Comparison of creatinine-based glomerular filtration rate estimation equations in voluntary Indian kidney donors: A single centre study

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ABSTRACT

Introduction: In transplantation, accurate estimation of the donor glomerular filtration rate (GFR) is crucial. While various creatinine-based equations are in use, none are validated in Indians.

Objectives: This study was conducted to judge the accuracy of creatinine-based GFR estimation equations and urinary creatinine clearance.

Patients and Methods: A single-centre, observational and retrospective study at a tertiary care hospital. Adult voluntary donors GFR measured (mGFR) by technetium-99m diethylenetriaminepentaacetic acid (Tc-99m DTPA) were included. The primary outcome was the performance of estimated GFR (eGFR) by “Cockcroft-Gault’s formula corrected for body surface area (CG-BSA) formula”, “modification of diet in renal disease (MDRD) 4 and 6 variable equation” and “Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation”; secondary outcome was the performance of “24-hour urinary creatinine clearance (Cr CI)”.

Results: 102 kidney donors were analysed with mean age of 45.89 ± 9.98 years and 85.3% females. Mean ± SD mGFR by Tc-99m DTPA was 82.11 ± 14.32 mL/min/1.73 m². Mean ± SD eGFR by “CG-BSA” was 99.68 ± 23.71 mL/min/1.73 m²; by “MDRD-4 variable equation” was 98.25 ± 28.61 mL/min/1.73 m²; by “MDRD-6 variable equation” was 93.66 ± 19.44 mL/min/1.73 m² and by “MDRD-6 variable equation” was 111.14 ± 31.61 mL/min/1.73 m². The lowest bias (2.3), highest precision (16.23), and accuracy (97.1%) were with “MDRD-6 variable equation”; “24-hour urinary Cr CI” highly overestimated GFR (158.27 mL/min/1.73 m²) with the highest bias, lowest precision, and accuracy.

Conclusion: The “MDRD-6 variable equation” was the most precise and accurate of the equations, whereas “24-hour urinary Cr CI” was the least dependable. This study highlights the need for a correction factor or a new GFR estimation equation and not to consider urinary Cr CI to assess donor GFR.

Implication for health policy/practice/research/medical education:

There are very few studies on Indian kidney donors and in this study among the existing estimated glomerular filtration rate (eGFR) equations, the modification of diet in renal disease (MDRD)-6 variable equation showed the highest precision and accuracy in correlation to measured (mGFR) by technetium-99m diethylenetriaminepentaacetic acid (Tc-99m DTPA) in our population. As per the authors’ knowledge, this is the first study wherein we are comparing the measured GFR by technetium-99m diethylenetriaminepentaacetic acid (Tc-99m DTPA) against all the creatinine-based GFR estimation equations and 24-hour urinary creatinine clearance. This study highlights the fact that for donor evaluation in the Indian population none of the existing GFR estimation equations is accurate and there is a need for a correction factor to existing equations or a newer equation for our population. 24-hour urinary creatinine clearance should not be considered as a donor GFR estimation measure due to its variability and poor reliability.

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Introduction
Kidney failure in India has a prevalence of about 150–230 per million people, out of which around 220,000 people need renal transplants but the actual number of transplants to occur is only about 7500 and approximately 90% of which come from live donors (1).

The best parameter to determine overall kidney function is by glomerular filtration rate (GFR). A precise assessment of GFR and prediction of future risk of kidney failure are the objectives in the evaluation of living kidney donors. GFR can be measured (mGFR) using different methods with Inulin clearance considered the gold standard, however, it is invasive and not easy to conduct in daily clinical practice. Thus radiotracer that are cleared exclusively by glomerular filtration without substantial tubular secretion or reabsorption are chosen. Technetium-99m diethyleneetriaminepentaacetic acid (Tc-99m DTPA) gamma camera (2) method is the most widely used method to measure GFR in kidney donors because of its simplicity and precision (3).

Among the various GFR estimation equations in kidney donors, “chronic kidney disease-epidemiology collaboration (CKD-EPI)” and “modification of diet in renal disease (MDRD)” which include variables such as age, gender, and race validated mostly in the Caucasian population are commonly used in practice to calculate estimated GFR (eGFR). Whenever eGFR is <60 mL/min/1.73 m² both are comparable but “CKD-EPI” is preferable at higher eGFR values (4).

While several eGFR equations using serum creatinine exist, none of them have proven to provide accurate results in Indian kidney donors, thus extrapolating these equations for Indians likely to yield inaccurate results which are validated by a recent Indian study by Kumar et al (4) which showed that the GFR estimation equations currently in practice overestimates GFR in Indians and hence the latest equation or correction factor for precise assessment is essential in our population (5).

Objectives
This study was conducted to assess the accuracy and reliability of creatinine-based GFR estimation equations for donor evaluation in comparison to mGFR by DTPA which is the most frequently used method in transplant centres across India.

Patients and Methods
Study design
This single-centre retrospective study was conducted from January 2015 to December 2019 after obtaining institutional ethics committee clearance.

Inclusion criteria; All adult voluntary kidney donors of either gender who were advised GFR measurement by Tc-99m DTPA as a part of donor evaluation were included after informed consent.

All donors had serum creatinine measured using kinetic compensated Jaffe assay traceable to isotope dilution mass spectrometry (IDMS traceable) in the Cobas 8000 analyser (Roche Diagnostics GmbH Mannheim, Germany) at our laboratory.

For mGFR by Tc-99m DTPA, donors were given bolus intravenous injection of Tc-99m-labeled DTPA, and scintigraphy images were taken by the Gamma camera (2 minutes per frame for 30 minutes each). A region of interest (ROI) was manually drawn for each kidney, background ROI was assigned, uptake by each kidney was assessed, and GFR was automatically calculated by Infinia Hawkeye software GE (3).

The primary outcome was the performance of creatinine-based eGFR by various equations (Table 1)

| Equations               | Formulae                                                                 |
|-------------------------|---------------------------------------------------------------------------|
| “Cockcroft and Gault’s formula (CG)” | (140-Age) × lean body weight (kg) × 0.85 (females) × Serum creatinine (mg/dL) × 72 |
| Correction of CG for BSA (“CG-BSA”) | CG Cr Cl × 1.73 / BSA                                                      |
| “MDRD-4 variable”        | 175 × [serum creatinine (mg/dL)] × [age]-1.154 × [0.742 if female] × 0.822 if patient is female | 0.742 if female |
| “MDRD-6 variable”        | 198 × [serum creatinine (mg/dL)] × [age]-0.329 × [urine urea nitrogen excretion (g/d)] × 0.249 |
| “CKD-EPI”                | GFR = 141 × min (Scr/κ, 1) × 0.85 × max (Scr/κ, 1)^-0.203 × 0.99345 × Scr/κ, 1)^-0.293 |
| “24-hour urinary Cr Cl”  | Urine creatinine (mg/dL) × Total urine volume (mL) / Serum creatinine (mg/dL) × 1440 |
| “24 hour urinary Cr Cl” normalised to BSA | Cr Cl × 1.73 / BSA |

BSA, body surface area; Cr Cl, creatinine clearance; CG-BSA, Cockcroft-Gault’s formula corrected for body surface area; MDRD, modification of diet in renal disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.
"Cockcroft and Gault’s corrected for body surface area (CG-BSA)”, MDRD 4 variable and 6 variable equations”, CKD-EPI] in comparison to mGFR using DTPA and secondary outcome was the reliability of 24-hour urinary creatinine clearance in comparison to mGFR.

**Statistical analysis**

The mean ± standard deviation (SD) of different variables was calculated and the differences were expressed in absolute values with confidence limits of 95%. In terms of their bias, precision, and accuracy, the efficiency of different prediction equations was evaluated. The mean difference between mGFR and each eGFR equation was termed as total bias; the mean percentage difference to mGFR was defined as relative bias. Total precision was defined as standard deviation (SD) of total bias and relative precision as SD of relative bias. Proportion (%) of patients with eGFR within 15% and 30% of the mGFR was termed accuracy. Statistical Package for the Social Sciences (SPSS) version 20.0 was conducted for data analysis.

**Results**

A total of 102 voluntary kidney donors included during the study period were analysed in this study. The majority were females 87 (85.3%) and the mean age was 45.89 ± 9.98 years. The mGFR by Tc-99m DTPA was 82.11 ± 14.32 mL/min/1.73 m².

**Primary outcome**

The performance of eGFR equations in the donor group in terms of bias, precision, and accuracy was estimated compared to mGFR.

Table 2 shows the correlation of mGFR by DTPA with other GFR predicting equations. Mean eGFR±SD calculated by CG-BSA (6) was 99.68 ± 23.71 mL/min/1.73 m², by “MDRD-4 variable equation” (7) was 98.25 ± 28.61 mL/min/1.73 m², by “MDRD-6 variable equation” (8) was 93.66 ± 19.44 mL/min/1.73 m², and by “CKD-EPI” equation (9) was 111.14 ± 31.61 mL/min/1.73 m².

Total bias (defined as a mean difference to measured GFR) among the equations was least with “MDRD-6 variable equation” (2.3), followed by “MDRD-4 variable equation” (6.89), “CG-BSA” (8.26), and highest with “CKD-EPI” (19.8).

The highest precision (defined as SD to bias) amongst equations was with “MDRD-6 variable equation” (16.23), followed by “MDRD-4 variable equation” (24.32), “CKD-EPI” (28.96), and least with “CG-BSA” equation (34.3).

In our study, the “MDRD-6 variable equation” (97.1%) had the highest accuracy followed by the “MDRD-4 variable equation” (91.2%), “CKD-EPI” (90.2%), and the least with the “CG-BSA” equation (86.3%).

**Secondary outcome**

The predictive capability of 24-hour urinary creatinine clearance in the donor group when compared to mGFR was analysed. In this study, 24-hour urinary creatinine clearance highly overestimated GFR (158.27 mL/min/1.73 m²) in comparison to mGFR by DTPA. It also showed the highest total bias (66.98), relative bias (0.13), lowest precision (94.92), and lowest accuracy (55.9%) when compared to eGFR estimation equations.

**Discussion**

The calculation of GFR is indeed a challenging task since several equations and methods have been developed and yet not one method correlates exactly with the other. As GFR is a valuable indicator in the evaluation of kidney donors there ought to be an effective and reproducible method for estimation in our population. Most of the creatinine-based GFR equations to estimate GFR have been derived based on studies on the western population who have a higher GFR when compared to the Indian population who typically have lower GFR values (5). Thus the primary objective of this research was to estimate GFR using different creatinine-based equations and compare it with measured GFR by DTPA.

In this study among the 102 voluntary kidney donors, the majority were females (85.3%) which is similar to the recent study by Sawinski et al (10) and Sakuja et al (11) in India, both of which portrayed that in the spectrum of living renal donor females were a majority.

### Table 2. Comparison of bias, precision and accuracy of estimation equations with measured GFR (DTPA-mean: 82.11 ± 14.32 mL/min/1.73 m²)

| eGFR equations | Total Bias | Relative Bias | Relative Precision | Accuracy |
|----------------|------------|---------------|--------------------|----------|
| CG-BSA         | -8.26      | -0.10         | 34.40              | 80.40%   | 86.30% |
| MDRD-4 variable | -6.89      | 0.04          | 24.32              | 89.20%   | 91.20% |
| MDRD-6 variable | -2.30      | 0.007         | 16.23              | 87.30%   | 97.10% |
| CKD-EPI        | -19.80     | -0.05         | 28.96              | 80.40%   | 90.20% |
| 24 hour urinary Cr Cl | -66.98 | -0.13         | 94.92              | 53.90%   | 55.90% |

eGFR, estimated GFR; CG-BSA, Cockcroft-Gault’s formula corrected for body surface area; MDRD, modification of diet in renal disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; Cr Cl, creatinine clearance; IQR, Interquartile range.

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In our study, the mean age of kidney donors was 45.89 ± 9.98 years which is similar to the study by Zhao et al (12) where 224 donors were evaluated with an average age of 45.1 ± 8.6 years and the Indian study by Prasad et al (13) wherein 897 donors were analysed with the median age of 44.81 years.

The mean ± SD GFR measured by Tc-99m DTPA was 82.11 ± 14.32 mL/min/1.73m² which is substantially lower in comparison to western literature (106-125 mL/min/1.73 m²), however, is similar to Indian study by Kumar et al (3) where analysis of 66 voluntary kidney donors showed an average mean measured GFR of 83.3 mL/min/1.73 m². The reason for a lower GFR in the Indian population is postulated due to two possible explanations, first lower animal protein consumption given the cultural and religious beliefs; a second explanation for lower GFR observed in Indians is the low-nephron number at birth associated with low birth weight (14).

In this study, we analysed the extent of bias, precision, accuracy of these GFR prediction equations and ranked them according to their performance. Our results showed that every single equation overestimated the GFR when compared to mGFR by DTPA.

The eGFR by “CG-BSA” in this study was 99.68 ± 23.71 mL/min/1.73 m² with a total bias of 8.26 and an accuracy of 86.3% (within 30%). The estimation of GFR by CG equation was understandably poorer because the equation was derived by creatinine clearance calculated from 24-hour urinary creatinine collections in healthy hospitalised adults (the majority were males), and also it overestimates GFR due to associated tubular creatinine excretion which is similar to Indian studies by Kumar et al (3) and Hephzibah et al (15).

Levey et al (7, 8) proposed “MDRD 4 and 6 variable equations” from a study involving the majority of Caucasian patients with CKD and excluded those with GFR >60 mL/min/1.73 m², thus it underestimates in patients with higher levels of GFR. Because of this inaccuracy at higher levels of GFR, it fares well only in those with GFR <60 mL/min/1.73 m² (8). In our study, the estimated GFR by “MDRD-4 variable equation” was 98.25 ± 28.61 mL/min/1.73 m² and by “MDRD-6 variable equation” was 93.66 ± 19.44 mL/min/1.73 m² with accuracy being highest for “MDRD-6 variable equation” (97.1%) followed by “MDRD-4 variable equation” (82.70%). Therefore, the “MDRD-6 variable equation” fared best in this study followed by the “MDRD-4 variable equation” which is similar to the study by Pöge et al (16) and also an Indian study on 173 kidney donors conducted by Mahajan et al (17). The possible explanation for the better performance of the “MDRD-6 variable equation” over other equations is the incorporation of urinary urea nitrogen in GFR estimation which overall improves the predictive ability. It is therefore tempting to assume that underestimation of urinary urea nitrogen can neutralise this creatinine dependant GFR overestimation.

To overcome the drawbacks of the “MDRD equation”, the “CKD-EPI” equation was developed which is as accurate as “MDRD equations” at GFR <60 mL/min/1.73 m² and is more accurate at higher GFR levels. It was derived using two slopes with multicentre samples involving the majority of patients with CKD and a small percentage without CKD (9). “CKD-EPI” formula eGFR was 111.14 ± 31.61 mL/min/1.73 m² with 90.2% accuracy in this study. Thus, compared to the MDRD equation, it did not do well in terms of accuracy and precision in our study which is similar to the study by Carter et al (18) in the United Kingdom (UK) wherein they assessed the predictive capability of “MDRD” and “CKD-EPI” formulae in a sizeable adult population which showed that “CKD-EPI” overestimated GFR in 18-59 years’ age group. This overestimation, lesser precision, and accuracy of the “CKD-EPI” equation has also been observed in the Chinese study by Ji et al (19) and also in the Japanese study by Horio et al (20) wherein they have suggested the requirement of correction coefficients which were derived from multiple linear regression models with variables involving age, gender, serum urea nitrogen, and serum albumin. Recently an Indian study by Kumar et al (4) also concluded that most of the GFR estimation equations overestimate GFR in our population, hence recommending the need for a correction coefficient.

Previously, “24-hour urine creatinine clearance (Cr Cl)” calculated by multiplying the urine creatinine to serum creatinine ratio by 24-hour urine volume was widely utilised for GFR measurement. However, the use of urinary Cr Cl for GFR estimation is obsolete for the last two decades as one of the earliest studies by Greenblatt et al (21), revealed that creatinine excretion differed significantly in healthy individuals leading to erratic GFR estimation since urinary creatinine clearance was related to timing and accuracy of collection, body surface area, dietary pattern and physical activity which is similar to this study where “24-hour urinary Cr Cl” grossly overestimated GFR and showed the highest total and relative bias, lowest precision, and accuracy when compared to all creatinine-based eGFR formulae (21).

**Conclusion**

In this study among the existing eGFR equations, the “MDRD-6 variable equation” showed the highest precision and accuracy in correlation to mGFR by DTPA in our population. “24-hour urinary creatinine clearance” should not be considered as a donor GFR estimation measure due to its variability and poor reliability. Thus this study highlights the fact that for donor evaluation in the Indian population none of the existing GFR estimation equations is accurate and there is a need for a correction factor to existing equations or a newer equation for our population.
Limitations of the study
The small sample size and retrospective nature of the study was the limitation of our study and serum cystatin-c was not measured.

Authors’ contribution
SPN, KS, MVB, and SVS were the principal investigators of the study. SPN, KS, MVB, SVS, VNK, and MNN were included in preparing the concept and design. IRR, RAP, DR, VG, VNK, and MNN revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript, and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest
The authors declare that they have no competing interests.

Ethical issues
The research followed the tenets of the Declaration of Helsinki. The institutional ethical committee at Kasturba Medical College, Manipal (Manipal Academy of Higher Education) approved all study protocols (IEC 943-2020). Accordingly, written informed consent was taken from all participants before any intervention.

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