# Discordance Between Using Estimated and Measured Glomerular Filtration Rate for Drug Dosing in Kidney Transplant Recipients

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**Introduction.** Estimating glomerular filtration rate (eGFR) using different formulas is common clinical practice for evaluating kidney function and drug dosing. But, the performance of available eGFR equations is questionable during early days after kidney transplantation.

**Methods.** This study compared the performance of three common eGFR equations (Cockcroft-Gault (CG), Modification of Diet in Renal Disease (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)) in relation with measured GFR (mGFR) using clearance of Tc-99m-diethylenetriaminepentaacetic acid, 7 to 10 days post kidney transplantation. Agreement of mGFR and different eGFR equations in the staging of kidney function and dosing of 8 common antimicrobials were assessed.

**Result.** Thirty kidney and 5 simultaneous pancreas-kidney transplant recipients were included. CG applying total body weight ($CG_{TBW}$) had the lowest bias (-12 mL/min/ 1.73 $m^2$) and the highest percentage of estimation within 30% of mGFR (71.4%). MDRD showed the best precision (13.14 mL/min/ 1.73$m^2$) and linear correlation with mGFR. CKD-EPI and MDRD acted better than CG for staging the level of kidney function. $CG_{TBW}$ had the lowest discordance rate with mGFR for antimicrobials dosing (33.6%). Discordance rates of drug dosing between mGFR and eGFR formulas were greater for drugs that have higher dosing levels such as (val)-ganciclovir ($\geq$ 54.3%).

**Conclusion.** Until developing more accurate methods for estimating kidney function during first 1 to 2 weeks after kidney transplantation, $CG_{TBW}$ method is suggested for drug dose adjustment and MDRD or CKD-EPI equation for the staging of kidney function in these patients, keeping in mind that these formulas underestimate the level of kidney function in new transplant recipients.

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## INTRODUCTION

Kidneys play important roles in the body and their dysfunction causes many complications necessitating regular assessment of kidney function.[1] Glomerular filtration rate (GFR) is an acceptable parameter for assessment of kidney function. For this evaluation, measurement of exogenous agents clearance (*e.g.* inulin, iohexol,

iothalamate) is the most accurate method but it is not applicable in routine clinical practice; because of this, estimating GFR with some equations that use endogenous markers has been substituted.[2] Nowadays Cockcroft-Gault (CG),[3] Modification of Diet in Renal Disease (MDRD),[4] and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)[5] are the most common equations for estimating GFR[2] (Table 1).

In kidney transplant recipients, estimation of GFR with these available equations is the matter of debate, since serum creatinine (SCr) concentration is in a non-steady state especially during early post-transplant days. In addition, several interfering factors such as high dose corticosteroid administration during the first days after transplantation and starting prophylactic antimicrobials such as trimethoprim-sulfamethoxazole alter SCr concentration in these patients.[6] Significant disagreements have been reported between the performance of different SCr-based estimated GFR (eGFR) equations at different times in the first post-transplant year.[7] At the moment, 4 variables MDRD and CKD-EPI seem to be the best SCr-based equations[8] in kidney transplant recipients. Due to immunosuppressions used for the prevention of organ rejection, antimicrobials are used extensively after transplantation for prophylaxis and treatment of infections;[9,10] most of these medications need renal dose adjustment.[11] Our purpose was to compare three popular eGFR equations (CG, MDRD, and CKD-EPI) with the gold standard measured GFR (mGFR) and investigating bias, precision, and accuracy of them in kidney transplant recipients. In addition, agreements of mGFR and eGFR equations in staging kidney function and dosing of common antimicrobials in kidney transplant recipients were evaluated.

## MATERIALS AND METHODS

### Study Design and Participants

This prospective study was conducted on kidney transplant recipients at days 7 to 10 after transplantation surgery. The study was performed in Imam Khomeini Hospital Complex (IKHC) from September 2018 through February 2020. Study participants were included if they aged 18 years or older, with stable SCr for 48 to 72 hours, and consented to participate in the study. Exclusion criteria included the occurrence of delayed graft function or acute allograft rejection in the first post-transplant week and receiving medications that interfere with the laboratory method of SCr measurement (*e.g.* cefazolin, ceftizoxime, and methyldopa) or medications that inhibit tubular secretion of creatinine (*e.g.* cimetidine) except for trimethoprim (because all new transplant recipients take trimethoprim-sulfamethoxazole for prophylaxis of *pneumocystis jiroveci* pneumonia during the first post-transplant year in this center). Pregnant and nursing women were also excluded. The study protocol was approved by the local ethical committee (IR.NIMAD.REC.1397.203). The immunosuppressive regimen consisted of anti-thymocyte globulin induction followed by oral prednisolone, tacrolimus, and mycophenolate mofetil/sodium as maintenance immunosuppressive regimen. Relevant clinical and laboratory data of kidney recipients and donors were gathered from medical records. Discordance between mGFR and different eGFR formulas in the staging of kidney function was assessed according to the staging system recommended by Kidney Disease Improving Global Outcomes (KDIGO).[12] Also, the discordance between mGFR and eGFR equations in the dosing of 8 commonly used antimicrobial medications (including ampicillin-sulbactam, fluconazole,

**Table 1.** Three Equations for Estimating GFR

| Equation | Formula |
|---|---|
| Cockcroft–Gault (CG)<br>CrCL (mL/min) | [ (140 – age (years)) × weight (kg) × 0.85 (if female)] / [72 × SCr (mg/dL)] |
| Modification of Diet in Renal Disease (MDRD 4-variable)<br>GFR (mL/min/ 1.73 $m^2$) | 186 × SCr (mg/dL)$^{-1.154}$ × age (years)$^{-0.203}$ × 1.212 (if African-American) × 0.742 (if female) |
| Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)<br>GFR (mL/min/ 1.73 $m^2$) | 141 × min [SCr (mg/dL)/k,1]$^{\alpha}$ × max [SCr (mg/dL)/k, 1]$^{-1.209}$ × 0.993$^{Age}$ × 1.018 (if female) × 1.159 (if black)<br>k is 0.7 for females and 0.9 for males,<br>α is -0.329 for females and -0.411 for males,<br>min indicates the minimum of SCr/k or 1,<br>and max indicates the maximum of SCr/k or 1. |

Abbreviations: CrCL, creatinine clearance; GFR, glomerular filtration rate; SCr, serum creatinine concentration.

ganciclovir, meropenem, piperacillin-tazobactam, trimethoprim-sulfamethoxazole, valganciclovir, and vancomycin) was evaluated according to dosing recommendations based on the Lexicomp database.[13] Antimicrobial dose modifications using mGFR and different eGFR formulas were simulated and no intervention was performed on patients' drug ordering. Patients' drugs were dosed by the responsible physician.

### GFR Measurement

Clearance of Tc-99m-diethylenetriaminepenta-acetic acid (Tc-99m-DTPA) was measured by dual plasma sampling as the gold standard method for mGFR in the nuclear medicine ward of IKHC. Blood samples were drawn at 60 and 180 minutes after 3 mCi of Tc-99m-DTPA injection. After centrifuging, plasma radioactivity was counted and GFR was calculated by Russell two-sample method formula.[14] mGFR was standardized to body surface area (BSA) of 1.73 $m^2$.

### GFR Estimation Methods

SCr measurement was performed by the Jaffe method. Estimation of GFR using SCr-based equations was done using CG, 4-variable MDRD, and CKD-EPI (Table 1). CG was calculated using both ideal body weight (IBW) and total body weight (TBW) of patients. CG equation results were standardized to BSA of 1.73 $m^2$.

### Statistical Analysis

Quantitative and qualitative variables are presented as mean ± standard deviation (SD) and number (percent), respectively. The Bland-Altman analysis was performed for detecting mGFR and eGFR equation difference. Mean of differences was calculated as bias and the SD of differences as precision. The level of agreement between mGFR and each eGFR methods was calculated by ± 1.96 × SD of differences. Percentages of estimation within 30% of the measured GFR (P30) were calculated as the accuracy of equations. Pearson correlation coefficient was used to investigate the linear relationship between mGFR and eGFR formulas. Gwet's[15] coefficient was calculated to evaluate the agreement of mGFR and each eGFR formulas in kidney function staging and drug dose adjustment. Paired t-test was used to compare the mean of mGFR with that of each eGFR equations. The analysis was performed using SPSS Statistics (version 26) and AgreeStat cloud-based available at AgreeStat360.com.

## RESULTS

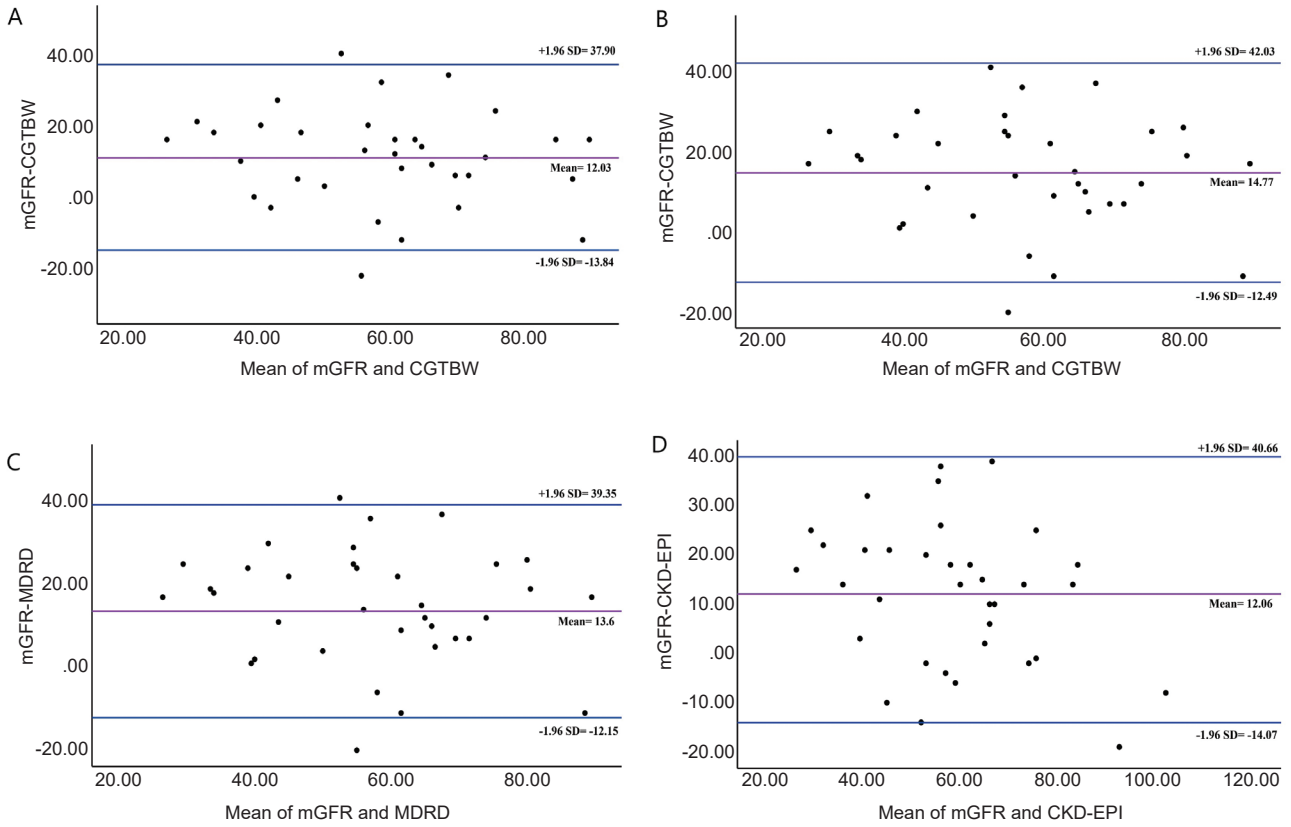
A total of 35 patients including 30 kidney transplant recipients and 5 simultaneous pancreas-kidney transplant recipients participated in this study. Twenty-two (62.9%) of them were male and the mean age of the patients was 45.8 ± 15.6 years old. All of the transplanted organs were from deceased donors. Diabetes mellitus and hypertension were the most common comorbidities of recipients. The mean mGFR of recipients was 64.7 ± 16.7 ml/min/1.73 $m^2$. Demographic and clinical data of transplant recipients are shown in Table 2.

Bland-Altman plots of mGFR versus eGFR equations have been shown in Figure. CG applying total body weight ($CG_{TBW}$) had the least bias (-12 mL/min/1.73 $m^2$), and highest P30 accuracy (71.4%). Furthermore, the MDRD formula showed the best precision (13.14 mL/min/1.73 $m^2$, Table 3). Limits of agreement with mGFR were as follows: $CG_{TBW}$ (-13.8 to 39.7 mL/min/1.73 $m^2$), CG applying ideal body weight ($CG_{IBW}$) (-12.5 to 42.0 mL/min/1.73 $m^2$), MDRD (-12.1 to 39.3 mL/min/1.73 $m^2$), and CKD-EPI (-14.1 to 40.7 mL/min/1.73 $m^2$) (Figure). We found that the means of all eGFR equations had significant differences with mGFR using paired t-test (for all comparisons $P < .001$) (Table 3).

**Table 2.** Demographic and Clinical Data of Kidney Transplant Recipients

| | n (%) |
|---|---|
| Gender | |
| Male | 22 (62.9) |
| Female | 13 (37.1) |
| ESRD Reason | |
| DM | 11 (31.4) |
| HTN | 9 (25.7) |
| ADPKD | 5 (14.3) |
| Others | 10 (28.6) |
| | **Mean ± SD** |
| Age, y | 45.8 ± 15.6 |
| Weight, kg | 61.2 ± 11 |
| BMI, $kg/m^2$ | 22.2 ± 2.3 |
| BSA, $m^2$ | 1.68 ± 0.17 |
| SCr, mg/dL* | 1.6 ± 0.7 |

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; BSA, body surface area; DM, diabetes mellitus; ESRD, end-stage renal disease; HTN, hypertension; SCr, serum creatinine; SD, standard deviation.
*Serum Creatinine on Day of Measurement of GFR




A-D Bland–Altman Plots Depict the Difference Between mGFR and eGFR Equations (A-D).
Abbreviations: $CG_{TBW}$, cockcroft-gault applying total body weight; $CG_{IBW}$, cockcroft-gault applying ideal body weight; CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated GFR; GFR, glomerular filtration rate; MDRD, modification of diet in renal disease; mGFR, measured GFR.

**Table 3.** Comparison of mGFR with eGFR Equations in Kidney Transplant Recipients

| | | | Paired Difference | | | |
|---|---|---|---|---|---|---|
| | **Mean ± SD** | **$r_p$** | **Mean Difference[a] ± SD[b]** | ***P*[c]** | **SMD** | **Accuracy of P30[d]** |
| mGFR | 64.74 ± 16.72 | | | | | |
| $CG_{TBW}$ | 52.71 ± 18.47 | 0.72 | 12.03 ± 13.20 | < .001 | 0.91 | 71.4 |
| $CG_{IBW}$ | 49.97 ± 18.47 | 0.69 | 14.77 ± 13.91 | < .001 | 1.06 | 57.1 |
| MDRD | 51.14 ± 19.10 | 0.74 | 13.60 ± 13.14 | < .001 | 1.04 | 65.7 |
| CKD-EPI | 52.69 ± 20.99 | 0.72 | 12.05 ± 14.59 | < .001 | 0.83 | 62.9 |

Abbreviations: $CG_{IBW}$, cockcroft-gault applying ideal body weight; $CG_{TBW}$, cockcroft-gault applying total body weight; CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated GFR; GFR, glomerular filtration rate; MDRD, modification of diet in renal disease; mGFR, measured GFR; $r_p$, pearson correlation coefficient; SD, standard deviation; SMD, standardized mean difference.
[a]Bias, [b]Precision, [c]paired sample t-test, [d]percentage of estimates within 30% of the measured GFR

Pearson's correlation test showed strong correlation between mGFR and all eGFR formulas (Table 3). Moreover, there were strong correlations between CG and MDRD (r = 0.93), CG and CKD-EPI (r = 0.95), and MDRD and CKD-EPI (r = 0.99) methods (All $P < .001$).

Overall, there were substantial agreements between mGFR and eGFR equations regarding the staging of kidney function. CKD-EPI and MDRD had the best agreement with mGFR in staging the level of kidney function (Gwet's coefficient = 0.76) (Table 4). Additionally, agreement analysis was done to investigate discrepancies in dosing of 8 antimicrobials between mGFR and eGFR equations. $CG_{TBW}$ showed the best agreement with mGFR in dosing of fluconazole, ganciclovir, meropenem, piperacillin-tazobactam, valganciclovir, and vancomycin. The agreement of $CG_{TBW}$ with mGFR was the same as those for MDRD and CKD-EPI in dosing of ampicillin-sulbactam and trimethoprim-

**Table 4.** Agreement Between mGFR and eGFR Equations in the Staging of the Kidney Function

| Kidney Function Category | mGFR n (%) | | | | | Overall Agreement (Gwet's Coefficient) | Discordance (%) |
|---|---|---|---|---|---|---|---|
| | G1 | G2 | G3 | G4 | G5 | | |
| $CG_{TBW}$ | | | | | | | |
| G1 | | 1 (2.9) | | | | 0.73 | 60 |
| G2 | 3 (8.6) | 7 (20) | 3 (8.6) | | | | |
| G3 | | 10 (28.6) | 7 (20) | | | | |
| G4 | | | 4 (11.4) | | | | |
| G5 | | | | | | | |
| $CG_{IBW}$ | | | | | | | |
| G1 | | 1 (2.9) | | | | 0.68 | 68.6 |
| G2 | 3 (8.6) | 6 (17.1) | 3 (8.6) | | | | |
| G3 | | 11 (31.4) | 5 (14.3) | | | | |
| G4 | | | 6 (17.1) | | | | |
| G5 | | | | | | | |
| MDRD | | | | | | | |
| G1 | 1 (2.9) | 1 (2.9) | | | | 0.76 | 51.4 |
| G2 | 2 (5.7) | 6 (17.1) | | | | | |
| G3 | | 11 (31.4) | 10 (28.6) | | | | |
| G4 | | | 4 (11.4) | | | | |
| G5 | | | | | | | |
| CKD-EPI | | | | | | | |
| G1 | 1 (2.9) | 1 (2.9) | | | | 0.76 | 51.4 |
| G2 | 2 (5.7) | 8 (22.9) | 1 (2.9) | | | | |
| G3 | | 9 (25.7) | 8 (22.9) | | | | |
| G4 | | | 5 (14.3) | | | | |
| G5 | | | | | | | |

Abbreviations: $CG_{IBW}$, cockcroft-gault applying ideal body weight; $CG_{TBW}$, cockcroft-gault applying total body weight; CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated GFR; GFR, glomerular filtration rate; mGFR, measured GFR; MDRD, modification of Diet in Renal Disease.
Notes. CKD categories: G1: ≥ 90 mL/min/ 1.73 $m^2$, G2: 60 to 89 mL/min/ 1.73 $m^2$, G3: 30 to 59 mL/min/ 1.73 $m^2$, G4: 15 to 29 mL/min/ 1.73 $m^2$, G5: < 15 mL/min/ 1.73 $m^2$.

sulfamethoxazole (Gwet's coefficient = 0.94) (Table 5). In all of the agreement analysis, $CG_{TBW}$ acted better than $CG_{IBW}$ for drug dosing when compared with the gold standard (mGFR). Generally, underdosing occurred more common than overdosing (92.3 versus 7.7%) when mGFR compared with different eGFR equations.

Lowest discordance rates between mGFR and eGFR in dosing of antimicrobials were seen for ampicillin-sulbactam and trimethoprim-sulfamethoxazole (11.4%). The highest discordance rates between mGFR and eGFR methods happened for ganciclovir and valganciclovir dosing and in the best way, discordance rate of 54.3% was seen between mGFR and $CG_{TBW}$. Overall in drug dose adjustment, $CG_{TBW}$ with an agreement rate of 66.4% with mGFR was the best eGFR equation followed by CKD-EPI with 63.9% agreement with mGFR (Table 5). There were significant differences in drug dosing determined by mGFR in comparison with those calculated by eGFR equations. Standardized mean difference (SMD) showed that these differences in dosing were not negligible (Table 6).

## DISCUSSION

According to the Kidney Disease Outcomes Quality Initiative (K/DOQI) recommendation, to evaluate the performance of an eGFR equation, bias, precision, and accuracy should be assessed.[16] We found that $CG_{TBW}$ and CKD-EPI had the lowest bias compared with mGFR; Besides, MDRD showed the best precision followed by $CG_{TBW}$. $CG_{TBW}$ had the best P30 accuracy followed by MDRD. Similar to our study, among different eGFR formulas, CG showed the lowest bias in Kamaruzaman *et al.* study on kidney transplant patients over 1-year post-transplantation.[17] The study by Salvador *et al.* 10 weeks after kidney transplantation showed that MDRD had the lowest bias and highest

**Table 5.** Agreement of mGFR and eGFR Equations in Renal Dose Adjustment of Antimicrobials in Kidney Transplant Recipients

| | CGTBW | CGIBW | MDRD | CKD-EPI |
|---|---|---|---|---|
| Ampicillin-Sulbactam | | | | |
| Discordance (%) | 11.4 | 14.3 | 11.4 | 11.4 |
| Gwet's Coefficient | 0.94 | 0.92 | 0.94 | 0.94 |
| Fluconazole | | | | |
| Discordance (%) | 31.4 | 37.1 | 40 | 34.3 |
| Gwet's Coefficient | 0.42 | 0.29 | 0.23 | 0.36 |
| Ganciclovir | | | | |
| Discordance (%) | 54.3 | 62.9 | 68.6 | 54.3 |
| Gwet's Coefficient | 0.66 | 0.62 | 0.57 | 0.64 |
| Meropenem | | | | |
| Discordance (%) | 42.9 | 45.7 | 45.7 | 42.9 |
| Gwet's Coefficient | 0.76 | 0.74 | 0.73 | 0.75 |
| Piperacillin-Tazobactam | | | | |
| Discordance (%) | 22.9 | 31.4 | 28.6 | 34.3 |
| Gwet's Coefficient | 0.90 | 0.84 | 0.87 | 0.83 |
| Trimethoprim-Sulfamethoxazole | | | | |
| Discordance (%) | 11.4 | 17.1 | 11.4 | 11.4 |
| Gwet's Coefficient | 0.94 | 0.90 | 0.94 | 0.94 |
| Valganciclovir | | | | |
| Discordance (%) | 54.3 | 68.8 | 60 | 62.9 |
| Gwet's Coefficient | 0.71 | 0.62 | 0.65 | 0.63 |
| Vancomycin | | | | |
| Discordance (%) | 37.1 | 45.7 | 37.1 | 40 |
| Gwet's Coefficient | 0.80 | 0.75 | 0.79 | 0.78 |
| Overall Discordance (%) | 33.6 | 40.4 | 38.2 | 36.1 |

Abbreviations: $CG_{IBW,}$ cockcroft-gault applying ideal body weight; $CG_{TBW,}$ cockcroft-gault applying total body weight; CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated GFR; GFR, glomerular filtration rate; mGFR, measured GFR; MDRD, modification of diet in renal disease.

accuracy.[18] Also, some other studies revealed that bias, precision, and accuracy of MDRD was better than CKD-EPI in kidney transplant recipients.[8,19] Another study concluded that CKD-EPI was not superior to MDRD in estimating GFR in kidney transplant patients.[20] Results of one study on simultaneous pancreas-kidney transplant recipients, one year after transplant, showed that CKD-EPI and MDRD equations had low performance for GFR estimation in this population.[21] A review on the performance of creatinine-based eGFR equations in solid organ transplant recipients concluded that CKD-EPI and MDRD had the lowest bias and were more accurate than other equations in estimation of GFR in kidney transplant recipients.[22] In several studies, eGFR equations overestimated GFR in kidney transplant recipients,[23-27] however in our study underestimation of kidney function by eGFR equations found evident which was compatible with the findings of White *et al.* studies.[28,29] This underestimation may be due to the evaluation of the patients in the early weeks after transplantation during which the kidney recipients were taking high doses of corticosteroid which have direct catabolic action and can overproduce creatinine.[30]

Our results showed that the accuracy of $CG_{IBW}$ was 14.3% lower than $CG_{TBW}$; therefore, using ideal body weight to calculate creatinine clearance with CG equation in kidney transplant recipients may cause more inaccuracy, and using TBW is recommended.

Good correlations between mGFR and eGFR equations were found in our study, and MDRD had the best correlation but all of the correlation coefficients were lower than 0.9 that is the cut-off for a strong relationship. These findings were similar to Luis-Lima's study on kidney transplant patients after at least 6 months of transplantation.[31] These rates of correlations do not let us trust above-mentioned eGFR methods in clinical practice.[32]

Regarding kidney function staging, the discordance rate of mGFR with CKD-EPI and MDRD was better than CG, but for all equations, discordance rates were more than 50%, which

**Table 6.** Difference of Antimicrobials Daily Dose Between mGFR and eGFR Equations in Kidney Transplant Recipients

| | mGFR | CGTBW | CGIBW | MDRD | CKD-EPI |
|---|---|---|---|---|---|
| Ampicillin-Sulbactam | | | | | |
| Dose, mg/d* | 6000 ± 0 | 5657 ± 968 | 5571 ± 1065 | 5657 ± 968 | 5657 ± 968 |
| Difference, mg/d | | 343 ± 968 | 429 ± 1065 | 343 ± 968 | 343 ± 968 |
| SMD | | 0.35 | 0.40 | 0.35 | 0.35 |
| Fluconazole | | | | | |
| Dose, mg/d | 354 ± 82 | 303 ± 101 | 291 ± 101 | 286 ± 100 | 297 ± 101 |
| Difference, mg/d | | 51 ± 101 | 63 ± 105 | 66 ± 108 | 57 ± 104 |
| SMD | | 0.51 | 0.59 | 0.64 | 0.55 |
| Ganciclovir | | | | | |
| Dose, mg/d | 190 ± 95 | 135 ± 80 | 116 ± 53 | 111 ± 55 | 121 ± 62 |
| Difference, mg/d | | 55 ± 94 | 74 ± 84 | 79 ± 84 | 69 ± 87 |
| mGFR | | 0.58 | 0.88 | 0.94 | 0.80 |
| Meropenem | | | | | |
| Dose, mg/d | 2743 ± 433 | 2371 ± 646 | 2343 ± 639 | 2371 ± 690 | 2400 ± 695 |
| Difference, mg/d | | 371 ± 547 | 400 ± 553 | 371 ± 646 | 342 ± 639 |
| SMD | | 0.68 | 0.72 | 0.58 | 0.54 |
| Piperacillin-Tazobactam | | | | | |
| Dose, mg/d | 13114 ± 1278 | 12150 ± 2246 | 11700 ± 2428 | 12150 ± 2196 | 11893 ± 2475 |
| Difference, mg/d | | 964 ± 1833 | 1414 ± 2188 | 964 ± 2134 | 1221 ± 2337 |
| SMD | | 0.53 | 0.65 | 0.54 | 0.45 |
| Trimethoprim-Sulfamethoxazole | | | | | |
| Dose, mg/d | 480 ± 0 | 453 ± 77 | 439 ± 92 | 453 ± 77 | 453 ± 77 |
| Difference, mg/d | | 27 ± 77 | 41 ± 92 | 27 ± 77 | 27 ± 77 |
| SMD | | 0.35 | 0.45 | 0.35 | 0.35 |
| Valganciclovir | | | | | |
| Dose, mg/d | 675 ± 256 | 552 ± 290 | 495 ± 281 | 466 ± 249 | 511 ± 289 |
| Difference, mg/d | | 126 ± 269 | 180 ± 287 | 208 ± 234 | 164 ± 271 |
| SMD | | 0.46 | 0.63 | 0.89 | 0.60 |
| Vancomycin | | | | | |
| Dose, mg/d | 1650 ± 512 | 1436 ± 494 | 1357 ± 494 | 1429 ± 509 | 1436 ± 501 |
| Difference, mg/d | | 214 ± 563 | 293 ± 541 | 221 ± 517 | 214 ± 522 |
| SMD | | 0.38 | 0.54 | 0.43 | 0.41 |

Abbreviations: $CG_{IBW,}$ cockcroft-gault applying ideal body weight; $CG_{TBW,}$ cockcroft-gault applying total body weight; CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated GFR; GFR, glomerular filtration rate; mGFR, measured GFR; MDRD, modification of diet in renal disease; SMD, standardized mean difference.
*Dose and dose differences were showed as mean ± SD.

was compatible with the findings of Luis-Lima *et al.* study.[31] More common kidney function underestimation in this study means that eGFR equations show kidney dysfunction worse than that actually is.

Kidney transplant recipients take a large number of medications and most of these drugs especially antimicrobials need dose adjustment according to the level of kidney function. Recent studies suggested that CKD-EPI, MDRD, $CG_{TBW}$, and $CG_{IBW}$ respectively, are the equations that can be used for the renal dose adjustment of drugs in the general population.[32] To our knowledge, except for Stevens *et al.* study[33] that included kidney transplant recipients, there is no other study regarding the evaluation of discrepancies in drug dosing between mGFR and eGFR equations in this population. Stevens *et al.* compared the dose agreement of 15 medications between mGFR and eGFR equations and showed that in kidney transplant patients MDRD, $CG_{IBW}$, and $CG_{TBW}$ had a higher rate of concordance with mGFR respectively. CKD-EPI formula was not included in this study and MDRD with approximately 70% agreement was the best equation for the renal dose adjustment of drugs in kidney transplant patients; however, its agreement rate was lower than that reported in non-transplant patients.[33] In our study, $CG_{TBW}$ showed the best agreement with mGFR in the dosing of antimicrobials followed by CKD-EPI.

Among 8 evaluated antimicrobial agents in the present study, the lowest rates of discordance in drug dosing between mGFR and eGFR methods were seen for trimethoprim-sulfamethoxazole and ampicillin-sulbactam. These findings may be due to no need for dose adjustment of these two drugs until reaching to stage 4 of kidney dysfunction (eGFR < 30 mL/min/1.73 $m^2$). Conversely, ganciclovir and valganciclovir, showed the greatest number of dosing levels among these 8 antimicrobials and require dose modifications from the eGFR level of less than 70 and 60 mL/min, respectively; revealed the highest discordance in dosing between mGFR and eGFR methods. Based on our findings, only 45.7% of kidney transplant patients in the first days after transplantation get the correct doses; which is not an acceptable rate in the clinic. For 8 antimicrobials that we evaluated, underdosing were more common than overdosing when eGFR equations substituted for mGFR; therefore, using these eGFR equations in this situation might put the patients at risk of prophylaxis/treatment of infectious diseases failure.

In this study, we compared mGFR and eGFR in early days post kidney transplantation, at the first time that SCr was stable for 2 to 3 days and calculation of eGFR with equations was feasible. At this time many patients receive drugs that need renal dose adjustment. Most available studies in this field have been performed during later than first month after transplantation. However, this study suffers some limitations. It was a single center research with a low sample size. We did not include the Nankivell equation which was derived from kidney transplant recipients[34] and cystatin C based equations in our study.

## CONCLUSION

This study concluded that in general, the performance of GFR estimation equations is not acceptable in early days after kidney transplantation surgery and these formulas are not reliable in clinical practice especially for dosing of drugs that have high dosing levels. Although the overall performance of the $CG_{TBW}$ method was better than MDRD and CKD-EPI equations; but this difference was not significant and the use of these eGFR formulas may be interchangeable. Up to developing a more accurate equation for estimating GFR in kidney transplant recipients, in centers that measurement of GFR is not applicable, we recommend using the CG method applying TBW for drug dose adjustment. We suggest designing larger studies in the early post-transplant period using SCr and other markers as cystatin C to develop a more accurate equation.

## CONFLICT OF INTEREST

All authors declare no conflict of interest.

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