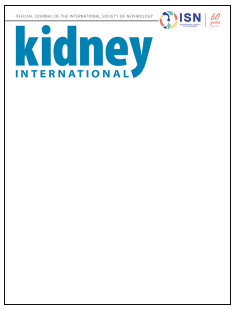

Single-sample measured glomerular filtration rate in Malawi, South Africa, and Uganda

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kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Cohort

2578 community-based participants

Age: 50 yrs (38 – 60)
Female: 59% (57 – 61)
BMI: 24.2 kg/m^2 (21.1 – 28.9)
Hypertension: 36% (34 – 38)
Diabetes: 5.9% (4.9 – 6.8)
HIV +ve: 13% (12 – 15)

Methods

Each participant:

- Multi-sample measured GFR (plasma clearance of iohexol)
- Seven different single-sample mGFR equations
- Estimated GFR (creatinine & cystatin C)

Outcomes

Multi-sample mGFR: 81 mL/min/1.73m^2 (64 – 97)
Single-sample mGFR: 83 mL/min/1.73m^2 (68 – 98)
Estimated GFR (CKD-EPI creatinine): 99 mL/min/1.73m^2 (83 – 111)

Concordance within 30% (P30) and 10% (P10) of multi-sample mGFR:

Single-sample mGFR	**P30 (95% CI)**	**P10 (95% CI)**
Iterative Jacobsson at 240-min	93.5% (92.5 – 94.4)	74.0% (72.3 – 75.6)
Simplified Jacobsson at 180-min	94.1% (93.2 – 95.0)	71.1% (69.3 – 72.8)
Estimated GFR		
eGFR CKD-EPI (Cr) 2021	60.0% (58.1 – 61.9)	23.9% (22.2 – 25.2)
eGFR CKD-EPI (Cr + Cys C) 2021	70.1% (68.3 – 71.9)	30.7% (28.2 – 32.5)

Currin et al, 2024

CONCLUSION:

Single-sample mGFR is suitable for use in patients with a GFR between 30 – 120 mL/min/1.73m^2 in cohorts from South-East Africa

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

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Single-sample mGFR, Africa, South Africa, Malawi, Uganda

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Introduction

Measured glomerular filtration rate (mGFR) is considered the best index of kidney function.[1] Various mGFR methods exist; utilising 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 multi-sample test, between 4 and 6 hours depending on 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 both in 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 Caucasian patients, single-sample mGFR shows concordance with multi-sample techniques especially when the GFR is above 30 ml/min/1.73m^2.[4]

Prior to 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 to multi-sample plasma clearance of iohexol as the reference mGFR.

Methods

Publicly available data from the study by Fabian et al. was analysed.[6] Participants from Malawi, South Africa and Uganda had iohexol administered as an intravenous bolus. The final dataset containing 2578 participants was used to calculate multi-sample mGFR which was considered as the reference to which various single-sample mGFR equations were compared, as plasma clearance of iohexol is not without error, concordance between the two methods was considered instead of accuracy. Full methods are available in the supplementary material.

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 multi-sample mGFR ranged from 83.6% to 94.7% while 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 CKD-EPI estimated GFR (eGFR) 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. While bias was variable among equations all single-sample mGFR equations, except for the Peters at 240-minutes, showed improved precision compared to eGFR. Bias was also variable amongst 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% (72.3 – 75.6%) and bias of -0.05ml/min/1.73m^2 (-0.25 – 0.25ml/min/1.73m^2). The concordance, according to P10, of all the single-sample mGFR equations was best at the 240-minute time point except for the Flemming[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 – 120 ml/min/1.73m^2, with P10 of 80.8% (79.0 – 82.6%), this dropped to 63.1% (58.7 – 67.5%) between 30 - 60 ml/min/1.73m^2. Concordance dropped sharply when mGFR was outside of the 30 - 120 ml/min/1.73m^2 range with P10s of 12.5% (1.0 – 24.0%) and 42.1% (35.1 – 49.1%). Similarly, the best

concordance of single-sample mGFR was seen between the 30 - 120 ml/min/1.73m^2 range of eGFR. (**Supplementary Tables S3 and S4**)

Bias and concordance were consistent across the range of BMI, age, and sex. The differences in concordance among the range of BMI and age were all non-significant. (**Supplementary Tables S5 and S6, Supplementary Figure S1a-S1b**)

Predictably, the concordance of single-sample mGFR to multi-sample mGFR improved incrementally with increasing R^2, from a P10 of 46.7% (36.5 – 56.9%) when R^2 was ≤ 0.8 to 78.0% (76.1 – 80.0%) when R^2 was >0.95, this trend was significant ($P < 0.001$) (**Supplementary Table S7, 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 was best at the 180-minute time point for most equations. The best concordance was seen with the simplified Jacobsson equation at the 180-minute time point with a P10 of 84.1% (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 multi-sample mGFR is lower than that seen in other populations, where P10s of greater than 90% are commonly found.[4,7] In general, concordance was shown to be within desirable levels with most single-sample methods achieving P30s of greater than 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 Flemming to be the preferred choice.[4,7,8] Bias and imprecision were acceptable for the iterative Jacobsson, simplified Jacobsson and Flemming equations, with the other equations suffering from noticeable heterogeneity amongst

different time points. In keeping with the systemic review, we found that the 180-minute sample using the Flemming equation yielded the highest P30 of 94.7% (93.9 – 95.6%). However, when looking at P10s 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 amongst the three different countries, despite identical study protocols and centralised laboratory measurements. This likely reflects genetic diversity amongst 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 – 120 ml/min/1.73m^2.[7] In our population it would be reasonable to use single-sample mGFR regardless of BMI, age, or sex, 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 dataset. High GFR samples (>120 ml/min/1.73m^2) also suffered from poor performance in our cohort. This unsurprising finding likely reflects inaccuracies of both the reference mGFR and single-sample equations at high GFR.[S5]

We chose not to exclude any multi-sample mGFR results with low R^2 (representing the goodness of fit of the multi-sample mGFR line) as this represents the clinical situation in which single-sample mGFR will be used with no way to calculate a R^2 value with only a single data point. If only multi-sample mGFR with R^2 above 0.95 had been utilised 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 differ compared to cohorts in which they were established. Nevertheless, they

are suitable for clinical use in patients with GFR between 30 – 120ml/min/1.73m^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 to eGFR.

Disclosure

All the authors declare no competing interests.

Data sharing 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 de-identified individual participant data.

Supplementary material

Supplementary Methods

Supplementary Tables S1 – S8

Supplementary Figure S1

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Legend

Figure 1: Difference plot for iterative Jacobsson 240-minute single-sample mGFR versus multi-sample mGFR

Table 1: Bias, imprecision and concordance of single-sample mGFR equations within 30% (P30) and 10% (P10) of multi-sample mGFR

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

P30 and P10 values are % (95% confidence interval)
Bias measured as median of the differences between single- and multi-sample mGFR (95% confidence interval)
Imprecision measured as root mean square error (95% confidence interval)