Predictive performance of glomerular filtration rate estimation equations based on cystatin C versus serum creatinine values in critically ill patients

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Purpose. The predictive performance of glomerular filtration rate (GFR) estimation equations based on cystatin C versus serum creatinine (SCr) values in critically ill patients was evaluated.

Methods. A retrospective observational study was performed in the medical intensive care unit (ICU) of a university hospital from October 2006 through September 2007. All consecutively admitted critically ill patients older than 18 years who stayed in the ICU for more than 48 hours with a urinary bladder catheter in place were included in the study. Data collected included SCr, cystatin C, serum albumin, blood urea nitrogen, and 24-hour urine creatinine clearance ($CL_{cr_{24hr}}$) levels. The following equations were also used to determine the estimated GFR that was compared with the reference $CL_{cr_{24hr}}$ for all patients in the study: Arnal-Dade using cystatin C, Cockcroft-Gault using actual body weight, Cockcroft-Gault using ideal body weight, Jelliffe, Modification of Diet in Renal Disease (MDRD), and four-variable version MDRD (MDRD-4).

Results. This study included 241 measurements corresponding to 131 critically ill patients. The cystatin C–based equation underestimated $CL_{cr_{24hr}}$, whereas overestimation by every SCr-based formula was observed in the whole cohort and in the $CL_{cr_{24hr}} < 60$ mL/min/1.73 m^2 subgroup; MDRD-4 was the most biased equation in every analysis. There were no significant differences in precision, except for great variability in the subgroup with a $CL_{cr_{24hr}}$ of <60 mL/min/1.73 m^2, where the MDRD equation showed better results than the cystatin C–based equation (33.5% versus 38.9%). No equations fulfilled concordance requirements with $CL_{cr_{24hr}}$.

Conclusion. A retrospective observational study showed no evidence of superiority of a cystatin C–based equation over SCr-based equations to estimate the GFR in an ICU population.

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Renal function assessment in critically ill patients is of utmost importance for correct drug dosing, meeting nutrition and fluid requirements, and early detection of kidney failure, among other concerns. The estimation of the glomerular filtration rate (GFR) in this population is difficult for several reasons.[1-4] GFR can be measured with exogenous filtration markers such as inulin, iothalmate sodium I 125, chromium Cr 51 edetate, technetium Tc 99m pentetate, and iohexol. These agents are characterized by their complete filtration through the glomeruli without incurring tubular reabsorption or secretion; however, they are infrequently used in clinical practice due to their high cost, the complex laboratory measurements required, and the presence of radiation.[2-7] As an alternative, quantification of endogenous filtration measuring 24-hour urine creatinine clearance ($CL_{cr_{24hr}}$) or serum creatinine (SCr) levels is

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routinely performed.[1-6] Creatinine, a protein mainly formed by muscular catabolism,[8] is a very common biochemical marker used to assess renal function, and many equations have been developed to estimate creatinine clearance. Creatinine production is not constant and depends on age, sex, race, diet, muscular mass, drug–drug interactions, and pathologies. Although creatinine is filtered by the glomeruli, it also undergoes some tubular secretion; thus, $CL_{cr_{24hr}}$ overestimates the actual GFR.[2,4-9] The accuracy of SCr and its equations to provide a correct GFR estimation is suboptimal,[6-10] particularly for critically ill patients who frequently have low SCr values attributable to immobilization, undernourishment, sepsis, and fluid retention, among other factors.[1-4,7-13] Further, due to the fluctuation of SCr in many critically ill patients,[1-3,5,9] changes in renal function are not reflected as accurately with SCr[1,11,14,15] or SCr-based equations[1-3,5,7] during the early stages of renal dysfunction.

Cystatin C is a nonglycosylated basic protein expressed in all nucleated cells and is freely filtered in the glomeruli and almost completely reabsorbed and degraded in the proximal tubules.[9,16] Cystatin C has been proposed as a more precise endogenous filtration marker than SCr to assess renal function in children and the elderly[16] and to detect early mild renal impairment.[10] Serum cystatin C could be a potential endogenous marker of renal function in critically ill patients, as it may predict acute kidney injury six hours[11] to two days[14,15,17] earlier than when using SCr. Cystatin C appears to be superior to SCr in detecting acute renal dysfunction[18-20] since it is less affected[21] or possibly not influenced by variations in muscle mass.[11-13,16] To date, limited studies have investigated the use of cystatin C–based-formulas for estimating the GFR in critical care patients[5,13]; consequently, the usefulness of these formulas has not been clearly defined.

KEY POINTS

- Serum creatinine–based formulas overestimate glomerular filtration rate in critically ill patients.
- The cystatin C–based equation is not more accurate than serum creatinine—based formulas for estimating glomerular filtration rate in critically ill patients.
- The cystatin C–based equation could provide valuable guidance when dosing medications in patients suspected of having a low glomerular filtration rate.

The purpose of this study was to assess the predictive performance of several equations for estimating the GFR using cystatin C or SCr compared with a reference method, $CL_{cr_{24hr}}$, in critically ill patients.

Methods

A retrospective observational study was performed in the medical intensive care unit (ICU) of a university hospital from October 2006 through September 2007. All consecutively admitted critically ill patients older than 18 years who stayed in the ICU for more than 48 hours with a urinary bladder catheter in place were included in the study. Patients with incomplete demographic and biochemical data or those subjected to renal replacement therapies were excluded from the study.

Data were obtained from in-house electronic health records and were registered in a database only available to the study's researchers. Demographic data (age, sex, race, height, and weight) were collected. Height and weight were taken from the most recent registered entry in the medical history or by asking the patient or his or her relatives. When the information was not believable or available, the attending staff measured the height with a tape measure and estimated patient weight.

This study was approved by the hospital's clinical research ethics committee, and informed consent was waived.

Data collection and analysis. Data collected included SCr, cystatin C, serum albumin, blood urea nitrogen, and $CL_{cr_{24hr}}$ levels. $CL_{cr_{24hr}}$ was obtained from urine and collected through a urinary bladder catheter. Blood and urine samples were collected in the morning once daily. For patients who had more than one measurement, samples were collected a minimum of three days apart to avoid repetition of the same data for the same patient.

All routine analyses were performed at the CORE laboratory facility at our hospital on an Advia 2400 analyzer (Siemens Healthcare, Tarrytown, NY). All reagents were provided by Siemens Healthcare. SCr and urine creatinine were measured using the Jaffé method with sample correction and traceable to IDMS standards (reference range, <1.3 mg/dL). Serum albumin measured using the bromocresol green method (reference range, 37–53 g/dL), and blood urea nitrogen was measured by the urease/glutamate dehydrogenase assay (reference range, 10–25 mg/dL). All measurements followed strict external quality control schemes and fulfilled established quality criteria.

Cystatin C was measured with a particle-enhanced nephelometry assay performed on a BN II (Siemens Healthcare) (reference range, 0.53–0.95 mg/L).

Equations used to estimate the GFR. $CL_{cr_{24hr}}$ was considered the reference method for estimating the GFR in our clinical daily routine. The following equations were used to determine the estimated GFR (eGFR) for all patients in the study:

- Arnal-Dade[22]:

eGFR (mL/min/1.73 m^2) = 74.835 / cystatin C in mg/$dL^{1.333}$

- Cockcroft-Gault[23] with actual body weight:
  eGFR (mL/min) = (140 – age in years) × actual body weight in kg / (72 × SCr in mg/dL) × 0.85 (if female)
- Cockcroft-Gault[23] with ideal body weight (IBW):
  eGFR (mL/min) = (140 – age in years) × IBW in kg / (72 × SCr in mg/dL) × 0.85 (if female)
- Jelliffe:[24]
  eGFR (mL/min/1.73 m^2) = (98 – [0.8 × {age in years – 20}]) × 0.9 (if female) / SCr in mg/dL
- Modification of Diet in Renal Disease (MDRD):[25]
  eGFR (mL/min/1.73 m^2) = 170 × (SCr in mg/$dL)^{-0.999}$ × (age in $years)^{-0.176}$ × 0.762 (if female) × 1.180 (if black race) × (blood urea nitrogen in $mg/dL)^{-0.170}$ × (serum albumin in $g/dL)^{0.318}$
- MDRD four-variable version (MDRD-4):[26]
  eGFR (mL/min/1.73 m^2) = 186 × (SCr in $mg/dL)^{-1.154}$ × $(age\ in\ years)^{-0.203}$ × 0.742 (if female) × 1.212 (if black race)

IBW was calculated using the Devine[27] equations:

IBW for males (kg) = 50 + 0.91 × ([height in cm]) – 152.4)

IBW for females (kg) = 45.5 + 0.91 × (height in cm) – 152.4

Body surface area (BSA) was determined using the Mosteller[28] equation:

BSA (m^2) = [(actual body weight in kg × height in cm / 3600)]$^{0.5}$

Statistical analysis. Statistical analysis was conducted using XLSTAT 2008 (Excel, Microsoft Corp.). Data were expressed as means, standard deviations, and ranges. Data from all samples were compared using Pearson's coefficient of determination (r^2) and Bland–Altman plots, which evaluated agreement and concordance. In a Bland–Altman plot, the averages of the eGFR obtained by the evaluated formula and the reference $CLcr_{24hr}$ are represented on the *x* axis, and the differences between the eGFR obtained by the evaluated formula and the reference $CLcr_{24hr}$ on the *y* axis. Agreement is determined by bias and precision. The closer the mean error (mean of the differences) is to 0, the less biased the agreement. Greater precision is related to less spreading of the averages and differences, defined by the 95% limits of agreement, which are given by the mean ± 1.96 standard deviations of the differences. Agreement was determined by considering the maximum number of points outside the range between the 95% limits of agreement, which was determined by multiplying the total number of differences by 0.05. Concordance was assessed by the observance of both agreement and randomized distribution of the points from the mean error.

A subanalysis using correlation and bias and precision box plots was performed in a split cohort, which included patients who had a $CLcr_{24hr}$ of ≥60 mL/min/1.73 m^2 and those who had a $CLcr_{24hr}$ of <60 mL/min/1.73 m^2. We chose the cutoff value of 60 mL/min/1.73 m^2 because it is the threshold suggested by the National Kidney Foundation for consideration of the diagnosis of chronic kidney disease.[29]

Bias was defined by calculating the mean of the percentage prediction error (%PE):

%PE = (predicted value – measured value) / measured value × 100

Precision was defined by calculating the mean of the absolute PE:

%|PE| = (|predicted value – measured value|) / measured value × 100

where measured value corresponds to $CLcr_{24hr}$.

The median values of the box plots provide the global bias and precision for each formula.[30]

Significance was defined as a two-tailed *p* of ≤0.05.

Table 1. Patient Demographics and Characteristics[a]

Variable	Mean ± S.D. (Range)
Age, yr	59.2 ± 18.8 (17–86)
Height, cm	167.4 ± 8.4 (150–197)
Actual body weight, kg	72.7 ± 14.3 (40–130)
Ideal body weight, kg	61.9 ± 9.1 (43.3–90.4)
Body surface area, m^2	1.8 ± 0.2 (1.31–2.40)
Body mass index, kg/m^2	26.0 ± 5.0 (12–51)
Blood urea nitrogen, mg/dL	32.5 ± 26.1 (4–165)
Serum albumin, g/dL	2.9 ± 0.5 (1.2–4.9)
Serum creatinine, mg/dL	1.0 ± 0.6 (0.5–4.55)
Serum cystatin C, mg/L	1.5 ± 0.9 (0.35–4.07)
$CLcr_{24hr}$, mL/min	84.6 ± 49.5 (7–231)

[a] $CLcr_{24hr}$ = 24-hour urine creatinine clearance.

Results

Patient demographics. This study included 241 measurements corresponding to 131 critically ill patients (samples per patient, 1–8), 82 (62.6%) of whom were male. A total of 41 measurements (17.0%) corre-

sponded to 22 obese patients (body mass index of >30 kg/m^2), and 9 measurements (3.7%) corresponded to 6 patients with a body mass index of <18.5 kg/m^2. The most common admitting diagnoses were infections (nearly 60% of patients), postsurgical admissions, and respiratory, cardiovascular and neurologic diseases (Table 1). The GFR estimates calculated are shown in Table 2. Ninety-five measurements from 54 patients corresponded to a $CL_{cr_{24hr}}$ of <60 mL/min/1.73 m^2.

Comparative analysis of the cystatin C–based equation and $CL_{cr_{24hr}}$. Significant correlation was found between the cystatin C–based equation and $CL_{cr_{24hr}}$ ($r^2 = 0.573$, $p < 0.05$) (Table 2).

Bland–Altman plots (Figure 1 and Table 2) revealed a bias or mean difference of –9.0, indicating an underestimation of $CL_{cr_{24hr}}$ with the cystatin C–based equation. The standard deviation of the mean differences or precision of the cystatin C equation was 32.2, with 95% limits of agreement of –72.0 to 54.0. We found no agreement between the cystatin C–based equation and the reference $CL_{cr_{24hr}}$, as 14 points were outside of the limits of agreement, exceeding the maximum of $n \times 0.05$ point outside the range (approximately 12). Absence of agreement and nonrandom distribution of the points indicated a lack of concordance between the cystatin C equation and $CL_{cr_{24hr}}$.

Regarding the subgroup analysis of patients with a $CL_{cr_{24hr}} \geq 60$ mL/min/1.73 m^2 and $CL_{cr_{24hr}}$ <60 mL/min/1.73 m^2 the correlations between cystatin C and $CL_{cr_{24hr}}$ were significant ($r^2 = 0.296$ and $r^2 = 0.214$, respectively) ($p < 0.05$) (Table 3). The cystatin C equation also underestimated $CL_{cr_{24hr}}$ in both groups, as indicated by their negative medians in the bias box plots (–16.7% and –21.3%, respectively) (Figure 2, Panels A and C, and Table 3). Precision box plot medians were 24.9% and 38.9% for the $CL_{cr_{24hr}} \geq 60$ mL/min/1.73 m^2 and < 60 mL/min/1.73 m^2 groups, respectively (Figure 2, Panels B and D, and Table 3). Therefore, lack of precision was present in both groups.

Comparative analysis of cystatin C–based and SCr-based formulas to $CL_{cr_{24hr}}$. When compared with the SCr-based equations, the cystatin C–based equation showed the highest correlation coefficients with $CL_{cr_{24hr}}$, whereas MDRD had the best correlation with $CL_{cr_{24hr}}$ among the different SCr-based equations (Table 2).

Bland–Altman plots (Figure 1 and Table 2) showed an overestimation of $CL_{cr_{24hr}}$ by every SCr-based equation, with positive mean errors. Regarding bias, the cystatin C–based equation (–9.0) was in an intermediate position. The most- and least-biased equations were MDRD-4 (21.8) and Cockcroft-Gault based on IBW (3.0), respectively. With respect to precision, there were no significant differences, as similar extensions of 95% limits of agreement were obtained in all equations. None of the equations fulfilled concordance requirements with the reference $CL_{cr_{24hr}}$.

In the subgroup of patients with a $CL_{cr_{24hr}}$ of ≥60 mL/min/1.73 m^2, the cystatin C–based equation was the best correlated with $CL_{cr_{24hr}}$ among all equations (Table 3). However, this equation had the second-most biased median (–16.7%) following the MDRD-4 (17.5%) and the worst precision median (24.9%). The Jelliffe formula was the least biased (–1.1%), and the MDRD was the most precise (21.3%). No significant differences

Table 2. Comparative Analysis of GFR Between $CL_{cr_{24hr}}$ and GFR Estimation Equations for All Study Patients (n = 131)[a]

Equation for Estimating GFR	Mean ± S.D. (Range) GFR Estimates (mL/min/1.73 m^2) for All Patients	r^2[b]	Bias[c]	Precision[d]
$CL_{cr_{24hr}}$	79.5 ± 45.5 (5.9–228.1)	NA	NA	NA
Cystatin C from Arnal-Dade equation[22]	70.5 ± 46.3 (11.5–303.3)	0.573	–9.0	32.2 (–72.0 to 54.0)
Cockcroft-Gault using actual body weight[23]	93.5 ± 45.9 (12.8–212.8)	0.552	14.0	32.8 (–50.2 to 78.1)
Cockcroft-Gault using ideal body weight[23]	82.5 ± 46.0 (9.5–221.4)	0.473	3.0	36.2 (–67.9 to 73.9)
Jelliffe[24]	84.0 ± 42.3 (11.8–180.7)	0.503	4.5	33.6 (–61.4 to 70.3)
MDRD[25]	82.9 ± 41.9 (10.3–187.2)	0.565	3.4	31.0 (–57.4 to 64.1)
MDRD-4[26]	101.3 ± 48.6 (12.1–206.1)	0.544	21.8	34.2 (–45.2 to 88.8)

[a]A total of 241 measurements were evaluated. GFR = glomerular filtration rate, $CL_{cr_{24hr}}$ = 24-hour urine creatinine clearance, NA = not applicable, MDRD = Modification of Diet in Renal Disease, MDRD-4 = four-variable version MDRD.

[b]$p < 0.05$ for all comparisons.

[c]Mean of the differences, calculated using Bland–Altman plots.

[d]S.D. with 95% limits of agreement of the mean differences, calculated using Bland–Altman plots.

Figure 1. Bland–Altman plots showing mean differences between prediction and reference values. Panel A depicts mean difference between Arnal-Dade from cystatin C and $CL_{Cr_{24hr}}$, Panel B depicts mean difference between the Cockcroft-Gault calculated using actual body weight and $CL_{cr_{24hr}}$, Panel C depicts mean difference between Cockcroft-Gault calculated using actual body weight and $CL_{Cr_{24hr}}$, Panel D depicts mean difference between Jelliffe equation and $CL_{Cr_{24hr}}$, Panel E depicts mean difference between MDRD and $CL_{Cr_{24hr}}$, and Panel F depicts mean difference between MDRD-4 and $CL_{Cr_{24hr}}$. CC = Arnal-Dade equation from cystatin C clearance, $CL_{Cr_{24hr}}$ = 24-hour urine creatinine clearance, CG-RW = Cockcroft-Gault equation using actual body weight, CG-IW = Cockcroft-Gault equation using ideal body weight, MDRD = Modification of Diet in Renal Disease, MDRD-4 = four-variable version MDRD.

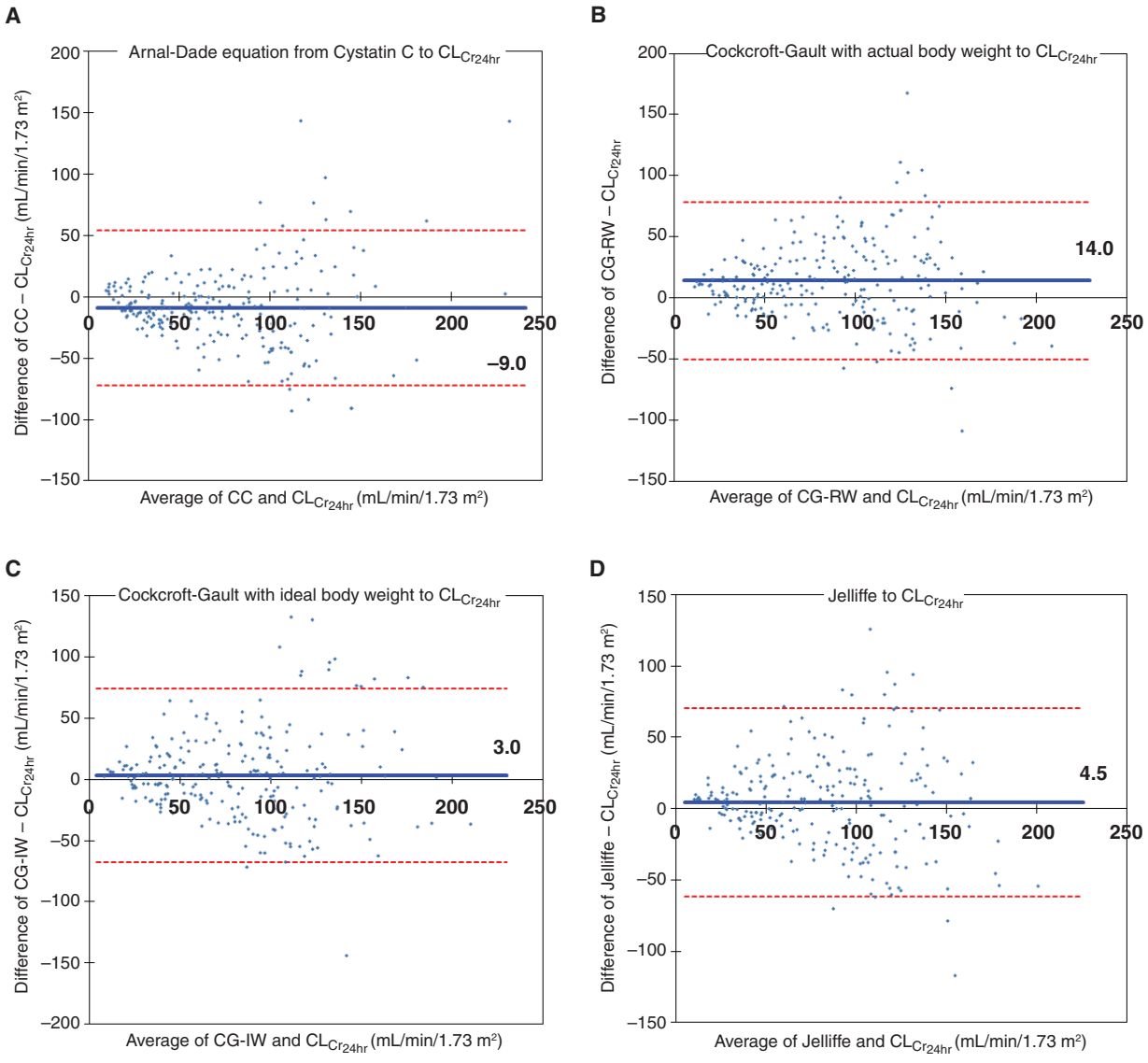

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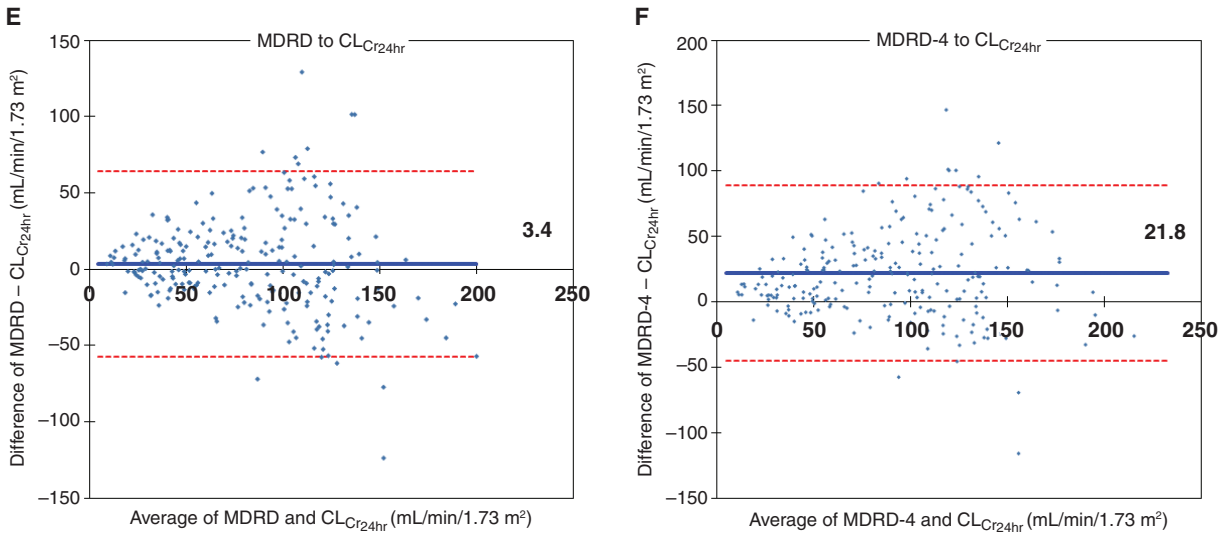
Figure 1 *(continued)*



in precision among all equations were seen. In this group of patients with normal renal function, four equations underestimated CL_{cr24hr}; interestingly, the cystatin C–based equation had the most pronounced underestimation value (Figure 2 and Table 3).

In the subgroup of patients who had a CL_{cr24hr} of <60 mL/min/1.73 m², the cystatin C–based equation showed one of the worst correlation indexes of the studied equations, and the MDRD had the best correlation ($r^2 = 0.299$, $p < 0.05$) (Table 3). Bias box plots showed that the cystatin C–based equation underestimated CL_{cr24hr} in this group of patients with decreased renal function. In contrast, all SCr-based equations overestimated these values. The cystatin C–based equation (–21.3%) was the least biased, followed by Cockcroft-Gault based on IBW (22.4%), whereas MDRD-4 had the greatest bias (62.7%). In terms of precision, great variability was present among all equations, where MDRD (33.5%) showed better results than the cystatin C–based equation (38.9%) (Figure 2 and Table 3).

Discussion

This study found no evidence of superiority of cystatin C–based equation performance over the SCr-based equations. The results also revealed a clear underestimation of CL_{cr24hr} by the cystatin C–based equation at low values of CL_{cr24hr} (<60 mL/min/1.73 m²), indicating that the cystatin C–based equation could provide valuable guidance in patients with a suspected low GFR, as SCr-based equations provided misleading eGFR values.

The eGFR predictive performances of several equations based on cystatin C alone or with other variables is not superior to SCr-based equations in adult non-ICU patients.[22,31-34] However, in ICU patients, there are more limited data of cystatin C comparisons with different references.[5,13,18-20] To date, cystatin C has mainly been used as a marker for early detection of acute kidney injury[11,14,15,17,35] or discrimination of normal from low GFRs[17,18-20,34] rather than for GFR estimation.[5,13]

Creatinine production can vary greatly, depending on factors commonly present in critically ill patients (e.g., muscle mass, thyroid disease, inflammation, corticotherapy). It is for this reason that attempts have been made to find a reliable SCr-based formula for GFR estimation. Cystatin C appears to be much more stable and less influenced by other variables[10-12]; therefore, it could offer a more reliable GFR estimate in these patients. However, there is controversy that the aforementioned factors that influence SCr may also affect cystatin C levels, albeit to a lesser extent.[10-13,16,21,31,32,36,37] In some critically ill patients, cystatin C levels could be affected by other nonrenal factors, such as inflammation, rather than the renal condition.[12,34,38]

We demonstrated that the cystatin C–based equation underestimated CL_{cr24hr}, both in the whole cohort and in the two studied subgroups depending on CL_{cr24hr}. In contrast, every SCr-based equation we analyzed overestimated CL_{cr24hr} in the whole cohort and in the group with a CL_{cr24hr} of <60 mL/min/1.73 m². There may be several explanations for this.

SCr-based equations have been shown to overestimate the actual

Figure 2. Bias and precision box plots. Panel A depicts bias box plots of $CL_{Cr_{24hr}} \geq 60$ mL/min/1.73 m^2, Panel B depicts precision box plots of $CL_{Cr_{24hr}} \geq 60$ mL/min/1.73 m^2, Panel C depicts bias box plots of $CL_{Cr_{24hr}} < 60$ mL/min/1.73 m^2, and Panel D depicts precision box plots of $CL_{Cr_{24hr}} < 60$ mL/min/1.73 m^2. CC = Arnal-Dade equation from cystatin C clearance, $CL_{Cr_{24hr}}$ = 24-hour urine creatinine clearance, CG-RW = Cockcroft-Gault equation using actual body weight, CG-IW = Cockcroft-Gault equation using ideal body weight, MDRD = Modification of Diet in Renal Disease, MDRD-4 = four-variable version MDRD.

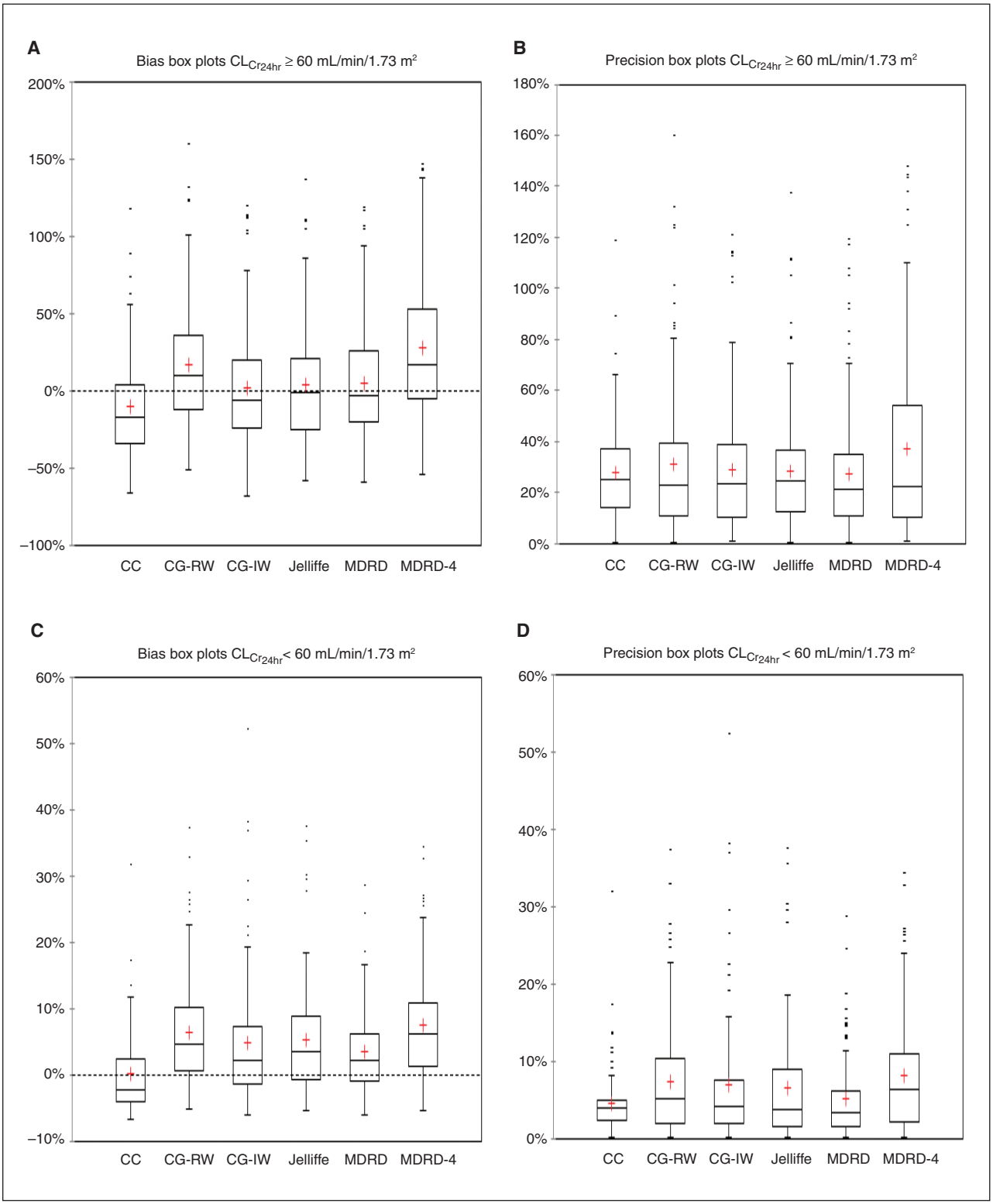


Table 3. Comparative Analysis of GFR Between $CL_{cr_{24hr}}$ and GFR Estimation Equations in Patients With $CL_{cr_{24hr}}$ of ≥60 and <60 mL/min/1.73 m²[a]

Equation for Estimating GFR	$CL_{cr_{24hr}}$ ≥ 60 mL/min/1.73 m² (*n* = 77)[b]			$CL_{cr_{24hr}}$ < 60 mL/min/1.73 m² (*n* = 54)[c,45]		
	r^2[d]	Bias[e]	Precision[f]	r^2[d]	Bias[e]	Precision[f]
Cystatin C from Arnal-Dade equation[22]	0.296	–16.7	24.9	0.214	–21.3	38.9
Cockcroft-Gault using actual body weight[23]	0.197	10.2	22.5	0.236	45.8	50.3
Cockcroft-Gault using ideal body weight[23]	0.206	–5.8	23.2	0.157	22.4	41.9
Jelliffe[24]	0.178	–1.1	24.2	0.218	35.9	37.0
MDRD[25]	0.182	–2.4	21.3	0.299	23.2	33.5
MDRD-4[26]	0.158	17.5	22.2	0.286	62.7	62.7

[a]GFR = glomerular filtration rate, $CL_{cr_{24hr}}$ = 24-hour urine creatinine clearance, MDRD = Modification of Diet in Renal Disease, MDRD-4 = four-variable version MDRD.

[b]A total of 146 measurements were evaluated.

[c]A total of 95 measurements were evaluated.

[d]$p < 0.05$ for all comparisons.

[e]Mean of percentage prediction error, calculated as follows: (Predicted value – measured value before division sign/ measured value) × 100, where measured value corresponds to $CL_{cr_{24hr}}$.

[f]Mean of absolute percentage error, calculated as follows: (|predicted value – measured value|) / measured value × 100, where measured value corresponds to $CL_{cr_{24hr}}$.

GFR, and thus renal function, in critically ill patients due to (1) the presence of SCr tubular secretion[2,4-9] and (2) the influence of certain clinical situations that decrease SCr values over time (which falsely elevate GFRs),[11-13,35] such as immobilization and malnourishment (resulting in a loss of muscle mass), sepsis, liver impairment, and positive fluid balance (possibly "diluting" SCr levels).[1-4,7-13] Contrarily, cystatin C values decrease less[11] or even increase over time, at least during the first week after ICU admission.[11,12,35] Although cystatin C would be affected by overhydration, similar to SCr, it may not be influenced as much by the aforementioned factors that affect SCr.

On the other hand, cystatin C has a higher sensitivity as a renal function marker than does SCr in critically ill patients, since cystatin C levels detect changes in the GFR 6–48 hours earlier compared with SCr levels,[11,14,15,17] especially in the setting of acute renal dysfunction.[4,11,14,15,17-20] In two previous studies involving critically ill patients, cystatin C was notably more likely than equations calculated from plasma creatinine levels to detect low GFRs, defined as $CL_{cr_{24hr}}$ of <80 mL/min/1.73 m².[19,20] Lipcsey et al.[4] also found that a cystatin C–based equation performed far better (92%) than plasma creatinine levels (46%) or the MDRD (47%) in patients with an eGFR of <80 mL/min/1.73 m². More recently, Delanaye et al.[34] found that cystatin C was superior in detecting a GFR of <60 mL/min, though the CKD-Epidemiology Collaboration with cystatin C and the combined equation (SCr and cystatin C) did not improve GFR estimations compared with SCr-based equations, possibly due to the fact that the equations were developed in noncritically ill populations. However, some other studies have questioned the value of cystatin C for the detection of acute kidney failure.[35]

Cystatin C–based equations could be more sensitive to decreases in the GFR because, as cystatin C is a larger molecule than SCr, glomerular filtration of cystatin C gets impaired earlier and to a greater extent with the reduction of glomerular pore size.[12] Furthermore, cystatin C has a half-life of two hours, three times shorter than that of SCr in humans with normal renal function[13,16] and therefore reaches steady state faster.[13]

Finally, one potential limitation of cystatin C–based equations is that some cystatin C studies have revealed a lower specificity of cystatin C compared with SCr,[18,39] with a higher proportion of false-positive values among patients with normal GFRs. However high negative predictive value associated with levels of cystatin C < 0.80 mg/L has also been reported, suggesting cystatin C could be a useful tool for ruling out the diagnosis of renal dysfunction.[39] Although there is a lack of evidence to change medication dosing based on the cystatin C equation at this time, high levels of cystatin C should at least heighten the clinician's awareness of the possibility for the development of renal dysfunction.

We also found that all SCr-based equations overestimated $CL_{cr_{24hr}}$ at lower values (<60 mL/min/1.73 m²), bias values among different GFR estimations were fairly variable, that MDRD-4 showed the

highest bias in both the entire cohort and the two subgroups, and that MDRD showed the best precision, especially in the subgroup with the lower GFR (<60 mL/min/1.73 m^2). Although comparison of our data with other studies could be difficult due to differences in population and methodology,[5,31,32,39] other authors have also reported an overestimation of the GFR when using SCr-based equations in critically ill patients.[2,5,34] While a number of previous studies have detected a high level of bias with the MDRD-4 equation,[7,34] results have been inconsistent.[1,5] However, other studies have reported different results, with no differences or even an underestimation of the actual GFR by SCr-based equations.[1,3,7] Regarding the absence of notable precision differences and no equation fulfilling concordance requirements with $CL_{cr_{24hr}}$, several studies have found similar results.[1-3,5,7,34]

This study had several limitations. First, $CL_{cr_{24hr}}$ was used as a reference method. Ideal $CL_{cr_{24hr}}$ measurement requires a steady-state situation,[7,23] which is rarely present in critically ill patients.[1-3,5,7,9] However, $CL_{cr_{24hr}}$ is currently the most used filtration marker to assess renal function in daily clinical practice in the ICU setting and has often been used as a reference method in the literature for validating GFR-estimating equations in this population.[2,3,7,19,20] Second, there was no sample-size calculation, as we included every patient who met the inclusion criteria. Third, the Jelliffe, Cockcroft-Gault using actual body weight and Cockcroft-Gault using IBW equations produce $CL_{cr_{24hr}}$ estimations, whereas the cystatin C–based, MDRD, and MDRD-4 equations estimate the GFR. Nevertheless, in literature and clinical practice, both $CL_{cr_{24hr}}$ and GFR values are used interchangeably.[9] Fourth, standardization of every measured $CL_{cr_{24hr}}$ value by BSA was needed to effectively compare all the studied methods. However, BSA could distort the creatinine clearance in obese patients (17.0% of the measurements) or low-weight patients (3.7% of the measurements).[40] Creatinine clearance could also be incorrect in patients with altered total body water,[1,5,12] which occurs quite frequently in ICU patients, as the correlation between BSA and lean body mass may be lost.[40] Regrettably, in this study, body weight was recorded only once, despite its noteworthy susceptibility of changes during the ICU stay, as this was a retrospective study and body weight was rarely registered more than once during the ICU stay.[12] Finally, SCr and cystatin C reference intervals and equations were derived from non-ICU populations, and their performance worsens in other populations,[3,7,9,10,22,31,32,39] laboratory methods, or GFR references.[9-12,31-33,39,41]

Conclusion

A retrospective observational study showed no evidence of superiority of a cystatin C–based equation over SCr-based equations to estimate GFR in an ICU population.

Disclosures

The authors have declared no potential conflicts of interest.

Additional information

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