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Research Article

The Performance of Equations That Estimate Glomerular Filtration Rate against Measured Urinary Creatinine Clearance in Critically Ill Patients

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The performance of glomerular filtration rate- (GFR-) estimating equations was studied against creatinine clearance measured by 24-hour urine collection ($CrCl_{24h\text{-}urine}$) in critically ill patients. *Methods*. In this substudy of the PermiT trial (https://clinicaltrials.gov/ct2/show/ISRCTN68144998), patients from King Abdulaziz Medical City-Riyadh who had $CrCl_{24h\text{-}urine}$ were included. We estimated GFR using Cockroft–Gault (CG), modification of diet in renal disease study (MDRD), chronic kidney disease epidemiology collaboration (CKD-EPI), and Jelliffe equations. For the CG equation, we entered the actual weight in one calculation ($CG_{actual\text{-}wt}$), and if BMI ≥30 kg/m^2, we entered the ideal body weight ($CG_{ideal\text{-}wt}$) and the adjusted body weight ($CG_{adjusted\text{-}wt}$) in two calculations. We calculated the MDRD equation based on 4 (MDRD-4) and 6 variables (MDRD-6). The performance of these equations was assessed by different ways including Spearman correlation, bias (difference between estimated GFR and $CrCl_{24h\text{-}urine}$), precision (standard deviation of bias), and Bland–Altman plot analysis. *Results*. The cohort consisted of 237 patients (age 45 ± 20 years, males 75%, mechanically ventilated 99% with serum creatinine 101 ± 94 μmol/L and $CrCl_{24h\text{-}urine}$ 108 ± 69 ml/min/1.73 m^2). The correlations between the different equations and $CrCl_{24h\text{-}urine}$ were modest (r: 0.62 to 0.79; $p < 0.0001$). Bias was statistically significant for $CG_{actual\text{-}wt}$ (21 ml/min), $CG_{adjusted\text{-}wt}$ (12 ml/min), and MDRD-6 (-10 ml/min) equations. Precision ranged from 46 to 54 ml/min. The sensitivity of equations to correctly classify $CrCl_{24h\text{-}urine}$ 30–59.9 ml/min/1.73 m^2 was 17.2% for $CG_{actual\text{-}wt}$, 30.0% for $CG_{ideal\text{-}wt}$, 31.0% for $CG_{adjusted\text{-}wt}$, 31.0% for MDRD-4, 39.1% for MDRD-6, 13.8% for CKD-EPI, and 34.5% for Jelliffe equation. *Conclusions*. Commonly used GFR-estimating equations had limited ability to properly estimate $CrCl_{24h\text{-}urine}$ and to correctly classify GFR into clinically relevant ranges that usually determine dosing of medications.

1. Introduction

Appropriate dosing of medications is frequently dependent on renal function. The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines consider GFR as the preferred measure of kidney function rather than serum creatinine (Cr) and recommend estimating GFR in most circumstances and measuring it when greater accuracy is required [1]. To accurately measure GFR, exogenous substances, such as inulin, are used as filtration markers [2]. Despite being the gold standard for assessment of renal function, this measurement is not routinely performed in clinical practice as it is complex, impractical, costly, and not widely available. An alternative is the measurement of urinary Cr clearance (CrCl). However, the required timed urine collection is cumbersome and prone to errors and the result needs time to be reported. Hence, estimation of GFR using methods that are practical and timely is desirable in all patients in general. This might be more important in critically ill patients as they have increased prevalence of kidney dysfunction [3] and frequently exhibit augmented renal clearance (ARC) [4, 5]. Hence, proper dosing of medications in these patients would enhance their therapeutic effect, reduce potential toxicities, and improve patient outcomes [6, 7].

Multiple equations have been produced to estimate GFR, including Cockroft–Gault (CG) [8], modification of diet in renal disease study (MDRD) [9], chronic kidney disease epidemiology collaboration (CKD-EPI) [10], and Jelliffe [11] equations. These equations are primarily based on serum Cr and various anthropometric data. They were mostly derived from patients who were not critically ill [8–10]. Hence, there are concerns regarding their use in the ICU setting [12]. Studies that tested the accuracy of these equations in estimating renal function in the ICU setting are not many. Some focused on certain patient groups, especially those with ARC [13, 14], while others had low number of patients [13, 15–17]. The objective of this study was to assess the performance of commonly used formulas that estimate GFR against measured urinary CrCl in critically ill patients with different degrees of kidney function.

2. Methods

2.1. Study Design. This is a substudy of the PermiT (Permissive Underfeeding versus Target Enteral Feeding in Adult Critically Ill Patients) trial (https://clinicaltrials.gov/ct2/show/ISRCTN68144998), a multicenter randomized controlled trial which compared permissive underfeeding (40–60% of caloric requirements) versus target feeding (70–100% of caloric requirements) in ICU patients with similar protein intake in both groups (November 2009 to September 2014) [18]. Eligible patients were those who received tube feeding within 48 hours of ICU admission, were expected to stay in the ICU >72 hours, and were not on high doses of vasopressors [18]. The trial found no difference in the primary outcome (90-day mortality: 27.2% vs. 28.9%, respectively; relative risk: 0.94, 95% CI, 0.76–1.16; $p = 0.58$) [18]. The trial required serial 24-hour urine collection to measure nitrogen balance. In this retrospective study, we included the patients enrolled in the trial at King Abdulaziz Medical City-Riyadh who had at least one 24-hour urine collection for Cr, allowing CrCl ($CrCl_{24h\text{-}urine}$) measurement. Patients with end-stage renal disease requiring dialysis and those with anuria for any other reasons were excluded. Subjects with missing variables needed for calculations of the different equations were also excluded. The original trial was approved by the Institutional Review Board of Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia.

2.2. Data Collection. At baseline, we collected data on patients' demographics, chronic comorbid conditions, admission category (medical, surgical, and trauma), presence of traumatic brain injury, presence of sepsis on admission, Acute Physiology and Chronic Health Evaluation (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, use of mechanical ventilation, need for vasopressor therapy because of shock, daily caloric and protein intake, and laboratory results. We also obtained data about clinical outcomes, including mortality, duration of mechanical ventilation, and length of stay in the ICU and hospital.

In the study patients, urine was collected over 24 hours at baseline and then weekly as required by the trial when applicable. Measured $CrCl_{24h\text{-}urine}$ was then calculated using the standard equation: (urine Cr × urinary flow in ml/min)/serum Cr, where urine and serum Cr were expressed in μmol/L. To estimate GFR using different equations, we used the following variables taken on the same day of urine collection: age, weight, serum Cr, blood urea nitrogen, and albumin. In our laboratory, serum and urinary Cr concentrations were analyzed by a standardized Jaffe method (alkaline picrate reaction) traceable to isotopic dilution mass spectrometry using Abbott Architect c16000 platform.

2.3. Estimation of Kidney Function. We estimated GFR using CG [8], MDRD [9], CKD-EPI [10], and Jelliffe [11] equations. These different equations are described in Table 1. For CG equation, we entered the actual weight in one calculation ($CG_{actual\text{-}wt}$), and if body mass index (BMI) $\geq 30\,kg/m^2$, the ideal body weight ($CG_{ideal\text{-}wt}$) and the adjusted body weight ($CG_{adjusted\text{-}wt}$) were used in two calculations. We calculated the MDRD equation based on 4 (MDRD-4) and 6 variables (MDRD-6). Acute kidney injury in the enrollment day was assessed using the KDIGO classification [19].

2.4. Statistical Analysis. Continuous variables were reported as mean and standard deviation (SD). The coefficient of variation (SD/mean × 100) for $CrCl_{24h\text{-}urine}$ and the estimated GFR were also calculated. Categorical data were presented as frequency with percentage. Chi square test was used to assess between-group differences in categorical variables. Student's t or ANOVA tests were used to assess between-group differences in continuous variables as indicated.

The performance of the GFR-estimating equations compared with $CrCl_{24h\text{-}urine}$ was assessed in several ways.

Table 1: Renal function estimating equations.

Cockcroft and Gault formula (ml/min)
For males: [(140—age) × actual BW]/sCr × 72
For females: ([(140—age) × actual BW]/sCr × 72) × 0.85
sCr in mg/dL
The equation was calculated three times:
(1) Using actual BW for all patients
(2) Using actual BW for patients with BMI <30 kg/m^2 and ideal BW for those with BMI >30 kg/m^2
(3) Using actual BW for patients with BMI <30 kg/m^2 and adjusted BW for those with BMI >30 kg/m^2
Ideal BW
Males: 50 kg + 2.3 kg for each inch above 60 inches of height
Females: 45.5 kg + 2.3 kg for each inch above 60 inches of height
Adjusted BW = ideal BW + [0.4 × (actual BW—ideal BW)]
Modification of diet in renal disease study equations (ml/min/1.73 m^2)
Four-variable equation: $175 \times \text{sCr}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female)
Six-variable equation: $170 \times \text{sCr}^{-0.999} \times (\text{Age})^{-0.176} \times (0.762 \text{ if patient is female}) \times (\text{BUN})^{-0.170} \times (\text{albumin})^{0.318}$
sCr in mg/dL, albumin in g/dL, BUN in mg/dL; to convert BUN from mmol/L to mg/dL, divide by 0.3571
Chronic kidney disease epidemiology collaboration (CKD-EPI) equations (ml/min/1.73 m^2)
For females with sCr ≤ 0.7: $\text{GFR} = 144 \times (\text{sCr}/0.7)^{-0.329} \times (0.993)^{\text{age}}$
For females with sCr > 0.7: $\text{GFR} = 144 \times (\text{sCcr}/0.7)^{-1.209} \times (0.993)^{\text{age}}$
For males with sCr ≤ 0.9: $\text{eGFR} = 141 \times (\text{sCr}/0.9)^{-0.411} \times (0.993)^{\text{age}}$
For males with sCr > 0.9: $\text{eGFR} = 144 \times (\text{sCr}/0.9)^{-1.209} \times (0.993)^{\text{age}}$
Age in years and sCr in mg/dL
Jelliffe equation (ml/min/1.73 m^2)
For males: (98–16) × (age—20/20)/sCr
For females: [(98–16) × (age—20/20)/sCr] × 0.9
Age in years and sCr in mg/dL

BUN: blood urea nitrogen, BW: body weight, sCr: serum creatinine

Correlations were reported using Spearman correlation coefficient (r). Bias represented the mean difference between $\text{CrCl}_{24\text{h-urine}}$ and each of the equations estimating GFR [20]. Precision was defined as one SD of the bias [20]. Error was defined as double SD of the bias divided by the mean of the equation under study and $\text{CrCl}_{24\text{h-urine}}$. An acceptable between-method error was defined as 30% or less [21]. Accuracy was defined as percentage of GFR estimations within ±15, ±30, and ±50% range of respective $\text{CrCl}_{24\text{h-urine}}$ measurements. The 2002 Kidney Disease Outcomes Quality Initiative guidelines recommended that ≥90% of estimates be within 30% [22]. Bland–Altman plots were generated by plotting bias on the Y-axis and the mean of the equation under study and $\text{CrCl}_{24\text{h-urine}}$ on the X-axis [23]. The limits of agreement (bias ± two SD of the bias) were shown in the plots.

The predictive performance of the different equations was assessed when $\text{CrCl}_{24\text{h-urine}}$ was <30, 30–59.9, 60–130, and > 130 ml/min. We also assessed the ability (sensitivity) of the different equations to correctly classify $\text{CrCl}_{24\text{h-urine}}$ within clinically relevant ranges (<30, 30–59.9, 60–130, and >130 ml/min). Moreover, Spearman correlation was calculated in selected subgroups of patients: age < versus ≥ 65 years, BMI < versus ≥ 30 kg/m^2, APACHE II score < versus ≥ median value, which was 20, admission categories (medical, surgical, and nonoperative trauma), diagnosis of traumatic brain injury, presence of sepsis on ICU admission, baseline Cr < versus ≥ 110 μmol, presence of AKI, and presence of ARC (baseline $\text{CrCl}_{24\text{h-urine}}$ >130 ml/min/173 m^2) [4, 5].

Tests were two-sided and statistical significance was determined at $p < 0.05$. Bias was considered significant if the null hypothesis (bias = 0) was rejected. Analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC) and SPSS version 15.

3. Results

3.1. Characteristics of Patients. Two hundred and thirty-seven patients were included in this study. Table 2 describes their characteristics. The mean age was 45.0 ± 20.2 years, 74.7% were men, 32.5% were obese (BMI >30 kg/m^2), 31.7% had diabetes, 98.7% required mechanical ventilation, and 26.2% had traumatic brain injury.

The baseline serum Cr was 100.8 ± 93.9 μmol/L. Most patients (53%) had 24-hour urine collection once, 17.7% twice, 13.9% three times, and 15.2% four times. Thus, there were 453 measurements of urinary CrCl. Whereas 18.1% had AKI, 38.4% had ARC based on $\text{CrCl}_{24\text{h-urine}}$ >130 ml/min at baseline. The measured $\text{CrCl}_{24\text{h-urine}}$ and estimated GFRs based on the various equations are presented in Figure 1. The mean $\text{CrCl}_{24\text{h-urine}}$ was 108.4 ± 68.9 ml/min in the first 237 measurements. The estimated GFR by the different equations were 129.6 ± 65.6 ml/min for $\text{CG}_{\text{actual-wt}}$ ($p = 0.001$), 113.5 ± 59.2 ml/min for $\text{CG}_{\text{ideal-wt}}$ ($p = 0.39$), 119.9 ± 59.9 for $\text{CG}_{\text{adjusted-wt}}$ ($p = 0.053$), 108.9 ± 52.5 ml/min for MDRD-4 ($p = 0.93$), 102.2 ± 48.7 ml/min for MDRD-6 ($p = 0.27$), 102.1 ± 40.4 ml/min for CKD-EPI ($p = 0.22$), and 102.0 ± 49.3 ml/min for Jelliffe equation ($p = 0.24$). However, precision was high for all equations.

Table 2: Characteristics and outcomes of the 237 patients in the study cohort.

	All patients $N = 237$
Age—(year), mean ± SD	45.0 ± 20.2
Female sex—no. (%)	60 (25.3)
Height—(cm), mean ± SD	166.3 ± 9.7
Weight—(kg), mean ± SD	78.2 ± 19.6
Body mass index—(kg/m^2), mean ± SD	28.3 ± 7.2
Chronic illnesses—no. (%)	
Diabetes	75 (31.7)
Chronic respiratory disease	27 (11.3)
Chronic cardiac disease	23 (9.7)
Immunocompromised disorder	6 (2.5)
Chronic renal disease	6 (2.5)
Chronic liver disease	11 (4.6)
Admission category, no. (%)	
Medical	112 47.3)
Surgical	11 (4.6)
Nonoperative trauma	114 (48.1)
Traumatic brain injury—no. (%)	62 (26.2)
Sepsis on admission—no. (%)	51 (21.5)
APACHE II—mean ± SD	20.4 ± 8.1
SOFA score day 1—mean ± SD	10.0 ± 2.8
Vasopressor use—no. (%)	135 (57.0)
Mechanical ventilation—no. (%)	234 (98.7)
Intervention group—no. (%)	
Standard feeding	120 (50.6)
Permissive underfeeding	117 (49.4)
Total caloric intake (kcal/day)—mean ± SD	1143.6 ± 466.1
Total protein intake—(g/day) mean ± SD	55.9 ± 21.0
Laboratory tests	
Inclusion blood glucose—(mmol/L), mean ± SD	9.0 4.1
Creatinine—(μmol/L), mean ± SD	100.8 ± 93.9
Bilirubin—(μmol/L), mean ± SD	25.4 ± 39.2
Platelets—(10^9/L), mean ± SD	214 ± 128
Albumin—(g/L), mean ± SD	28.8 ± 5.6
Outcomes	
Mechanical ventilation duration—(days), mean ± SD	13.0 ± 25.0
ICU LOS—(days), mean ± SD	15.9 ± 10.5
Hospital LOS—(days), mean ± SD	59.3 ± 83.1
90-day mortality	61 (25.7)
ICU mortality—no. (%)	38 (16.0)
Hospital mortality—no. (%)	56 (23.6)
ICU-acquired infections—no. (%)	96 (40.5)

SD: standard deviation; APACHE: acute physiology and chronic health evaluation; SOFA: sequential organ failure assessment; ICU: intensive care unit; LOS: length of stay.

3.2. Performance of the Equations Estimating GFR in the Whole Cohort. The performance of the different GFR-estimating equations against $CrCl_{24h\text{-urine}}$ is described in Table 3. The correlations between the different equations and $CrCl_{24h\text{-urine}}$ were significant ($p < 0.001$), with r ranging between 0.62 and 0.79. When using the first 237 urine measurements, bias was large and statistically significant for $CG_{actual\text{-wt}}$ (21.1 ml/min), $CG_{adjusted\text{-wt}}$ (11.5 ml/min), and MDRD-6 (-10.3 ml/min) equations. When using all 453 urine measurements, the bias was large and statistically significant for $CG_{actual\text{-wt}}$ (27.4 ml/min), $CG_{ideal\text{-wt}}$ (12.3 ml/min) $CG_{adjusted\text{-wt}}$ (18.3 ml/min), MDRD-4 (7.1 ml/min), and MDRD-6 (−5.7 ml/min) equations. In both calculations, CKD-EPI and Jelliffe equations had no significant bias. The error was >70% for all equations.

The accuracy values for the different equations were generally modest. When using the first 237 urine measurements, accuracy within ±10% of $CrCl_{24h\text{-urine}}$ ranged between 12.7% ($CG_{actual\text{-wt}}$ equation) and 30.0% ($CG_{adjusted\text{-wt}}$ equation). Accuracy within ±30% ranged between 47.4% (MDRD-6 equation) and 51.2% ($CG_{adjusted\text{-wt}}$ equation). Accuracy within ±57.4% ranged between 12.7% (Jelliffe equation) and 75.1% (MDRD-6 equation). The accuracy values were similar when all 453 measurements were used in calculation (Table 3).

Bland–Altman plots are depicted in Figure 2. The limits of agreement were 111.3 and −69.0 ml/min for $CG_{actual\text{-wt}}$, 103.0 and −92.9 for $CG_{ideal\text{-wt}}$, 101.4 and −78.4 ml/min for $CG_{adjusted\text{-wt}}$, 106.7 and −105.7 ml/min for MDRD-4, 95.2 and −116.2 ml/min for MDRD-6, 94.8 and −107.4 ml/min for CKD-EPI, and 95.2 and −108.1 ml/min for Jelliffe equations. Multiple points were outside the limits of agreement, which were wide for all equations.

3.3. Performance of the Equations Estimating GFR in Different Ranges of Urinary Creatinine Clearance and in Selected Subgroups of Patients. Correlation, bias, precision, and accuracy for the different equations are reported in Table 3 when $CrCl_{24h\text{-urine}} < 30$, 30–59.9, 60–130, and >130 ml/min using the 453 measurements, which were considered to be independent observations. Bias was significant for all equations except for $CG_{adjusted\text{-wt}}$ equation when $CrCl_{24h\text{-urine}} > 130$ ml/min.

The sensitivity of GFR equations to correctly classify $CrCl_{24h\text{-urine}}$ <30 ml/min was 44.7% for $CG_{actual\text{-wt}}$, 71.1% for $CG_{ideal\text{-wt}}$, 57.9% for $CG_{adjusted\text{-wt}}$, 60.5% for MDRD-4, 64.5% for MDRD-6, 59.5% for CKD-EPI, and 60.5% for Jelliffe equation. The sensitivity to correctly classify $CrCl_{24h\text{-urine}}$ 30–59.9 ml/min was 17.2% for $CG_{actual\text{-wt}}$, 30.0% for $CG_{ideal\text{-wt}}$, 31.0% for $CG_{adjusted\text{-wt}}$, 31.0% for MDRD-4, 39.1% for MDRD-6, 13.8% for CKD-EPI, and 34.5% for Jelliffe equation. The sensitivity to correctly classify $CrCl_{24h\text{-urine}}$ 60–129.9 ml/min was 59.5% for $CG_{actual\text{-wt}}$, 60.8% for $CG_{ideal\text{-wt}}$, 63.3% for $CG_{adjusted\text{-wt}}$, 58.2% for MDRD-4, 59.7% for MDRD-6, 79.7% for CKD-EPI, and 63.3% for Jelliffe equation. The sensitivity to correctly classify $CrCl_{24h\text{-urine}} \geq 130$ ml/min was 87.9% for $CG_{actual\text{-wt}}$, 70.3% for $CG_{ideal\text{-wt}}$, 79.1% for $CG_{adjusted\text{-wt}}$, 60.4% for MDRD-4, 49.4% for MDRD-6, 45.1% for CKD-EPI, and 53.3% for Jelliffe equation.

Table 4 shows the Spearman correlations between the different GFR-estimating equations and $CrCl_{24h\text{-urine}}$. The values of r were lowest in patients with the diagnosis of polytrauma, baseline Cr <110 μmol and baseline $CrCl_{24h\text{-urine}}$ >130 ml/min.

4. Discussion

In this study, we found that the commonly used equations to estimate GFR performed modestly against the measured

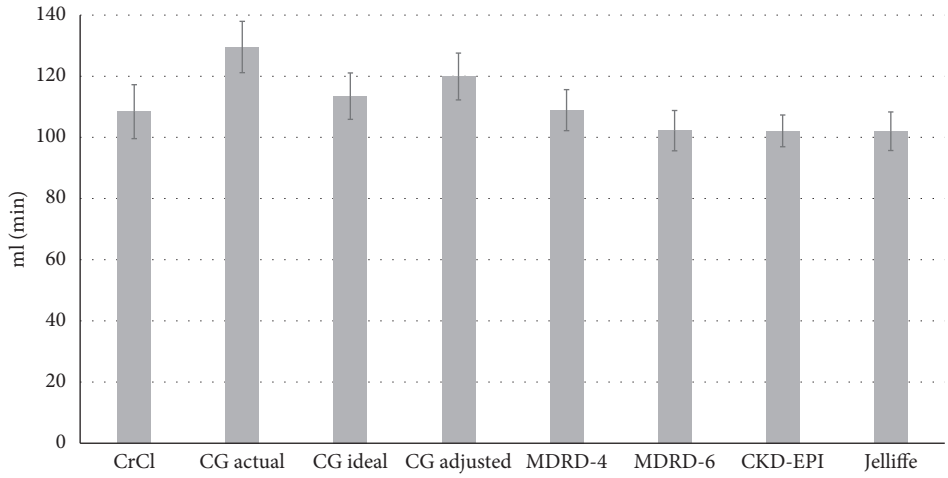

Figure 1: Mean values of the measured creatinine clearance by 24-hour urine collection ($CrCl_{24h\text{-}urine}$) and estimated glomerular filtration rate by different equations. The first 237 24-hour urine samples were used in this analysis. Error bars represent 95% confidence interval. The difference between the different methods was significant ($p < 0.001$) by ANOVA test. CG: Cockroft–Gault equation; MDRD-4: 4-variable modification of diet in renal disease equation; MDRD-6: 6-variable modification of diet in renal disease equation, and CKD-EPI: chronic kidney disease epidemiology collaboration equation.

urinary CrCl with high bias and accuracy within 30% present in approximately 50%. The equations with the highest sensitivity to correctly classify $CrCl_{24h\text{-}urine}$ 30–59 and ≥130 ml/min, ranges where medication dose adjustment is frequently needed, were MDRD-6 and $CG_{actual\text{-}wt}$.

Measuring GFR cannot be done routinely. Measured urinary CrCl is more widely available, but it may overestimate GFR because of Cr filtration and secretion; the latter can be affected by medications known to compete with active tubular secretion of Cr [24]. However, studies that compared $CrCl_{24h\text{-}urine}$ with measured GFR in the ICU are limited. One study found that urinary CrCl with short collection times (1–2 h) had the highest correlation with measured GFR using inulin clearance ($r = 0.921$). The median bias for measured urinary CrCl was 11 mL/min/1.73 m^2 for GFR <60ml/min, 24 mL/min/1.73 m^2 for GFR 60–90ml/min, and 44 mL/min/1.73 m^2 for GFR >90ml/min [17]. Another study evaluated 30 ICU patients with early AKI after complicated cardiac surgery and found low bias but high error when $CrCl_{24h\text{-}urine}$ was compared with GFR measured by the infusion clearance of chromium-ethylenediaminetetraacetic acid [15]. The magnitude of this overestimation increased as GFR declined [15]. On the other hand, the commonly used equations to estimate GFR have their own shortcomings. They were mostly derived from outpatients with stable kidney function [8–10]. Only the Jelliffe equation was validated to assess GFR in a non-steady state as in critically ill patients [25]. Besides, studies that evaluated their use in the ICU settings had many limitations. Nevertheless, they generally found modest performance of GFR-estimating equations. A study of 360 critically ill patients who had stable serum Cr in one French hospital compared estimated GFR by equations that included CG, MDRD, and CKD-EPI, with $CrCl_{24h\text{-}urine}$. The study found that the different equations tended to overestimate the CrCl for low eGFR values and to underestimate the CrCl for normal and high values [26]. In patients without ARC, the bias and precision were 11.3 and 25.3 ml/min for CKD-EPI, 18.8 and 31.7 ml/min for CG, and 22.5 and 34.6 ml/min, respectively [26]. Another study of 360 ICU subjects in Australia found that all tested equations (CG and CKD-EPI) showed limited agreement with 8-hour urinary CrCl [27]. $CG_{actual\text{-}wt}$ corrected for body surface area had the lowest bias (-3.2 ml/min for indigenous and 8.2 ml/min for nonindigenous patients) [27]. However, CKD-EPI had the narrowest 95% confidence interval for limits of agreement in the Bland–Altman analysis [27]. A study of 111 patients without renal impairment in a Japanese ICU found that eGFR calculated using the Japanese equation correlated well with CrCl based on 8-hour urine collection (Spearman $r = 0.75$; $p < 0.05$) [28]. In contrast, the Bland–Altman plots showed that the bias of the two variables was −46.1 mL/min/1.73 m^2, and the 95% limits of agreement were −128.9 to 36.7 mL/min/1.73 m^2 [28]. In a study of 54 ICU patients with normal Cr, a statistically significant, but poor, correlation was noted between CrCL by 8-hour urine collection and GFR estimated by CG, MDRD-4, and CKD-EPI ($r = 0.20$, 0.19, and 0.34, respectively) [16], The Bland–Altman plot showed poor agreement between pairs of comparisons (precision of 40.9, 39.8, and 33.4%, respectively) [16], When GFR-estimating equations were compared with measured GFR by inulin clearance in the ICU, CG, MDRD-6, MDRD-4, and CKD-EPI equations overestimated GFR (bias 24, 26, 37, and 13 mL/min/1.73 m^2, respectively) [17]. However, CKD-EPI had the lowest bias likely due to its better performance when GFR >90 mL/min/1.73 m^2 [17]. We evaluated seven different equations against $CrCl_{24h\text{-}urine}$. All had significant bias, inadequate precision, high error, low accuracy, and wide agreement limits on the Bland-Altman plots. The correlations were moderate to strong nevertheless. Importantly, the sensitivity to correctly identify $CrCl_{24h\text{-}urine}$ in the clinically important ranges (such as 30–59 and >130 ml/min) was low in general for all equations.

Studies on the performance of GFR-estimating equations in critically ill patients with AKI are scarce. One study evaluated 30 ICU patients with early AKI. GFR-estimating

Table 3: Predictive performance of equations estimating glomerular filtration rate compared with creatinine clearance ($CrCl_{24h\text{-}urine}$) measured by 24-hour urine collection.

	$CrCl_{24h\text{-}urine}$	$CG_{actual\text{-}wt}$	$CG_{ideal\text{-}wt}$	$CG_{adjusted\text{-}wt}$	MDRD-4	MDRD-6	CKD-EPI	Jelliffe
Data from the first 237 urine collections (all 237 patients)								
GFR estimate (mlH/min) ±SD	108.4 ± 68.9	129.6 ± 65.6	113.5 ± 59.2	119.9 ± 59.9	108.9 ± 52.5	102.2 ± 48.7	102.1 ± 40.4	102.0 ± 49.3
Coefficient of variation (%)	63.6	50.6	52.2	50.0	48.2	47.7	39.6	48.3
Correlation		0.77	0.71	0.75	0.63	0.62	0.67	0.66
Bias (ml/min)		21.1*	5.0	11.5*	0.5	−10.5*	−6.3	−6.4
Precision (ml/min)		±46.0	±49.9	±45.9	±54.2	±53.9	±51.6	±51.9
Error (%)		77.3	90.0	80.4	99.7	100.4	98.0	98.6
Accuracy								
±15%		12.7	27.4	30.0	25.7	22.8	28.3	25.7
±30%		49.4	48.1	51.2	48.9	47.4	48.9	49.4
±50%		66.7	72.2	71.3	69.2	75.1	70.5	57.4
Data from the 453 urine collections (all 237 patients)								
GFR estimate (ml/min) ±SD	102.7 ± 65.4	130.1 ± 65.9	114.9 ± 60.2	121.0 ± 60.6	109.8 ± 52.1	99.8 ± 47.1	103.2 ± 40.0	103.2 ± 49.3
Coefficient of variation (%)	63.7	50.7	52.4	50.1	47.4	47.2	38.8	47.8
Correlation		0.79	0.75	0.79	0.67	0.66	0.67	0.70
Bias (ml/min)		27.4*	12.3*	18.3*	7.1*	−5.7*	0.53	0.53
Precision (ml/min)		±43.0	±44.3	±40.9	±49.1	±49.3	±47.2	±46.8
Error (%)		73.9	81.5	73.2	92.5	96.1	91.8	90.9
Accuracy								
±15%		24.1	27.8	29.1	26.7	27.5	28.0	26.7
±30%		42.8	47.5	49.2	49.9	50.5	50.3	50.8
±50%		60.0	69.3	66.2	69.3	73.5	69.8	72.2
Urine collections with $CrCl_{24h\text{-}urine}$ < 30 ml/min (N = 72)								
GFR estimate (ml/min) ±SD	13.3 ± 8.4	39.7 ± 25.7	30.8 ± 25.7	34.4 ± 25.6	34.4 ± 33.3	32.1 ± 28.4	38.2 ± 30.6	33.7 ± 27.9
Coefficient of variation (%)	63.2	64.7	83.4	74.4	96.8	88.5	80.1	82.8
Correlation		0.58	0.50	0.54	0.55	0.58	0.56	0.54
Bias (ml/min)		26.4*	17.6*	21.1*	21.1*	18.7*	25.0*	20.4*
Precision (ml/min)		±21.9	±22.7	±21.8	±29.5	±24.4	±26.9	±24.4
Accuracy								
±15%		1.4	16.7	5.6	12.5	13.1	11.1	8.3
±30%		6.9	23.6	15.3	26.4	27.9	23.6	19.4
±50%		11.1	36.1	23.6	36.1	39.3	30.6	31.9
Urine collections with $CrCl_{24h\text{-}urine}$ 30–59.9 ml/min (N = 68)								
GFR estimate (ml/min) ±SD	45.3 ± 8.6	85.6 ± 34.5	76.9 ± 37.3	80.4 ± 35.4	84.8 ± 40.6	73.8 ± 36.5	86.3 ± 29.5	76.0 ± 35.3
Correlation		0.44	0.46	0.46	0.30	0.46	0.35	0.33
Coefficient of variation (%)	19.0	40.3	48.5	44.0	47.9	49.5	34.2	46.4
Bias (ml/min)		40.3*	31.6*	35.1*	39.5*	28.4*	41.0*	30.6*
Precision (ml/min)		±31.7	±34.3	±32.4	±38.9	±33.5	±27.6	±33.5
Accuracy								
±15%		5.9	11.8	14.7	7.4	15.5	7.4	11.8
±30%		16.2	26.5	25.0	20.6	32.8	14.7	35.3
±50%		27.9	44.1	39.7	38.2	53.4	23.5	51.5
Urine collections with $CrCl_{24h\text{-}urine}$ 60–129.9 ml/min (N = 156)								
	97.8 ± 20.5	134.2 ± 44.5	121.6 ± 43.8	126.6 ± 41.9	120.8 ± 37.6	107.7 ± 35.5	114.2 ± 26.4	111.7 ± 36.2
Coefficient of variation (%)	21.0	33.2	36.0	33.1	31.1	33.0	23.1	32.4
Correlation		0.37	0.38	0.40	0.12	0.18	0.32	0.23
Bias (ml/min)		36.4*	23.8*	28.8*	23.0*	9.6*	16.4*	13.9*

Table 3: Continued.

	$CrCl_{24h\text{-}urine}$	$CG_{actual\text{-}wt}$	$CG_{ideal\text{-}wt}$	$CG_{adjusted\text{-}wt}$	MDRD-4	MDRD-6	CKD-EPI	Jelliffe
Precision (ml/min)		±41.6	±40.6	±38.7	±40.7	±37.6	±20.7	±37.2
Accuracy								
±15%		24.4	27.6	29.5	27.6	32.6	42.3	28.8
±30%		44.2	46.2	49.4	53.8	54.5	61.5	55.8
±50%		66.7	71.8	69.2	72.4	73.1	84.0	78.8
Urine collection with $CrCl_{24h\text{-}urine}$ > 130 ml/min (N = 157)								
GFR estimate (ml/min) ±SD	173.3 ± 41.6	186.6 ± 44.2	163.3 ± 37.6	172.6 ± 34.3	144.1 ± 32.3	130.3 ± 30.5	129.4 ± 16.3	138.4 ± 31.3
Coefficient of variation (%)	24.0	23.7	23.0	19.9	22.4	23.4	12.6	22.6
Correlation		0.29	0.20	0.28	0.22	0.14	0.14	0.20
Bias (ml/min)		13.3*	−10.0*	−0.7	−29.2*	−43.7*	−44.0*	−34.9*
Precision (ml/min)		±51.3	±50.0	±45.8	±46.7	±48.2	±42.5	±46.8
Accuracy								
±15%		42.0	40.1	45.9	40.8	33.1	30.6	39.5
±30%		69.4	68.8	75.2	69.4	57.4	66.9	66.9
±50%		89.8	93.0	94.3	94.9	88.5	93.6	93.0

CKD-EPI: chronic kidney disease epidemiology collaboration; CG: Cockroft-Gault; $CrCl_{24h\text{-}urine}$: creatinine clearance measured by 24-hour urine collection; GFR: glomerular filtration rate; MDRD: modification of diet in renal disease study; SD: standard deviation. $CG_{actual\text{-}wt}$: the CG equation was calculated using actual body weight. $CG_{ideal\text{-}wt}$: the CG equation was calculated using ideal body weight. $CG_{adjusted\text{-}wt}$: the CG equation was calculated using adjusted body weight. MDRD-4: the MDRD equation was calculated using four variables. MDRD-6: the MDRD equation was calculated using six variables. * $p < 0.05$ using one-sided t test indicating that the bias was significant.

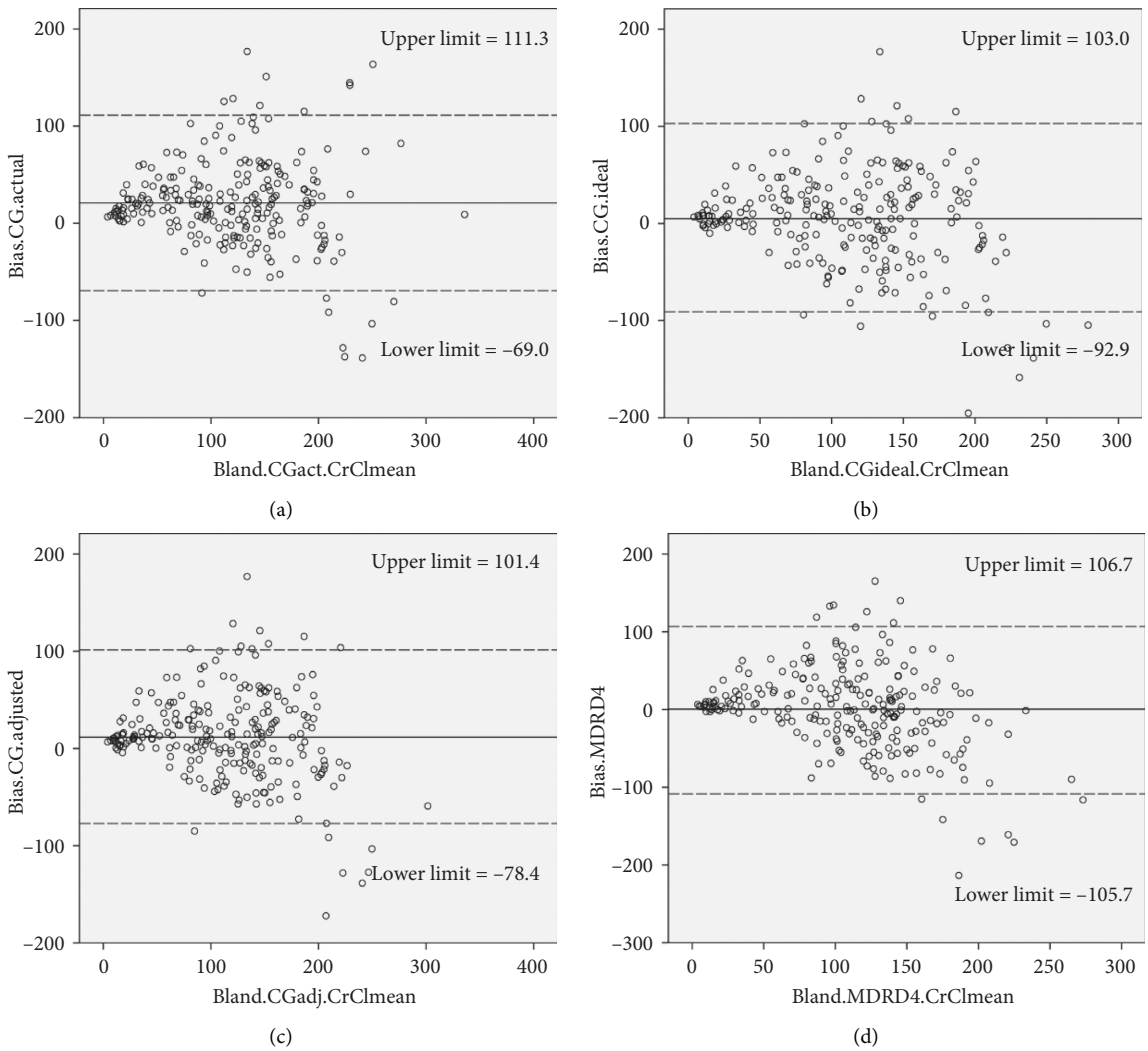

Figure 2: Continued.

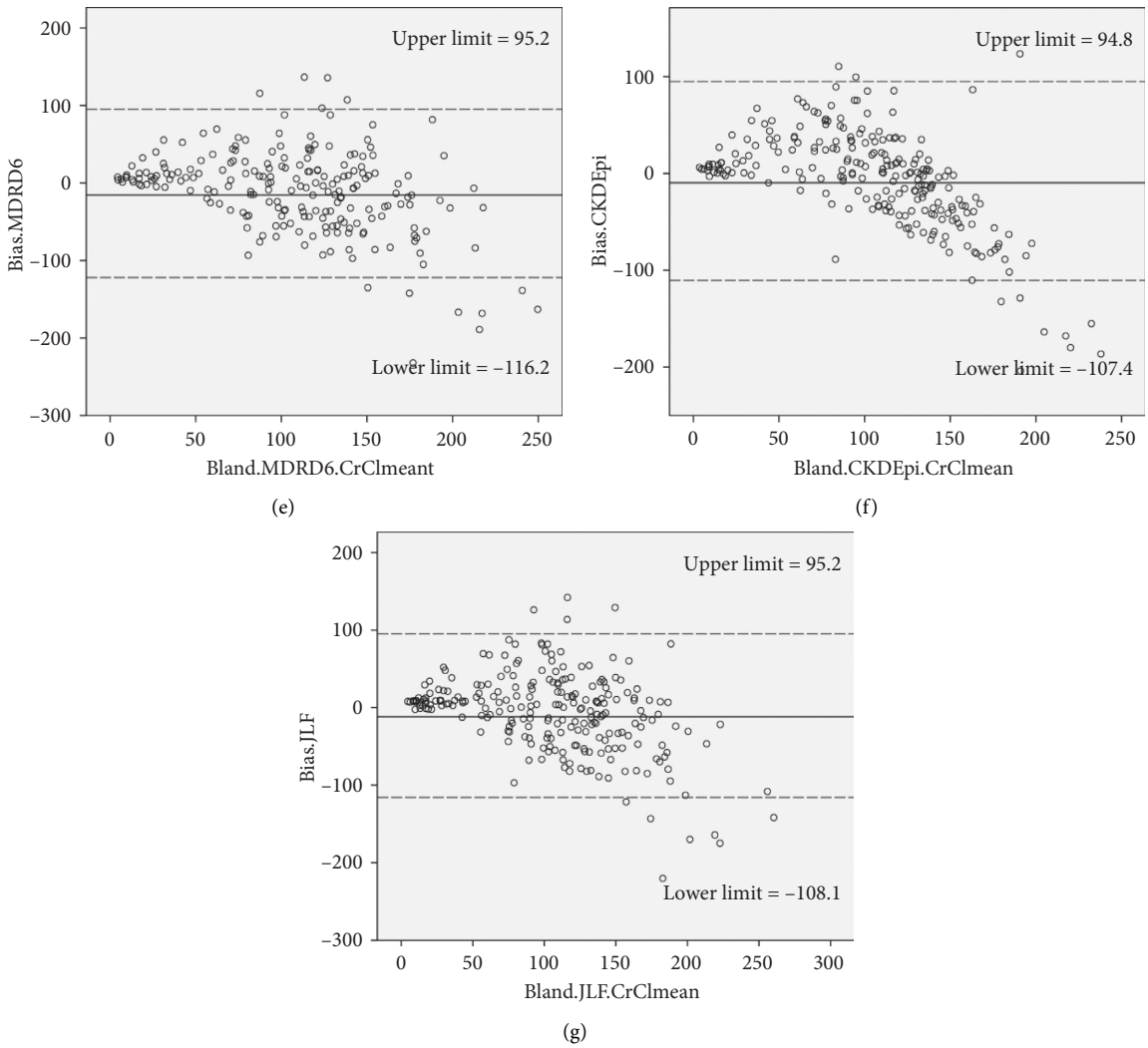

Figure 2: Bland–Altman plot of the creatinine clearance measured by 24-hour urine collection ($CrCl_{24h\text{-}urine}$) versus the equations estimating glomerular filtration rate. (a) Cockroft–Gault equation using actual body weight; (b) Cockroft–Gault equation using ideal body weight; (c) Cockroft–Gault equation using adjusted body weight; (d) 4-variable modification of diet in renal disease equation; (e) 6-variable modification of diet in renal disease equation; (f) chronic kidney disease epidemiology collaboration equation; and (g) Jelliffe equation. The X-axis represents the difference between $CrCl_{24h\text{-}urine}$ and the equation estimating glomerular filtration rate. The Y-axis represents the mean of $CrCl_{24h\text{-}urine}$ and the equation estimating glomerular filtration rate. The solid line represents the bias (mean difference obtained across the range of values), whereas the dashed lines are the limits of agreement ($\pm 1.96 \times$ standard deviation).

equations, CG, MDRD-4, and CKD-EPI equations, performed poorly when compared with measured GFR. The biases ranged from 7.4 ml/min for $CG_{actual\text{-}wt}$ to 11.6 ml/min for MDRD-4 [15]. Additionally, the limits of agreement were wide for all the equations [15]. We found that the bias was generally high, but MDRD-6 had the lowest bias (28.4 ml/min). Jelliffe equation had the highest accuracy ±30%, but was only 35.3%. The correlations of studies equations with $CrCl_{24h\text{-}urine}$ were fair. Moreover, MDRD-6 had the highest sensitivity (39.1%) to correctly classify $CrCl_{24h\text{-}urine}$ 30–59.9 ml/min. This was mostly due to overestimation of GFR.

Other studies evaluated GFR-estimating equations in patents with ARC. A study of 390 patients with ARC in a surgical ICU in Belgium showed fair correlation between measured and estimated clearances (Spearman $r = 0.34$; $p < 0.001$ for CG equation and 0.29; $p < 0.001$ for MDRD-4 equation) [14]. The bias was −11.2 ml/min with limits of agreement (−131.7; 109.3 ml/min) for CG equation and −19.9 ml/min with limits of agreement (−170.4; 130.7 ml/min) for MDRD-4 [14]. Post hoc analysis of prospectively collected data in 86 patients with ARC at two tertiary ICUs in Australia and Portugal found that GFR estimated by CG, modified CG, MDRD-4, and MDRD-6 equations significantly underestimated $CrCl_{24h\text{-}urine}$, with CG displaying the smallest bias [13]. The correlation was poor between $CrCl_{24h\text{-}urine}$ and CG ($r = 0.26$, $p = 0.02$) and MDRD-4 ($r = 0.22$, $p = 0.047$), and neither had acceptable precision for clinical application in this setting [13]. CG estimates had the highest sensitivity for correctly identifying ARC (62%) [13]. In the

Table 4: Correlation between equations estimating glomerular filtration rate and creatinine clearance measured by 24-hour urine collection.

	Spearman correlation (r)						
	$CG_{actual\text{-}wt}$	$CG_{ideal\text{-}wt}$	$CG_{adjusted\text{-}wt}$	MDRD-4	MDRD-6	CKD-EPI	Jelliffe
Age ≥ 65 years ($N = 53$)	0.70	0.62	0.67	0.60	0.61	0.67	0.61
Age < 65 years ($N = 184$)	0.71	0.62	0.69	0.57	0.56	0.57	0.58
BMI ≥ 30 kg/m^2 ($N = 77$)	0.82	0.82	0.83	0.76	0.73	0.81	0.78
BMI < 30 kg/m^2 ($N = 160$)	0.73	0.73	0.73	0.61	0.64	0.63	0.64
Admission category: medical ($N = 112$)	0.79	0.72	0.78	0.63	0.66	0.70	0.67
Admission category: surgical ($N = 11$)	0.74	0.58	0.68	0.70	0.48	0.66	0.67
Admission category: nonoperative trauma ($N = 114$)	0.54	0.37	0.46	0.34	0.30	0.22	0.32
APACHE II ≥ 20 ($N = 118$)	0.77	0.74	0.77	0.68	0.67	0.71	0.71
APACHE II < 20 ($N = 119$)	0.71	0.59	0.67	0.48	0.46	0.53	0.55
Diabetes ($N = 75$)	0.78	0.70	0.77	0.65	0.62	0.67	0.68
No diabetes ($N = 162$)	0.70	0.62	0.68	0.52	0.52	0.57	0.55
Sepsis admission ($N = 51$)	0.76	0.74	0.77	0.62	0.64	0.69	0.65
No sepsis on admission ($N = 186$)	0.74	0.66	0.72	0.59	0.57	0.61	0.62
Traumatic brain injury ($N = 62$)	0.56	0.39	0.49	0.41	0.43	0.21	0.32
No traumatic brain injury ($N = 175$)	0.78	0.72	0.77	0.64	0.63	0.70	0.67
SOFA renal > 0 (Cr ≥ 110 μmol/L) ($N = 49$)	0.90	0.86	0.90	0.82	0.82	0.81	0.85
SOFA renal = 0 (Cr < 110 μmol/L) (N = 188)	0.64	0.54	0.62	0.41	0.43	0.45	0.46
Acute kidney injury on admission ($N = 43$)	0.79	0.68	0.75	0.68	0.63	0.68	0.70
No acute kidney injury on admission ($N = 188$)	0.65	0.56	0.63	0.41	0.45	0.46	0.47
Baseline $CrCl_{24h\text{-}urine}$ ≥ 130 ml/min ($N = 91$)	0.38	0.26	0.36	0.27	0.17	0.22	0.23
Baseline $CrCl_{24h\text{-}urine}$< 130 ml/min ($N = 146$)	0.70	0.68	0.70	0.62	0.62	0.71	0.64

APACHE: acute physiology and chronic health evaluation; BMI: body mass index; CKD-EPI: chronic kidney disease epidemiology collaboration; CG: Cockroft-Gault; $CrCl_{24h\text{-}urine}$: creatinine clearance measured by 24-hour urine collection; GFR: glomerular filtration rate; MDRD: modification of diet in renal disease study. $CG_{actual\text{-}wt}$: the CG equation was calculated using actual body weight. $CG_{ideal\text{-}wt}$: the CG equation was calculated using ideal body weight. $CG_{adjusted\text{-}wt}$: the CG equation was calculated using adjusted body weight. MDRD-4: the MDRD equation was calculated using four variables. MDRD-6: the MDRD equation was calculated using six variables.

current study, we found lower bias when $CrCl_{24h\text{-}urine}$ ≥ 130 ml/min than lower ranges. $CG_{adjusted\text{-}wt}$ had low bias (−0.7 ml/min), the highest accuracy± 30% (75.2%), and sensitivity to correctly classify $CrCl_{24h\text{-}urine}$ ≥130 ml/min (79.1%). It should be noted that failure to correctly identify ARC may lead to subtherapeutic dosing of medications increasing the risk of treatment failure, emerging microbial resistance, prolonged ICU stay, and increased mortality [29].

GFR-estimating equations may not perform well in certain populations, such as the very elderly [30, 31], patients with diabetes [32], or those who have liver cirrhosis [33]. We studied subgroups of ICU patients and found that the correlation between $CrCl_{24h\text{-}urine}$ and the different GFR-estimating equations was weak in patients with polytrauma, who commonly have ARC [34].

The findings of this study should be interpreted taking into consideration its strengths and limitations. The strength includes the prospective data collection, relatively large sample size, the study of seven GFR-estimating equations, and the evaluation of their performance using several methods. The limitations include being a single-center study and the use of $CrCl_{24h\text{-}urine}$ instead of more accurate GFR measures (e.g., inulin, ^{125}I-sodium iothalamate clearance or cystatin C-based equations). Serum cystatin C-based equations have been found to outperform serum creatine-based equations in estimating GFR in critically ill patients [35–37]. Moreover, $CrCl_{24h\text{-}urine}$ is less accurate when kidney function is not steady and dysfunction is evolving [15], which is frequent in the ICU.

In conclusion, GFR-estimating equations that are commonly used in clinical practice had limited ability to properly estimate $CrCl_{24h\text{-}urine}$ and likely true GFR. They had limited ability to correctly classify GFR into clinically relevant ranges that are usually needed to determine dosing of medications. The clinical significance of these findings needs to be studied further.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval

The PermiT trial was approved by the Institution Review Board of the Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia.

Consent

Informed consent was obtained from enrolled patients/next of kin.

Conflicts of Interest

All authors declare no conflicts of interest.

Authors' Contributions

Conception and design of the work was performed by HMD and YMA. Acquisition of data was done by AAA, ASA,

AMA, and MS. Analysis and interpretation of data were carried out by HMD, HT, AAA, ASA, AMA, MS, EE, and YMA. Manuscript was drafted by HMD. Manuscript was revised by HMD, HT, AAA, ASA, AMA, MS, EE, and YMA. All authors read and approved the final manuscript.

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