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Clinical Investigation

Impact of Recent Acute Kidney Injury on Creatinine Clearance Estimation in Critically Ill Patients Undergoing Cardiac Surgery

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Acute kidney injury (AKI), often present in critically ill patients and patients with cardiac dysfunction, may alter estimates of renal function. The impact of recent AKI on the accuracy of the Cockcroft-Gault creatinine clearance equation (CG-CrCl) before cardiac surgery is unknown.

This single-center, retrospective study included patients who underwent cardiac surgery from 1 January 2006 through 30 June 2012 and whose 24-hour urine creatinine clearance (24hr-CrCl) was measured in the intensive care unit before surgery. We evaluated CG-CrCl accuracy by calculating absolute differences between 24hr-CrCl and CG-CrCl estimates. Clinical impact was signified by discrepancies in United States Food and Drug Administration (FDA) renal impairment stage indicated by 24hr-CrCl versus CG-CrCl estimates. Acute kidney injury was evaluated by using Kidney Disease: Improving Global Outcomes criteria.

Of 161 patients, 93 (58%) had recent AKI: stage 1, 31 (33%); stage 2, 39 (42%); and stage 3, 23 (25%). In mL/min, the CG-CrCl overestimated 24hr-CrCl (absolute difference: total, −10 ± 25; no AKI, −7 ± 26; stage 1, −8 ± 17; stage 2, −16 ± 28; and stage 3, −10 ± 26; P=*0.29). Renal impairment stages assigned by CG-CrCl did not match 24hr-CrCl in 70 (43%) of the 161 patients, especially those with recent AKI: no AKI, 24/68 (35%); stage 1, 13/31 (42%); stage 2, 23/39 (59%); and stage 3, 10/23 (43%).*

The CG-CrCl consistently overestimated 24hr-CrCl in critically ill patients before cardiac surgery. Clinicians should use the CG-CrCl cautiously when estimating renal function and medication dosages in this population. ***(Tex Heart Inst J 2022;49(3):e207382)***

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Acute kidney injury (AKI) occurs in 36% to 67% of critically ill patients, 5% to 6% of whom ultimately need renal replacement therapy.[1] Furthermore, AKI is associated with long hospital and intensive care unit (ICU) stays, high hospital costs, and high mortality rates.[2,3] To optimize dosages of medications eliminated by the kidneys, maximize medication effectiveness, and avoid adverse effects, renal function must be evaluated accurately in critically ill patients who are scheduled for cardiac surgery.

The Cockcroft-Gault creatinine clearance equation (CG-CrCl) is widely used to approximate the glomerular filtration rate, and the United States Food and Drug Administration (FDA) has adopted it as a standard method for determining renal dosage adjustments in pharmacokinetic studies.[4,5] However, the equation's numerous constraints may limit its accuracy among critically ill patients who have large fluctuations in renal function.[4] Limited mobility, older age, lost muscle mass, and protein malnutrition in this population can decrease serum creatinine (SCr) values and perhaps alter CG-CrCl estimates.[6-11] The CG-CrCl also performs poorly during ongoing AKI and should not be used when kidney function is deteriorating rapidly. Erroneous estimates of kidney function can lead to medication dosage errors, inadequate treatment, further kidney damage, and poor clinical outcomes.

Urine collection over 24 hours to measure creatinine clearance (24hr-CrCl) is the reference standard for evaluating renal function in pharmacokinetic studies, and it is the criterion for validating equations that enable estimation of renal function.[4,12,13] However, 24hr-CrCl measurement is not routinely feasible in ICU patients; instead, ICU clinicians typically use SCr and the CG-CrCl to estimate renal function.

The accuracy of the CG-CrCl has been evaluated among critically ill patients after cardiac surgery.[14] The degree of discrepancy among patients with recent AKI is unknown. Therefore, we studied CG-CrCl accuracy by comparing it with the reference-standard 24hr-CrCl among ICU patients with recent AKI who were scheduled for cardiac surgery. We hypothesized that the CG-CrCl would overestimate 24hr-CrCl among ICU patients with recent AKI, and that this difference would be largest for those with severe AKI. Furthermore, we expected that overestimating 24hr-CrCl would lead to misclassification of patients according to FDA renal impairment stages and thus particularly affect medication dosage decisions.

Patients and Methods

This single-center, retrospective cohort study included patients admitted to one of 2 ICUs before cardiac surgery at an academic medical center between 1 January 2006 and 30 June 2012. For study inclusion, patients had to have undergone at least one preoperative 24hr-CrCl measurement as part of routine care in accordance with institutional evaluation protocols. Patients were excluded when daily SCr or hourly urine output was not available during the AKI evaluation period (described below) or when urine was collected for less than or more than 24 hours.[15] Patients who had a transplanted kidney or who underwent dialysis during urine collection were also excluded. When patients had more than one 24hr-CrCl measurement, only the index measurement was included. Our medical center's institutional review board approved this study and waived requirements for informed consent.

Severity of Acute Kidney Injury

Recent AKI was detected and staged according to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines during the observation period between ICU admission and the start of 24-hour urine collection.[16] To detect AKI, we used one of 3 criteria: a ≥0.3-mg/dL absolute increase in SCr within a 48-hour rolling window, a ≥50% relative increase in SCr within a 7-day rolling window, or urine output at a rate of <0.5 mL/kg/hr for 6 hours.

The AKI was staged as follows: no AKI; stage 1 if SCr increased to 1.5 to 1.9 times the baseline level, if SCr increased by ≥0.3 mg/dL, or if the rate of urine output was <0.5 mL/kg/hr for 6 to 12 hours; stage 2 if SCr increased to 2.0 to 2.9 times the baseline level or the rate of urine output was <0.5 mL/kg/hr for ≥12 hours; and stage 3 if SCr increased to 3.0 times the baseline level, if SCr increased to ≥4 mg/dL, if the rate of urine output was <0.3 mL/kg/hr for ≥24 hours, if anuria lasted ≥12 hours, or if kidney replacement therapy was initiated.[16] Patients were classified according to the highest stage of AKI observed before 24-hour urine collection began. Stable SCr was defined as a change in SCr of less than 0.3 mg/dL during the 48 hours before urine collection.

Outcome Measures

Serum creatinine and urine output values were extracted from the patient's electronic medical records. A "collection SCr" that was obtained from the 24-hour urine collection was used for the analyses. This collection SCr sample was usually drawn with the morning laboratory samples.

Two modifications were introduced to potentially improve the CG-CrCl calculation: using adjusted body weight (AdjBW; actual body weight adjusted by a correction factor of 0.4 when body mass index was ≥25); and rounding SCr values ≤1 mg/dL up to 1 mg/dL in patients ≥65 years of age.[17-22] Therefore, 3 versions of the CG-CrCl equation were used to estimate SCr clearance (Supplemental Equations):

1) CG-CrCl with use of actual body weight and the exact collection SCr,
2) CG-CrCl 0.4 with use of AdjBW and the exact collection SCr, and
3) CG-CrCl 0.4 round with use of AdjBW and the rounded collection SCr.

We used 24hr-CrCl as the reference standard. The primary endpoint was the absolute difference between 24hr-CrCl and CG-CrCl estimates, stratified across KDIGO stages of AKI. A positive difference indicated underestimation of 24hr-CrCl by the CG-CrCl, and a negative difference indicated overestimation.

The secondary endpoint was discrepancy between FDA renal impairment stages indicated by 24hr-CrCl versus CG-CrCl estimates, because disagreement between stages may influence the dosages of medications that are cleared by the kidney. The FDA defines 5 stages that guide medication dosage: normal function (CrCl >80 mL/min), mild impairment (CrCl 50–80 mL/min), moderate impairment (CrCl 30–49 mL/min), severe impairment (CrCl 15–29 mL/min), and end-stage disease (CrCl <15 mL/min or dialysis).[5]

Statistical Analysis

The primary analysis for the absolute difference between 24hr-CrCl and CG-CrCl measurements among AKI stages was conducted by using analysis of

variance (ANOVA) with Bonferroni-corrected *P* values for pairwise comparisons. The secondary analysis for the discrepancy between FDA renal impairment stages among AKI stages was conducted by using a χ^2 test. Agreement between FDA stages was evaluated by using the weighted κ statistic (Supplemental Equations). Multivariable linear and logistic regressions and CG-CrCl 0.4 and CG-CrCl 0.4 round were used to conduct sensitivity analyses (Supplemental Equations). The covariates for multivariable regressions were selected on the basis of biologic plausibility. Using ANOVA with an assumed standard deviation of 30 mL/min and including at least 84 patients (21 patients in each of 4 groups) provided 80% power to detect a significant difference in CrCl of 10 mL/min between AKI stages. A 2-sided *P* value <0.05 was considered statistically significant. Analyses were conducted with use of Stata 15 (StataCorp LLC).

Results

In total, 161 patients (mean age, 59 ± 14 yr) admitted to a cardiac ICU (79%) or a cardiothoracic surgery ICU (21%) were included in the study (Fig. 1). The population was predominantly male (114/161, 71%) and not black (117/161, 73%) (Table I). The mean ICU length of stay before urine collection was 2 ± 3 days. The mean SCr value at hospital admission was 1.6 ± 0.9 mg/dL, and the mean collection SCr value was 1.6 ± 1.0 mg/dL. Urine collection was systematically ordered as part of cardiac evaluation for heart failure (98/161, 61%), left ventricular assist device implantation (55/161, 34%), heart transplantation (6/161, 4%), and extracorporeal membrane oxygenation (2/161, 1%). Four patients (2%) underwent dialysis, on average 2 ± 1 days before urine collection. During urine collection, furosemide was administered to 103 patients (64%), and vasopressin to 11 patients (7%).

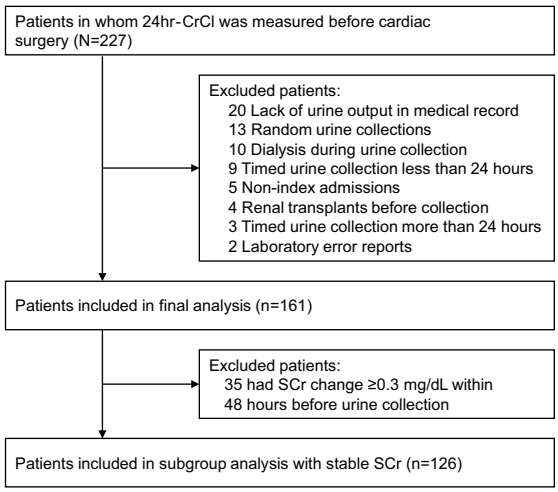

Fig. 1 *Diagram shows the selection of patients included in the study.*

24hr-CrCl = creatinine clearance from using 24-hour urine collection; ICU = intensive care unit; SCr = serum creatinine

Absolute Differences in Creatinine Clearance

Of the 161 patients, 93 (58%) had recent AKI (Table I). Of these 93 patients, 31 (33%) had stage 1 AKI; 39 (42%), stage 2; and 23 (25%), stage 3. The mean 24hr-CrCl was 62 ± 38 mL/min, and the mean CG-CrCl was 72 ± 39 mL/min. The CG-CrCl overestimated the 24hr-CrCl by 10 ± 25 mL/min (Table II and Fig. 2).

In the primary analysis, no differences were found between 24hr-CrCl and CG-CrCl estimates when stratified by recent AKI stage (overall *P*=0.29), and also none for pairwise comparisons (all *P* >0.05). In the unadjusted linear regression, CG-CrCl overestimated the 24hr-CrCl by 10 mL/min for patients with stage 2 as compared with no AKI (*P*=0.06), but not significantly (Supplemental Table I). In the multivariable linear regression adjusted for covariates, the absolute differences between 24hr-CrCl and CG-CrCl by AKI stage did not differ. When compared with the original CG-CrCl that used actual body weight, the 24hr-CrCl was more closely estimated by CG-CrCl 0.4 (*P* <0.001) and by CG-CrCl 0.4 round (*P* <0.001).

Differences in FDA Stage

Discrepancies in FDA renal impairment stage on the basis of CG-CrCl and 24hr-CrCl were observed in 70 patients (43%) (Table II). Agreement between 24hr-CrCl and CG-CrCl was moderate overall (κ=0.59) but was worse in patients with AKI (κ=0.67 for no AKI versus κ=0.53 for stage 1 AKI, κ=0.48 for stage 2, and κ=0.54 for stage 3) (Table III). The CG-CrCl overestimated 24hr-CrCl by ≥2 FDA stages in 13 patients (8%), and this overestimation increased along with AKI stage: 3 patients (4%) with no AKI, 2 patients (6%) with stage 1 AKI, 4 patients (10%) with stage 2, and 4 patients (17%) with stage 3. Logistic regression revealed that CG-CrCl disagreed with 24hr-CrCl for stage 2 AKI as compared with no-AKI patients in unadjusted analyses (odds ratio=2.6; 95% CI, 1.2–5.9, *P*=0.02) and adjusted analysis (odds ratio=2.7; 95% CI, 1.1–6.5, *P*=0.03) (Supplemental Table II). Discrepancies between 24hr-CrCl and CG-CrCl 0.4 and CG-CrCl 0.4 round are reported in Supplemental Tables III and IV, respectively.

Absolute Differences in Creatinine Clearance in Patients with Stable Serum Creatinine Levels

Within the 48 hours before urine collection, 126 patients (78%) had stable SCr. In an unadjusted linear regression, CG-CrCl overestimated 24hr-CrCl for patients with recent stage 2 AKI by 9 mL/min (*P*=0.13)

TABLE I. Baseline Characteristics in Accordance With KDIGO Acute Kidney Injury Stage

Variable or Covariate	No AKI (n=68)	Stage 1 (n=31)	Stage 2 (n=39)	Stage 3 (n=23)	Total (N=161)	*P* Value
Age[a] (yr)	60 ± 14	59 ± 13	60 ± 15	56 ± 15	59 ± 14	0.69
Male[a]	51 (75)	22 (71)	26 (67)	15 (65)	114 (71)	0.74
Black[a]	19 (28)	5 (16)	13 (33)	7 (30)	44 (27)	0.43
Actual body weight (kg)	85 ± 25	80 ± 17	87 ± 23	90 ± 17	85 ± 22	0.33
Body mass index[a]	—	—	—	—	—	0.24
<25	27 (40)	13 (42)	11 (28)	3 (13)	54 (34)	—
25–29	18 (26)	9 (29)	10 (26)	9 (39)	46 (29)	—
≥30	23 (34)	9 (29)	18 (46)	11 (48)	61 (38)	—
Urine collection location	—	—	—	—	—	0.03
Cardiac ICU	57 (84)	25 (81)	30 (77)	15 (65)	127 (79)	—
Cardiothoracic surgery ICU	11 (16)	6 (19)	9 (23)	8 (35)	34 (21)	—
ICU stay before urine collection[a] (d)	1 ± 2	2 ± 3	3 ± 2	4 ± 4	2 ± 3	<0.01
Dialysis before urine collection	0	0	0	4 (17)	4 (2)[b]	<0.01
Time from dialysis to urine collection (d)	—	—	—	2 ± 1	2 ± 1	—
Furosemide use[a,c]	44 (65)	23 (74)	21 (54)	15 (65)	103 (64)	0.37
Vasopressin use[c]	3 (4)	3 (10)	4 (10)	1 (4)	11 (7)	0.58
Collection SCr[d] (mg/dL)	1.4 ± 0.8	1.7 ± 0.8	1.7 ± 0.8	2.1 ± 1.5	1.6 ± 1	0.02
SCr at admission[a] (mg/dL)	1.6 ± 1	1.5 ± 0.8	1.7 ± 0.7	1.8 ± 1	1.6 ± 0.9	0.63
SCr >1.5 mg/dL at admission	27 (40)	9 (29)	19 (49)	12 (52)	67 (42)	0.26

AKI = acute kidney injury; ICU = intensive care unit; KDIGO = Kidney Disease: Improving Global Outcomes; SCr = serum creatinine

[a] Included in the multivariable model for sensitivity analyses

[b] Continuous renal replacement therapy (n=2, 1%) and intermittent hemodialysis (n=2, 1%)

[c] Medication use during 24-hour urine collection

[d] Serum creatinine value obtained from 24-hour urine collection

Data are presented as mean ± SD or as number and percentage. *P* <0.05 was considered statistically significant.

and for those with recent stage 3 AKI by 12 mL/min (*P*=0.12) relative to patients with no AKI, although the differences were not significant (Supplemental Table V). In a multivariable linear regression analysis adjusted for covariates, the absolute differences in creatinine clearance between patients with AKI and patients with no AKI were attenuated and not significant.

Discussion

In this retrospective analysis, we compared 2 creatinine-clearance estimation methods (the CG-CrCl equation and the urinalysis-based 24hr-CrCl) among ICU patients before cardiac surgery. Three versions of the CG-CrCl were evaluated.

The 58% incidence of AKI observed in this study is consistent with previous studies of critically ill patients.[1,23-26] We found that the CG-CrCl overestimated renal function among ICU patients before cardiac surgery. Unexpectedly, the primary unadjusted analysis and sensitivity-adjusted analyses did not yield significant associations between AKI stage and the magnitude of difference between the 24hr-CrCl and the CG-CrCl estimates.

Adjustment for body weight (CG-CrCl 0.4) improved the accuracy of the estimates. However, including the rounded SCr for patients ≥65 years old (CG-CrCl 0.4 round) did not appear to improve equation accuracy further. The 3 CG-CrCl versions agreed moderately to substantially with 24hr-CrCl for assigning patients into FDA renal impairment stages. The performance was worse for stage 2 AKI when CG-CrCl was used (κ=0.48; proportion with discrepancy, 59%). However, using AdjBW improved the performance for stage 3 AKI (CG-CrCl, κ=0.54; CG-CrCl 0.4, κ=0.70; and CG-CrCl 0.4 round, κ=0.66). Thus, for critically ill patients with recent AKI, using AdjBW instead of actual body weight improved the accuracy of CG-CrCl estimates.

Clinical relevance was evaluated by assigning patients into FDA renal impairment stages and comparing CG-CrCl with 24hr-CrCl. Because the FDA stages are often

used to guide medication dosages, assignment to the wrong stage may result in a medication dosage error. The CG-CrCl was incorrect for 43% of patients and consistently overestimated renal function—a clinically relevant finding. The discrepancies were larger and more prevalent in patients with recent stage 2 AKI.

Results of previous studies indicate that CG-CrCl inaccurately estimates renal function among patients who have AKI, because their SCr levels are unstable[4,27,28]; our study adds to this evidence by showing that CG-CrCl inaccurately estimates renal function in patients who have recent AKI before cardiac surgery, even if their SCr level has been stable during the previous 48 hours. Using 24hr-CrCl to measure and monitor renal function is more expensive and burdensome than using CG-CrCl is; however, using 24hr-CrCl might be indicated for prescribing narrow therapeutic medications that are cleared by the kidneys to critically ill patients who have recent AKI. Further research in a broader group of critically ill patients is needed to identify additional risk factors associated with clinically significant discrepancies between measured and calculated creatinine clearance.

TABLE II. Creatinine Clearance at Time of Urine Collection in Accordance With KDIGO Acute Kidney Injury Stage

Variable	No AKI (n=68)	Stage 1 (n=31)	Stage 2 (n=39)	Stage 3 (n=23)	Total (N=161)	*P* Value
Creatinine clearance (mL/min)						
24hr-CrCl	74 ± 42	50 ± 28	50 ± 31	61 ± 43	62 ± 38	<0.01
CG-CrCl	81 ± 41	59 ± 27	67 ± 40	71 ± 42	72 ± 39	0.04
CG-CrCl 0.4	72 ± 35	53 ± 26	56 ± 29	59 ± 35	62 ± 33	0.02
CG-CrCl 0.4 round	70 ± 35	53 ± 26	55 ± 28	59 ± 35	61 ± 33	0.03
Difference from 24hr-CrCl estimate (mL/min)						
CG-CrCl	–7 ± 26	–8 ± 17	–16 ± 28	–10 ± 26	–10 ± 25	0.29
CG-CrCl 0.4	3 ± 25	–2 ± 15	–5 ± 20	2 ± 22	0 ± 22	0.28
CG-CrCl 0.4 round	4 ± 26	–2 ± 15	–4 ± 20	2 ± 23	1 ± 23	0.22
Discrepancy in FDA renal impairment stages based on the 24hr-CrCl versus CG-CrCl estimates						
CG-CrCl	24 (35)	13 (42)	23 (59)	10 (43)	70 (43)	0.13
CG-CrCl 0.4	27 (40)	16 (52)	22 (56)	8 (35)	73 (45)	0.23
CG-CrCl 0.4 round	30 (44)	16 (52)	20 (51)	9 (39)	75 (47)	0.72

24hr-CrCl = creatinine clearance from using 24-hour urine collection; AKI = acute kidney injury; CG-CrCl = creatinine clearance from using Cockcroft-Gault equation with actual body weight and exact collection serum creatinine; CG-CrCl 0.4 = CG-CrCl from using adjusted body weight with correction factor of 0.4 if body mass index was ≥25 and exact collection serum creatinine; CG-CrCl 0.4 round = CG-CrCl from using adjusted body weight with correction factor of 0.4 if body mass index was ≥25 and serum creatinine was rounded up to 1 mg/dL in patients ≥65 years of age; FDA = United States Food and Drug Administration; KDIGO = Kidney Disease: Improving Global Outcomes

Data are presented as mean ± SD or as number and percentage. *P* <0.05 was considered statistically significant.

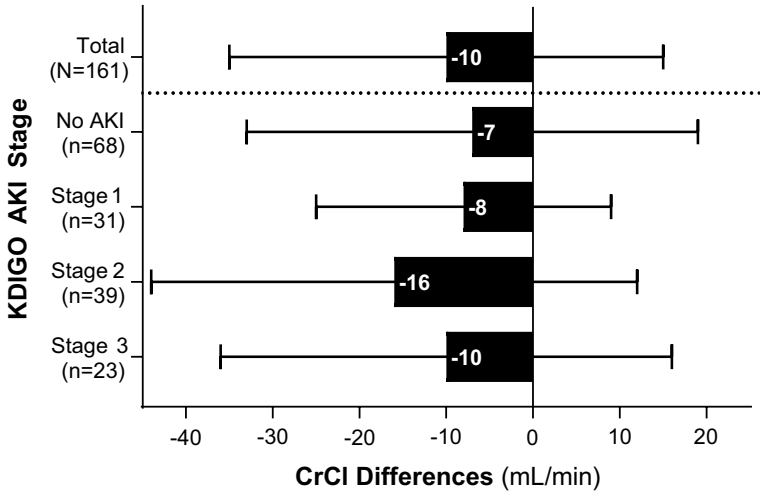

Fig. 2 *Graph shows mean difference between 24hr-CrCl and CG-CrCl by KDIGO AKI stage. Boxes show unadjusted mean differences, and bars show SD. A negative mean difference for 24hr-CrCl minus CG-CrCl indicates that the CG-CrCl overestimated true renal function; a positive difference indicates underestimated function. Overall, the CG-CrCl overestimated renal function in patients with a recent history of in-hospital AKI, and this effect was largest for patients with recent stage 2 or 3 AKI.*

24hr-CrCl = creatinine clearance from using 24-hour urine collection; AKI = acute kidney injury; CG-CrCl = creatinine clearance by Cockcroft-Gault equation; KDIGO = Kidney Disease: Improving Global Outcomes

Study Limitations

This retrospective study used secondary data from electronic medical records of patients from 2 ICUs at a single medical center. Inconsistent nursing practices related to documentation of urine output in the ICU may have influenced the detection of AKI. Acute heart

TABLE III. Cross-Tabulation of FDA Renal Impairment Stages on the Basis of Creatinine Clearance Estimated by 24hr-CrCl Versus CG-CrCl

	24hr-CrCl						
CG-CrCl	**Normal**	**Mild**	**Moderate**	**Severe**	**ESRD**	**Total**	**κ**
Total cohort[a]							
Normal	29	12	6	0	0	47	—
Mild	7	19	12	3	0	41	—
Moderate	0	6	31	10	4	51	—
Severe	0	0	3	10	5	18	—
ESRD	0	0	1	1	2	4	—
Total	36	37	53	24	11	161	0.59
No AKI[b]							
Normal	18	5	3	0	0	26	—
Mild	4	9	4	0	0	17	—
Moderate	0	3	12	3	0	18	—
Severe	0	0	0	5	1	6	—
ESRD	0	0	0	1	0	1	—
Total	22	17	19	9	1	68	0.67
Stage 1 AKI[c]							
Normal	2	0	1	0	0	3	—
Mild	1	5	4	0	0	10	—
Moderate	0	1	10	4	1	16	—
Severe	0	0	0	0	1	1	—
ESRD	0	0	0	0	1	1	—
Total	3	6	15	4	3	31	0.53
Stage 2 AKI[d]							
Normal	3	6	0	0	0	9	—
Mild	1	5	3	2	0	11	—
Moderate	0	2	4	2	2	10	—
Severe	0	0	3	3	2	8	—
ESRD	0	0	0	0	1	1	—
Total	4	13	10	7	5	39	0.48
Stage 3 AKI[e]							
Normal	6	1	2	0	0	9	—
Mild	1	0	1	1	0	3	—
Moderate	0	0	5	1	1	7	—
Severe	0	0	0	2	1	3	—
ESRD	0	0	1	0	0	1	—
Total	7	1	9	4	2	23	0.54

24hr-CrCl = creatinine clearance from using 24-hour urine collection; AKI = acute kidney injury; CG-CrCl = creatinine clearance by Cockcroft-Gault equation; ESRD = end-stage renal disease; FDA = United States Food and Drug Administration

[a] CG-CrCl overestimated 24hr-CrCl in 52 patients and underestimated it in 18.
[b] CG-CrCl overestimated 24hr-CrCl in 16 patients and underestimated it in 8.
[c] CG-CrCl overestimated 24hr-CrCl in 11 patients and underestimated it in 2.
[d] CG-CrCl overestimated 24hr-CrCl in 17 patients and underestimated it in 6.
[e] CG-CrCl overestimated 24hr-CrCl in 8 patients and underestimated it in 2.

failure decompensation and volume overload can influence CG-CrCl performance; however, cardiac function and fluid status were not evaluated in this study. Our findings should be confirmed by the results of a prospective study.

Conclusion

Critically ill patients can have substantial AKI before cardiac surgery. In this situation, use of the CG-CrCl consistently overestimates creatinine clearance relative to the reference standard of 24-hour urine collection, with consequent risk of medication dosage errors in many patients. The degree by which the CG-CrCl overestimates creatinine clearance is exaggerated among patients who have recent and severe AKI, even those whose SCr levels were stable during the previous 48 hours. The CG-CrCl should be used cautiously when estimating renal function and when prescribing narrow therapeutic medications for critically ill patients before cardiac surgery. If the CG-CrCl is used, adjusting actual body weight by applying a 0.4 correction factor when the patient's body mass index is ≥25 improves accuracy.

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Supplementary Materials

Supplemental materials for this article are available at 10.14503_THIJ-20-7382.s1.pdf.

Author contributions: AF and JTS developed the hypothesis and designed the study; all authors conducted the analysis; AF managed data collection and wrote the first draft of the manuscript; and TI assisted with data quality assurance. All authors critically revised the manuscript and approved the final version.

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Conflict of interest: The authors declare no financial conflicts of interest related to this study.

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