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Single-sample measured glomerular filtration rate in Malawi, South Africa, and Uganda

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Measured glomerular filtration rate (mGFR) is considered the best index of kidney function.[1] Various mGFR methods exist, using urinary or plasma clearance of exogenous markers, each with their own advantages and disadvantages.[2] Most commonly, mGFR is calculated from multipoint sampling using the slope intercept method and applying the Brochner-Mortensen correction.[3] Because of the time needed for the multisample test, between 4 and 6 hours depending on glomerular filtration rate (GFR), various single-sample methods have evolved to simplify the mGFR procedure while aiming to preserve accuracy.[4]

The routine use of mGFR is complicated by the need for exogenous markers as well as the complexity, cost, and time required for such procedures. Yet, mGFR is still a valuable tool in both research and public health settings as well as in certain clinical scenarios, such as living kidney donors, non-kidney solid organ recipients, liver cirrhosis, and dosing of certain drugs.[5] In most studies, almost exclusively in white patients, single-sample mGFR shows concordance with multisample techniques, especially when the GFR is >30 ml/min per 1.73 m^2.[4]

Before implementing any new testing strategy, such as single-sample mGFR, it is essential to validate the accuracy of the test in populations for which its use is intended. Our aim was to compare the performance of various single-sample mGFR equations with multisample plasma clearance of iohexol as the reference mGFR.

METHODS

Publicly available data from the study by Fabian *et al.* was analyzed.[6] Participants from Malawi, South Africa, and Uganda had iohexol administered as an i.v. bolus. The final dataset containing 2578 participants was used to calculate multisample mGFR, which was considered the reference to which various single-sample mGFR equations were compared. As plasma clearance of iohexol is not

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Table 1 | Bias, imprecision, and concordance of single-sample mGFR equations at P30 and P10 of multisample mGFR

Single-sample mGFR equation	P30	P10	Bias	Imprecision
Iterative Jacobsson 120-min[7]	87.8 (86.5 to 89.0)	57.7 (55.8 to 59.6)	0.93 (0.38 to 1.49)	14.3 (13.9 to 14.6)
Iterative Jacobsson 180-min[7]	93.8 (92.9 to 94.7)	68.9 (67.1 to 70.6)	1.88 (1.66 to 2.29)	10.9 (10.6 to 11.2)
Iterative Jacobsson 240-min[7]	93.5 (92.5 to 94.4)	74.0 (72.3 to 75.6)	−0.05 (−0.25 to 0.25)	12.5 (12.1 to 12.8)
Simplified Jacobsson 120-min[9]	87.9 (86.6 to 89.2)	59.7 (57.8 to 61.6)	2.86 (2.44 to 3.26)	14.3 (13.9 to 14.7)
Simplified Jacobsson 180-min[9]	94.1 (93.2 to 95.0)	71.1 (69.3 to 72.8)	0.72 (0.39 to 0.98)	10.5 (10.2 to 10.8)
Simplified Jacobsson 240-min[9]	94.5 (93.6 to 95.4)	67.2 (65.4 to 69.0)	−1.85 (−2.10 to −1.56)	12.8 (12.5 to 13.2)
Christensen and Groth 120-min[S6]	83.6 (82.1 to 85.0)	39.7 (37.8 to 41.6)	7.33 (6.75 to 7.82)	18.7 (18.2 to 19.2)
Christensen and Groth 180-min[S6]	92.7 (91.7 to 93.7)	62.3 (60.5 to 64.2)	4.26 (3.94 to 4.57)	12.4 (12.0 to 12.7)
Christensen and Groth 240-min[S6]	92.6 (91.5 to 93.6)	72.1 (70.4 to 73.9)	1.59 (1.41 to 1.85)	13.2 (12.9 to 13.6)
Fleming 120-min[8]	89.6 (88.4 to 90.8)	65.5 (63.7 to 67.4)	−0.57 (−1.00 to −0.11)	12.4 (12.1 to 12.7)
Fleming 180-min[8]	94.7 (93.9 to 95.6)	69.7 (68.0 to 71.5)	−1.15 (−1.61 to −0.92)	10.6 (10.3 to 10.9)
Fleming 240-min[8]	93.8 (92.9 to 94.7)	69.0 (67.2 to 70.8)	−0.59 (−0.89 to −0.29)	12.8 (12.5 to 13.2)
Peters 120-min[S3]	89.1 (87.9 to 90.3)	55.3 (53.4 to 57.2)	6.33 (5.96 to 6.65)	16.1 (15.7 to 16.6)
Peters 180-min[S3]	89.0 (87.8 to 90.2)	50.7 (48.7 to 52.6)	6.82 (6.32 to 7.25)	19.6 (19.1 to 20.1)
Peters 240-min[S3]	88.2 (86.9 to 89.4)	61.8 (60.0 to 63.7)	1.51 (1.01 to 2.03)	25.9 (25.2 to 26.6)
Tauxe quadratic 120-min[S7]	87.2 (85.9 to 88.5)	49.3 (47.3 to 51.2)	7.73 (6.75 to 7.82)	18.2 (17.8 to 18.8)
Tauxe linear 120-min[S7]	87.1 (85.8 to 88.4)	47.1 (45.2 to 49.1)	8.12 (7.68 to 8.51)	18.1 (17.6 to 18.6)
eGFR CKD-EPI (creatinine) 2021[S1]	60.0 (58.1 to 61.9)	23.9 (22.2 to 25.2)	14.98 (13.80 to 16.28)	28.7 (27.9 to 29.5
eGFR CKD-EPI (creatinine + cystatin C) 2021[S1]	70.1 (68.3 to 71.9)	30.7 (28.2 to 32.5)	7.01 (6.04 to 7.80)	25.2 (24.5 to 25.9)
eGFR CKD-EPI (cystatin C) 2012[S2]	70.4 (68.6 to 72.3)	27.7 (26.0 to 29.5)	−1.69 (−2.65 to −0.55)	25.9 (25.2 to 26.6)

CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate; P10, within 10%; P30, within 30%.
P30 and P10 values are % (95% CI). Bias measured as median of the differences between single-sample and multisample mGFR (95% CI). Imprecision measured as root mean square error (95% CI).

without error, concordance between the 2 methods was considered instead of accuracy. Full methods are available in the Supplementary Methods.

RESULTS

The demographic and clinical characteristics of the cohort are shown in Supplementary Table S1. Concordance of single-sample mGFR equations within 30% (P30) of multisample mGFR ranged from 83.6% to 94.7%, whereas concordance within 10% (P10) ranged from 39.7% to 74.0%. All single-sample mGFR equations showed better concordance according to P30 and P10 than the race-neutral Chronic Kidney Disease Epidemiology Collaboration estimated GFR for creatinine, creatinine and cystatin C, and cystatin C alone[S1,S2] (Table 1).

Most single-sample mGFR equations showed the least bias and imprecision at the 180- and 240-minute time points. All single-sample mGFR equations, except for the Peters[S3] equation, showed the least imprecision at the 180-minute time point. Although bias was variable among equations, all single-sample mGFR equations, except for the Peters equation at 240 minutes, showed improved precision compared with estimated GFR. Bias was also variable among the different countries (Table 1 and Supplementary Table S2).

The best performance was seen with the iterative Jacobsson[7] equation at 240 minutes, which had a P10 of 74.0% (95% confidence interval [CI], 72.3%–75.6%) and bias of –0.05 ml/min per 1.73 m^2 (95% CI, –0.25 to 0.25 ml/min per 1.73 m^2). The concordance, according to P10, of all the single-sample mGFR equations, was best at the 240-minute time point, except for the Fleming[8] and simplified Jacobsson[9] equations, which had the best concordance at 180 minutes (Table 1).

All subsequent analysis was conducted on the iterative Jacobsson single-sample mGFR at 240 minutes as this equation showed the best performance and is the most used single-sample mGFR equation.[7]

Single-sample mGFR showed the best concordance between a mGFR of 60 and 120 ml/min per 1.73 m^2, with P10 of 80.8% (95% CI, 79.0%–82.6%); this decreased to 63.1% (95% CI, 58.7%–67.5%) between 30 and 60 ml/min per 1.73 m^2. Concordance decreased sharply when mGFR was outside of the 30 to 120 ml/min per 1.73 m^2 range, with P10 values of 12.5% (95% CI, 1.0%–24.0%) and 42.1% (95% CI, 35.1%–49.1%). Similarly, the best concordance of single-sample mGFR was seen between the 30 and 120 ml/min per 1.73 m^2 range of estimated GFR (Figure 1; Supplementary Tables S3 and S4).

Bias and concordance were consistent across the range of body mass index, age, and sex. The differences in concordance among the range of body mass index and age were all nonsignificant (Supplementary Tables S5 and S6 and Supplementary Figure S1A and B).

Predictably, the concordance of single-sample mGFR to multisample mGFR improved incrementally with increasing R^2, from a P10 of 46.7% (95% CI, 36.5%–56.9%) when R^2 was $\leq$0.8 to 78.0% (95% CI, 76.1%–80.0%) when R^2 was $>$0.95; this trend was significant ($P < 0.001$) (Supplementary Table S7 and Supplementary Figure S1C). Supplementary Table S8 shows the performance of single-sample mGFR after excluding results (n = 816) when R^2 is $<$0.95. The iterative Jacobsson equation at 240 minutes still showed the least bias; however, concordance and precision were best at the 180-minute time point for most equations. The best concordance was seen with the simplified Jacobsson equation

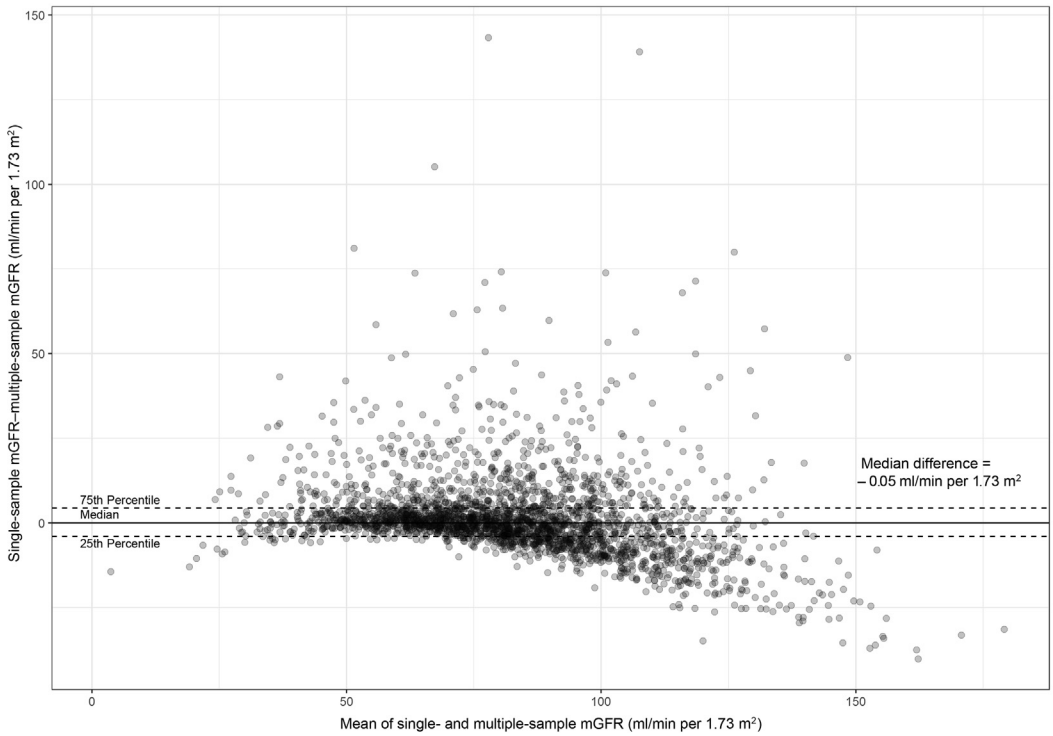


Figure 1 | Difference plot for iterative Jacobsson 240-minute single-sample measured glomerular filtration rate (mGFR) versus multisample mGFR.

at the 180-minute time point, with a P10 of 84.1% (95% CI, 82.3%–85.8%).

DISCUSSION

To our knowledge, this is the only study looking at the suitability of single-sample mGFR equations in African populations. Our results show that the concordance of single-sample mGFR with multisample mGFR is lower than that seen in other populations, where P10 values of >90% are commonly found.[4,7] In general, concordance was shown to be within desirable levels, with most single-sample methods achieving P30 values of >90% in our cohort.

We tested various single-sample mGFR equations. The iterative Jacobsson equation is the most widely used; however, a systemic review found the equation by Fleming to be the preferred choice.[4,7,8] Bias and imprecision were acceptable for the iterative Jacobsson, simplified Jacobsson, and Fleming equations, with the other equations experiencing noticeable heterogeneity among different time points. In keeping with the systemic review, we found that the 180-minute sample using the Fleming equation yielded the highest P30 value of 94.7% (95% CI, 93.9%–95.6%). However, when looking at P10 values and bias, the best performance was noted with the iterative Jacobsson equation at the 240-minute time point. In our population, the iterative Jacobsson equation at 240 minutes would be the equation of choice; however, the simplified Jacobsson equation would be a suitable alternative if earlier sampling at 180 minutes was required or if a simpler equation is preferred.

There was heterogeneity among the 3 different countries, despite identical study protocols and centralized laboratory measurements. This likely reflects genetic diversity among African populations.[S4] Despite this heterogeneity, the pattern of performance, including sample timing, of the various single-sample mGFR equations remained largely consistent.

Similar to previous studies, concordance was best between a GFR of 30 and 120 ml/min per 1.73 m^2.[7] In our population, it would be reasonable to use single-sample mGFR regardless of body mass index, age, or sex (sex as male or female as defined by the presence or absence of a Y chromosome); however, caution should be exercised at extremes of GFR. Adjusting the sample timing according to expected GFR has been shown to improve performance, especially for low GFR samples.[4,9] This, unfortunately, could not be tested with the current data set. High GFR samples (>120 ml/min per 1.73 m^2) also experienced poor performance in our cohort. This unsurprising finding likely reflects inaccuracies of both the reference mGFR and the single-sample equations at high GFR.[S5]

We chose not to exclude any multisample mGFR results with low R^2 (representing the goodness of fit of the multisample mGFR line) as this represents the clinical situation in which single-sample mGFR will be used with no way to calculate an R^2 value with only a single data point. If only multisample mGFR with R^2 >0.95 had been used, performance would have been closer to but still below that seen in other studies and the equation of choice would have been the simplified Jacobsson at 180 minutes.[4,7]

In conclusion, the performance of single-sample mGFR equations in cohorts from Malawi, South Africa, and Uganda differs compared with cohorts in which they were established. Nevertheless, they are suitable for clinical use in patients with GFR between 30 and 120 ml/min per 1.73 m^2. The iterative Jacobsson equation at 240 minutes and the simplified Jacobsson equation at 180 minutes are the most suitable options and show improved performance compared with estimated GFR.

DISCLOSURE

All the authors declared no competing interests.

DATA STATEMENT

This study is a secondary data analysis. The data repository link (https://github.com/ARKconsortium/iohexol_mGFR_eGFR) is that which is provided by the original study by Fabian *et al.*[6] and contains all the deidentified individual participant data.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Table S1. Sample population demographics.

Supplementary Table S2. Absolute bias (ml/min per 1.73 m^2) of different single-sample measured glomerular filtration rate (mGFR) equations compared with multisample mGFR.

Supplementary Table S3. Concordance within 10% of measured glomerular filtration rate (mGFR; P10) of the iterative Jacobsson 240-minute single-sample mGFR over different mGFR ranges.

Supplementary Table S4. Concordance within 10% of measured glomerular filtration rate (mGFR; P10) of the iterative Jacobsson 240-minute single-sample mGFR over different estimated glomerular filtration rate (eGFR) ranges.

Supplementary Table S5. Concordance within 10% of measured glomerular filtration rate (mGFR; P10) of the iterative Jacobsson 240-minute single-sample mGFR over different body mass index (BMI) ranges.

Supplementary Table S6. Concordance within 10% of measured glomerular filtration rate (mGFR; P10) of the iterative Jacobsson 240-minute single-sample mGFR over different age ranges.

Supplementary Table S7. Concordance within 10% of measured glomerular filtration rate (mGFR; P10) of the iterative Jacobsson 240-minute single-sample mGFR over different R^2 ranges.

Supplementary Table S8. Bias, imprecision, and concordance of single-sample measured glomerular filtration rate (mGFR) equations within 30% (P30) and 10% (P10) of multisample mGFR with $R^2 \geq 0.95$.

Supplementary Figure S1. Difference plots for iterative Jacobsson 240-minute single-sample measured glomerular filtration rate (mGFR) versus multisample mGFR.

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