioning graft 1 year post-transplantation. The performance of equations to estimate GFR at different time points (transversal analyses) is summarized in the Supplementary data, Table S1.

Accuracy within 30% for the different equations is between 70 and 75%.

Figure 1 presents the absolute GFR mean values for the recipients with a functioning graft, both for mGFR and eGFR in a longitudinal analysis. This figure shows that both mGFR and eGFR slightly decline over time during the first 15 years post-transplantation, with an acceleration over 15 years post-transplantation. However, this figure should not be overinterpreted, since this acceleration in mGFR and eGFR can be observed in each period immediately preceding graft loss (before the next planned follow-up visit) in every subgroup defined by patients with the same number of consecutive follow-up visits in the period considered (Figure 2). All eGFR equations show a similar pattern, very alike the mGFR time profiles.

In the same view, individual changes (slopes) of mGFR or eGFR were predictive for graft loss in the next months or years, following the decline in GFR. Table 2 illustrates this clearly, showing median slopes between consecutive time points that are becoming steeper with time, showing the largest decline before the period in which the graft is lost. This tendency is not only visible in mGFR, but also in eGFR, as illustrated by FAS in Table 3. In all except for the subgroup with only two points, we could not find evidence for a difference between median slopes in mGFR and FAS. Analogous results are obtained for CKD-EPI and MDRD equations (see Supplementary data, Tables S2a and S2b).

Then we focused on variation of GFR reaching 10 or 30%. Table 4 shows that the percentage of transplant patients with a decrease in mGFR of 10 or 30% between two consecutive time points increases over time, reaching ~50–60% (with a 10% decrease) and 30–40% (with a 30% decrease) in the last period before graft loss. Table 5 shows that eGFR (FAS) decreases >10% in ~50% of the transplant patients in that last period, quite equivalent with mGFR, but only shows 15–25% of transplant patients with >30%. Although the tendency is the same as for mGFR, the percentage of transplant patients with a >30% GFR decrease in the last period before graft loss is (significantly) lower for eGFR than for mGFR. Using the CKD-EPI or MDRD equation instead of the FAS equation leads to the same conclusions regarding variation of GFR of 10 or 30% (see Supplementary data, Tables S3a and S3b) (with concordance rate between eGFR equations >95%).

Table 1. Characteristics at the time of transplantation of patients with a functioning graft at different time points: 1, 5, 10, 15 and 20 years post-transplantation

						Cause of renal disease (%)[a]						
N	Time (year)	Age (years)[b]	Male (%)	Pre-emptive (%)	Retransplant (%)	1	2	3	4	5	6	7
488	1	45.4 ± 12.9	69.5	8.9	15.8	1.0	32.4	7.8	13.9	7.6	12.1	25.2
417	5	45.2 ± 12.5	69.5	8.9	15.6	1.0	33.5	7.2	14.1	7.2	12.5	24.5
312	10	45.0 ± 12.2	71.5	8.4	15.1	1.0	32.0	6.4	15.1	6.4	11.9	27.2
191	15	43.0 ± 12.2	77.0	10.0	13.0	1.0	30.4	5.8	13.1	7.3	12.0	30.4
64	20	40.7 ± 11.3	71.9	17.2	9.4	1.6	26.6	1.6	7.8	6.2	10.9	45.3

[a]1, diabetes; 2, glomerulopathy; 3, hypertension; 4, polycystic kidney disease; 5, interstitial nephritis; 6, other; 7, unknown. [b]Age at transplantation.

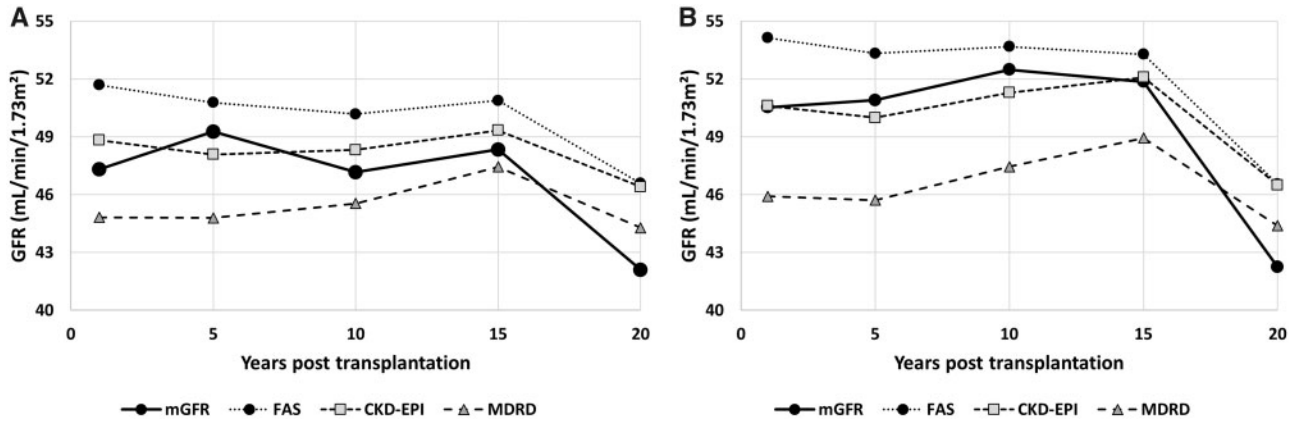

FIGURE 1: Mean mGFR and eGFR against years post-transplantation for (**A**) all patients with a functioning graft at each time point ($n = 488$ at 1 year, $n = 417$ at 5 years, $n = 312$ at 10 years, $n = 191$ at 15 years and $n = 64$ at 20 years) and for (**B**) $n = 59$ patients with a functioning graft after 20 years.

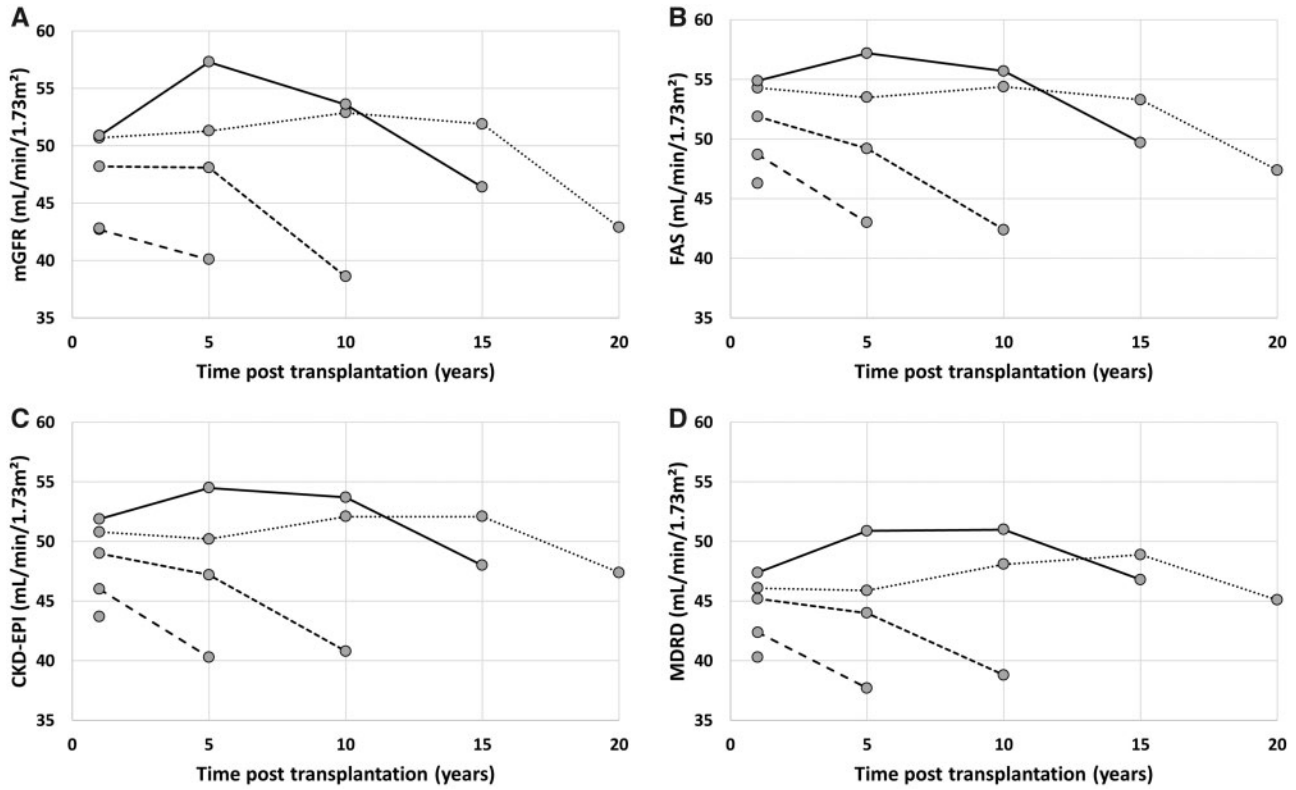

FIGURE 2: Mean (**A**) mGFR and eGFR for (**B**) FAS, (**C**) CKD-EPI and (**D**) MDRD against years post-transplantation for patients with only one follow-up visit (single point, $n = 63$; 1 year post-transplantation), two follow-up visits (dashed line, $n = 112$; 1 and 5 years), three follow-up visits (dashed line, $n = 114$; 1, 5 and 10 years), four follow-up visits (dotted line, $n = 120$; 1, 5, 10 and 15 years) and five follow-up visits (solid line, $n = 59$; 1, 5, 10, 15 and 20 years).

Table 2. Median slope (quartile 1–quartile 3) for mGFR, calculated from two consecutive time points and from linear regression using all available time points

Group	1–5 years	5–10 years	10–15 years	15–20 years	First–last time point	From regression
Two visits ($n = 112$)	−0.38 (−3.25–+2.75)	Graft loss	–	–	−0.38 (−3.25–+2.75)	−0.38 (−3.25–+2.75)
Three visits ($n = 114$)	1.00 (−2.75–+3.25)	−1.60 (−4.20–+0.40)	Graft loss		−1.11 (−2.56–+0.56)	−1.12 (−2.63–+0.48)
Four visits ($n = 120$)	1.13 (−1.38–+3.50)	−0.40 (−1.90–+1.10)	−1.00 (−3.70–+0.40)	Graft loss	−0.11 (−1.39–+0.57)	−0.28 (−1.47–+0.58)
Five visits ($n = 59$)	−0.25 (−2.00–+2.75)	0.20 (−1.80–+3.00)	−0.20 (−2.20–+1.80)	−2.20 (−4.00–0.00)	−0.42 (−1.16–+0.11)	−0.33 (−0.98–+0.25)

Table 6 shows whether variations in eGFR (using different equations) and mGFR are concordant or not. In other words, when a change of 30% in mGFR is reached in a given patient, is a change in eGFR of 30% also obtained? The ability of the FAS or CKD-EPI equation to classify patients with variations of GFR < −30% (or −10%) is the same (concordance of 90–95% between the two equations), whereas the discordance of classification of both equations with mGFR is 30–40% (for the criterion ΔGFR < −10%) and 20–30% (for the criterion ΔGFR < −30%). The same conclusions are drawn with the MDRD equation (data not shown).

Figure 3 illustrates the potential discrepancies between variations of GFR by the reference method versus eGFR (FAS in the current example, but the pattern is the same with other equations). The change in FAS (as a continuous variable) against the change in mGFR for the patients with only two successive visits (1 and 5 years), together with the −30% medical decision thresholds (horizontal and vertical lines) is shown in Figure 3.

DISCUSSION

In this study we have shown that the current equations used to estimate GFR correctly reflect the trajectory of mGFR in a longitudinal analysis of GFR results in renal transplant patients followed over a long period of time (up to 20 years of follow-up). The ability of eGFR to reflect the trajectory of mGFR is actually good at the population level, and comparing equations between them, we cannot prove the superiority of one equation compared with the others. As a specific example, eGFR decline, as well as mGFR, accelerates in the 5-year period preceding the loss of the graft, as expected [27]. Although there were small differences between slopes based on mGFR and eGFR

Table 3. Median slope (quartile 1–quartile 3) for FAS calculated from two consecutive time points and from linear regression using all available time points

Group	1–5 years	5–10 years	10–15 years	15–20 years	First–last time point	From regression
Two visits ($n = 112$)	−0.91 (−3.35–+0.78)*	–	–	–	−0.91 (−3.35–+0.78)	−0.91 (−3.35–+0.78)*
Three visits ($n = 114$)	−0.09 (−2.01–+1.11)	−0.92 (−2.91–+0.11)	–	–	−0.97 (−2.25 to -0.01)	−1.01 (−2.28 to −0.05)
Four visits ($n = 120$)	0.46 (−1.42–+2.14)	−0.27 (−1.87–+1.08)	−1.24 (−2.43–+0.08)	–	−0.41 (−1.20–+0.17)	−0.44 (−1.12–+0.20)
Five visits ($n = 59$)	−0.34 (−2.16–+1.89)	0.10 (−1.22–+1.31)	−0.29 (−1.49–+1.07)	−1.28 (−2.87–+0.28)	−0.37 (−0.87–+0.08)	−0.23 (−0.89–+0.20)

*Indicates a significant difference ($P < 0.05$) from the equivalent parameter in Table 2.

Table 4. Percentage of patients (95% CI) with a decrease in mGFR of >10% and >30% calculated from two consecutive measurements and from the first (baseline value at 1 year) and the last available time points

Group	1–5 years	5–10 years	10–15 years	15–20 years	First–last time point
mGFR >10%					
Two visits ($n = 112$)	38.4 (29.2–47.5)	–	–	–	38.4 (29.2–47.5)
Three visits ($n = 114$)	34.2 (25.4–43.1)	61.4 (52.3–70.5)	–	–	62.3 (53.2–71.3)
Four visits ($n = 120$)	25.8 (17.9–33.8)	35.8 (27.1–44.5)	50.0 (40.9–59.1)	–	46.7 (37.6–55.7)
Five visits ($n = 59$)	35.6 (23.0–48.2)	44.1 (31.0–57.1)	37.3 (24.6–50.0)	62.7 (50.0–75.4)	54.2 (41.1–67.3)
mGFR >30%					
Two visits ($n = 112$)	26.8 (18.5–35.1)	–	–	–	26.8 (18.5–35.1)
Three visits ($n = 114$)	19.3 (11.9–26.7)	39.5 (30.4–48.6)	–	–	38.6 (29.5–47.7)
Four visits ($n = 120$)	9.2 (3.9–14.4)	16.7 (9.9–23.4)	30.0 (21.7–38.3)	–	30.8 (22.5–39.2)
Five visits ($n = 59$)	10.2 (2.2–18.1)	11.9 (3.4–20.4)	13.6 (4.6–22.6)	33.9 (21.5–46.3)	35.6 (23.0–48.2)

Table 5. Percentage of patients (95% CI) with a decrease in FAS >10% and >30% calculated from consecutive measurements and from the first (baseline value at 1 year) and last available time points

Group	1–5 years	5–10 years	10–15 years	15–20 years	First–last time point
FAS >10%					
Two visits ($n = 112$)	50.0 (40.6–59.4)*	–	–	–	50.0 (40.6–59.4)
Three visits ($n = 114$)	28.9 (20.5–37.4)	51.8 (42.4–61.1)	–	–	62.3 (53.2–71.3)
Four visits ($n = 120$)	24.2 (16.4–31.9)	36.7 (27.9–45.4)	54.2 (45.1–63.2)		52.5 (43.4–61.6)
Five visits ($n = 59$)	33.9 (21.5–46.3)	25.4 (14.0–36.9)*	30.5 (18.4–42.6)	52.5 (39.4–65.7)	50.8 (37.7–64.0)
FAS >30%					
Two visits ($n = 112$)	24.1 (16.1–32.2)	–	–	–	24.1 (16.1–32.2)
Three visits ($n = 114$)	13.2 (6.9–19.5)	26.3 (18.1–34.5)*	–	–	34.2 (25.3–43.1)
Four visits ($n = 120$)	6.7 (2.1–11.2)	9.2 (3.9–14.4)	17.5 (10.6–24.4)*	–	26.7 (18.6–34.7)
Five visits ($n = 59$)	5.1 (0.0–10.9)	1.7 (0.0–5.1)	1.7 (0.0–5.1)*	20.3 (9.8–30.9)	27.1 (15.4–38.8)

*Indicates a significant difference ($P < 0.05$) with the corresponding result in Table 4.

Table 6. Comparison between the change in FAS and the change in CKD-EPI using ΔmGFR as the criterion for two consecutive visits

		% Correct at ΔmGFR <−10%				% Correct at ΔmGFR <−30%			
Subgroup	Visits	FAS (%)	CKD-EPI (%)	Agreement (%)	P-value	FAS (%)	CKD-EPI (%)	Agreement (%)	P-value
Two visits ($n = 112$)	1–5	72.3	73.2	97.3	1	83.0	82.1	95.5	1
Three visits ($n = 114$)	1–5	73.7	72.8	99.1	1	86.8	86.0	99.1	1
	5–10	67.5	67.5	96.5	1	71.1	72.8	96.5	0.625
Four visits ($n = 120$)	1–5	75.0	73.3	96.7	0.625	87.5	88.3	99.2	1
	5–10	69.2	70.0	95.8	1	84.2	82.5	98.3	0.5
	10–15	74.2	71.7	92.5	0.508	82.5	80.8	98.3	0.5
Five visits ($n = 59$)	1–5	71.2	72.9	94.9	1	84.8	86.4	98.3	1
	5–10	61.0	55.9	94.9	0.25	86.4	81.4	94.9	0.25
	10–15	66.1	67.8	98.3	1	88.1	86.4	98.3	1
	15–20	69.5	71.2	94.9	1	76.3	74.6	94.9	1

Percentage correct at ΔmGFR <−30% (10%) means that ΔeGFR is also <−30% (10%), resulting in the same clinical decision. Agreement is the percentage of agreement between FAS and CKD-EPI (including correct and incorrect decisions). The P-value is obtained with McNemar's exact test, comparing the correct/incorrect decisions for FAS and CKD-EPI, using ΔmGFR as the criterion to define correct/incorrect.

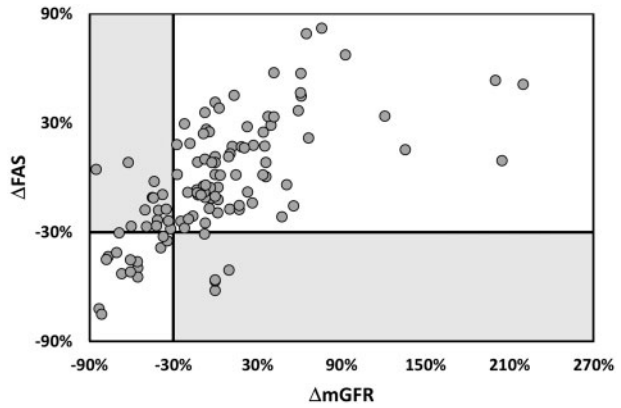

FIGURE 3: ΔFAS against ΔmGFR for the patients with two successive visits (1 and 5 years) ($n = 112$). The −30% lines for medical decisions are drawn for comparison. Discrepant medical decisions ($n = 20$) on eGFR and mGFR are made for those patients lying in the off-diagonal rectangles (shaded area).

equations in all subgroups, concordance between eGFR and mGFR is good. However, the performance of eGFR is less impressive at the individual level. First, in our analyses, the P30 values are ~70–75%, meaning that the eGFR result is very different (in 25–30% of the cases, the difference is >30%) from mGFR, confirming previous data in renal transplant patients [2, 25]. The P30 of the MDRD equation is slightly better than other equations, as already shown by other publications [1, 11, 28–30], which is explained by the fact that this equation performs slightly better in CKD populations [28, 31]. The performance of equations must also be tempered at the individual level for longitudinal analyses. Indeed, if variations of 10 or 30% are considered clinically relevant for potential medical decisions, such variations of mGFR are missed by eGFR in 30–40% and 20–30%, respectively. In other words, all estimating equations lack sensitivity to detect variations of 30% in GFR results, with one-quarter of such variations being missed. We thus confirmed, on a much longer follow-up, previous data obtained in renal transplant patients [21, 22, 32]. Comparing different creatinine-based equations, we could not find sufficient differences between them to claim that one equation is better than another.

Our study must be read in the light of its limitations. This is a monocentric study and a retrospective analysis. Even if creatinine is claimed by the manufacturer to be IDMS traceable, some changes in creatinine calibration are possible over such a long period of time [33, 34]. We also considered only a limited number of time points separated by a 5-year period. It would be interesting to evaluate the possible non-linear change in GFR during the period preceding graft loss and investigate whether other criteria, as suggested by Lee *et al.* [35], could be of interest to predict graft loss more accurately. Lastly, only creatinine-based equations could be tested, as testing other biomarkers, like cystatin C, was not possible [36]. All results in the longitudinal analyses were indexed for body surface area, which is questionable in such analyses where the patient is compared to him-/herself. Unfortunately, analyses with de-indexed results were not possible as too many weight values were lacking during the 20-year period [37].

In conclusion, we showed that estimating equations correctly predict the slope or trajectory of mGFR in renal transplant patients in the long term and at the population level. However, at the individual level and to detect variations of mGFR potentially impacting clinical decisions, all current estimating equations lack precision and discordant results with large (<−30%) differences from mGFR have been observed in 25% of the cases. We therefore believe that our results encourage the follow-up of transplant patients not solely based on eGFR, but on mGFR at specific follow-up moments post-transplantation [9, 38–40].

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

AUTHORS' CONTRIBUTIONS

H.P. participated in data analysis and writing of this article. A.D. and N.M. participated in the performance of the research. C.M. participated in research design, the performance of the research and the writing of the article. P.D. participated in data analysis and writing of the article.

CONFLICT OF INTEREST STATEMENT

None declared.

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